PRODUCTION OF DISPERSIONS FORMED BY ISOLATED MAGNETIC NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

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In the last decade, nanoscaled magnetic particles have shown great potential as magnetic functional probes in tumour imaging by Magnetic Resonance (MRI)[1].

MRI is a non-invasive technique routinely used as a very important diagnostic tool in medical practice. Although paramagnetic gadolinium compounds (chelates) have been developed as useful as T_1 contrast agents causing positive contrast enhancement [2], with their increasing use for MRI, some important shortcomings have been found, such as fast elimination in tissue; non-specific distribution in vivo and limited effect in improving MR imaging.

On the other hand, superparamagnetic Fe_3O_4 magnetic nanoparticles (MNPS) are suitable for MRI contrast since the MNPs can enhance the alterations of proton relaxation in the tissue microenvironment and thus provide better MR imaging and longer life time in the bloodstream than Gd-chelate compound [3]. However these materials present two main limitations for their application: 1) magnetic nanoparticles are usually hydrophobic moieties and are therefore easily recognizable for the immune system; this problem can be solved by coating with a hydrophilic polymer; and 2) the usual synthesis methods of magnetic nanoparticles often do not allow to obtain colloidal grade pharmaceutical suspensions formed by isolated magnetic nanoparticles. Therefore, in this study we explored and optimized a facile synthetic route to obtain stable suspensions mostly formed by isolated hydrophilic magnetic nanoparticles.

This synthesis method is based on the thermal decomposition of iron organic compounds in presence of triethylene glycol (TREG) [4,5]. 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 (30ml) containing $(Fe(acac)_3$ (2mmol) was prepared. After being purged with argon, the reaction mixture was kept at 180ºC for 30 min followed by 30min at 280ºC. After that, 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.

Fig.1 presents a representative high resolution transmission microscopy (HR-TEM) image of Fe_3O_4 nanocrystals finally obtained in a water suspension. It can be seen from the figures that the morphology of the reaction products obtained under different conditions are quite different. Depending on the heating rate, the HR-TEM images (Fig 1a, 1b), show that individual and uniform magnetic nanoparticles have already formed, however most of the nanoparticles are aggregated even after sonication forming nanorod-like structures. In contrast, when heating rates were increased to 10ºC/min y 15ºC/min (Fig 1c, 1d) non-agglomerated magnetic particles with uniform shape and narrow size distribution can be observed.

Fig.2 shows the X-ray diffraction (XRD) patterns of the nanoparticles that were synthesized in TREG. The nanoparticles are well-crystallized, showing the spinel cubic structure (fcc) and the diffraction peaks match well with the XRD patterns for bulk magnetite (JCPDS file No 19-0629), though it is not possible to reject the existence of the maghemite phase.

In summary, we have demonstrated that the synthesis of magnetic nanoparticles from $Fe(acac)_3$ precursor in a TREG environment can be tailored to obtain non-aggregated nanoparticles, which form a stable dispersion in water. The control of the rate of heating seems to be the key parameter in the balance of nucleation/growth processes and therefore in the control of the final morphology of the particles. Because of this, the optimized synthesis is a good candidate to prepare contrast agents for NMR imaging.

References:

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Figures:

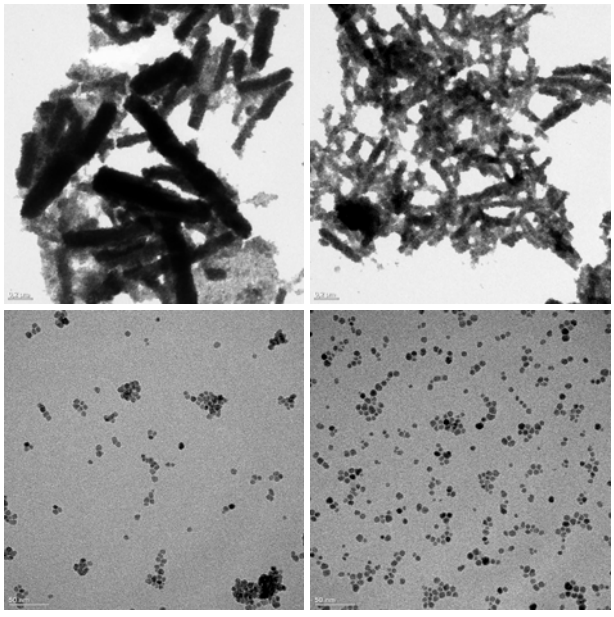

Fig.1 HR-TEM image of the Fe_3O_4 nanoparticles dispersed in water. Rate of heating: 2ºC/min (a), 5ºC/min (b), 10ºC/min(c), 15ºC/min(d).

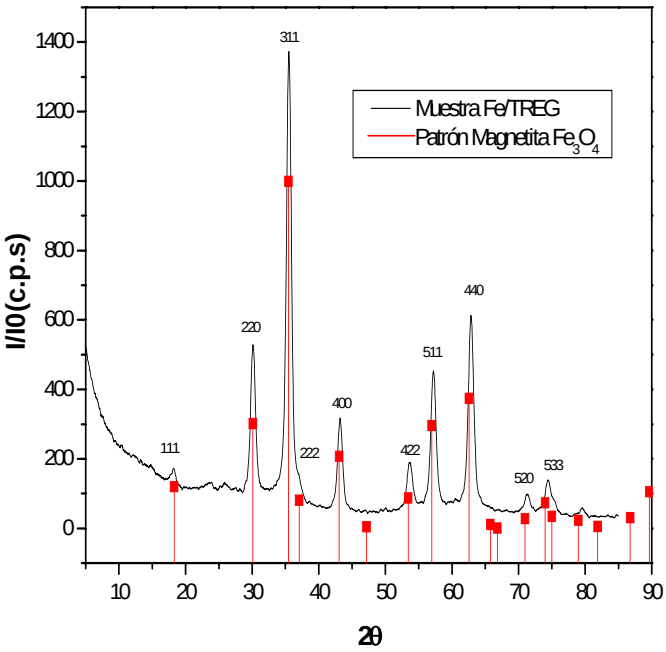

Fig.2. XRD for the Fe_3O_4 nanoparticles and standard XRD for magnetite (JCPDS19-0629)