OPTIMIZATION AND SCALED-UP OF A METHOD FOR THE PREPARATION OF DISPERSIONS FORMED BY ISOLATED MAGNETIC NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

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Superparamagnetic Fe_3O_4 magnetic nanoparticles (MNPs) have been shown as a suitable MRI contrast agent. Because of their larger magnetic moment in comparison to paramagnetic ions, particulate contrast agents produce enhanced proton relaxation rates in the tissue microenvironment at significantly lower doses. In addition, MNPs show long blood half-life time that depends of coating and the aggregate size particles [1]. The principal limitations of the commercial contrast agents in NMR are their lack of crystallinity and the broad size distribution of the particles obtained by conventional synthesis methods. Recently, these problems were overcomed by the use of the thermal decomposition where iron organic compounds generate magnetic nanoparticles at high temperatures in high boiling point organic solvents in the presence of oleic acid. However, the as-synthesized particles are hydrophobic in nature; therefore, these particles are incompatible with the physiological medium.

In this study monodisperse iron oxide magnetic nanoparticles were obtained with a precise control of size, high crystallinity and good magnetic properties by optimized "one-pot" synthetic route. The synthesis has been scaled-up in order to produce large amounts. This synthesis method is based on the thermal decomposition of iron organic compounds in presence of triethylene glycol (TREG) [2, 3]. The role of TREG is to provide a biocompatible, water-dispersible coating, which also acts during the synthesis process as a reagent, reducing partially the iron precursor. Furthermore, TREG is absorbed on the magnetic nanoparticles surface forming a hydrophilic coating, retards oxidation of the particle surface, reduce toxicity, and delays detection by the immune system.

In a typical preparation a TREG solution (30 mL) containing $Fe(acac)_3$ (2 mmol) was prepared. After being purged with argon, the reaction mixture was kept at 180 ºC for 30 min followed by 30 min at 280 ºC. Finally, Fe_3O_4 nanocrystals were obtained after a postreatment that included precipitation, decantation and washing in water. The process has been optimized controlling diverse parameters as mechanical stirrer, heating rates and time of reaction. The process of scaled has been realized TREG solution (90 mL) containing $Fe(acac)_3$ (6 mmol).

The morphology of the so-obtained products were quite different in function of the heating rate of this process. Thus, for heating rate under 10 ºC/min, individual and uniform magnetic nanoparticles have already formed, however these nanoparticles were agglomerated forming nanorod-like structures. In contrast, when heating rates were increased over 10 ºC/min non-agglomerated magnetic particles with uniform shape and narrow size distribution were observed.

Fig.1 presents a representative TEM image of scale-up synthesis Fe_3O_4 nanocrystals finally obtained in a PBS buffer solution which has the same pH values and ionic strength as physiological conditions. The non-aggregated nature of the particles in a physiological buffer was confirmed by TEM. The mean size of particles is 7.0 nm (σ= 0.18). Hydrodynamic size is around 11 nm in PBS.

The magnetic properties of the optimized magnetite nanoparticles were investigated with a Superconducting Quantum Interference Devices (SQUID). Figure 2 shows the room-temperature magnetization of as-prepared magnetite nanocrystals. The nanocrystal exhibited the superparamagnetic characteristics. Their saturation magnetization was 56 emu/g. Magnetic size calculated by Chantrell equation is 5.1 nm showing that all the magnetic moments of the particles rotate coherently inside the particles.

Their potential MRI agents contrast was investigated in vitro and ex vivo. In vitro, the r_1 and r_2 relaxivities of as-synthesized magnetite nanoparticles were found to be 15 (Fe) mM $^{-1}s^{-1}$ and 49 (Fe) mM $^{-1}s^{-1}$ respectively. Such values for r_1 and r_2 suggest that as-synthesized magnetite nanoparticles can act as both T_1 and T_2 contrast agent taking into account their ultra-small size, but seem to be more favourable as T_2 contrast agents due to their much larger r_2 value.

In summary, we have demonstrated that the synthesis of magnetic nanoparticles from $Fe(acac)_3$ precursors in a TREG environment can be tailored to obtain non-aggregated nanoparticles, which form a stable dispersion in water and PBS buffer solution. The control of the rate of heating and the concentration of the iron precursor species seem to be the key parameter in the balance of nucleation/growth processes and therefore in the production rates of this process, as well as in the control of the final morphology of the so-obtained particles. In vitro experiments have shown that these MNPs have an excellent enhancement T_2 contrast in MRI imaging. Therefore, this optimized synthesis is a good candidate to prepare contrast agents for NMR imaging.

References:

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Figures:

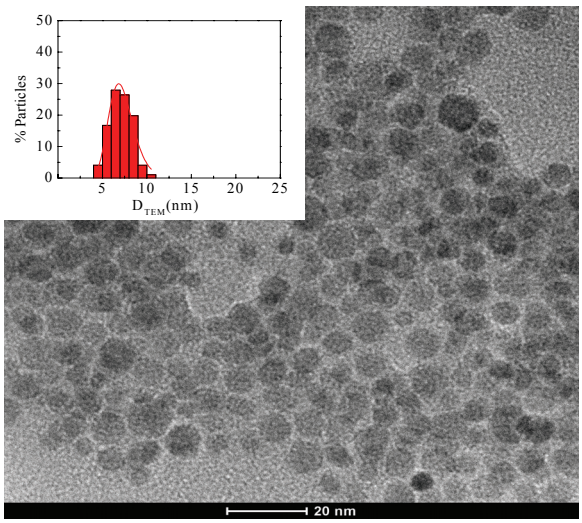

Fig.1 TEM image of the scaled-up Fe_3O_4 nanoparticles dispersed in a PBS buffer solution

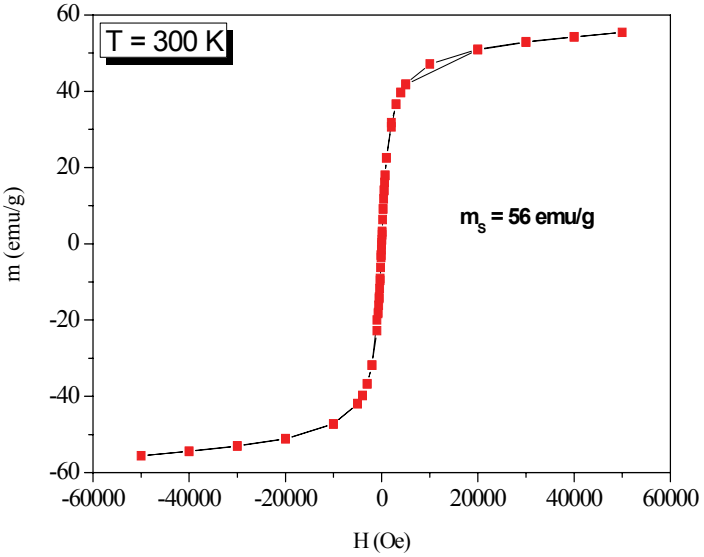

Fig.2. SQUID for the optimized nanoparticles