New Nanodevice Based On Cobalt Ferrite for Hyperthermia

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Abstract

Magnetic nanoparticles have attracted increasingly attention due to their potential applications in many industrial fields. The main features of magnetic nanoparticles are the possibility to be driven by external magnetic fields, the ability to pass through capillaries without occluding them and to absorb and convert electromagnetic radiation into heat (Magnetic Fluid Hyperthermia). This article will concentrate on the latter two, presenting the synthesis of cobalt ferrite nanoparticles dispersed in diethylen glycol via polyol-mediated strategy, the crystal size control through successive synthesis and how it affects magnetic properties in order to increase hyperthermic efficiency.

1 Introduction

The development of nanometer sized colloidal particles has been intensively studied because of the many technological and fundamental scientific interests (Gunther Schmidt 2004). One of the main features of nanoparticles is that they can form stable fluid dispersion, moreover, due to their small dimension, the dispersion can pass through capillaries without occluding them. This feature is of paramount importance in many applications and especially in medicine as blood vessels have an average diameter of 8 micrometers.

Another particular aspect of magnetic nanoparticles is their ability of self heating when irradiated by electromagnetic irradiation (magnetic fluid hyperthermia - MFH) (Rosenweig 2002).

In MFH the size of the magnetic material exposed to the EM radiation is very important as the magnetism of massive materials and nanoparticles are completely different.

The magnetic properties of nanoparticles are very dependant on the size and then it is of paramount importance to control it in order to maximize the efficiency for a specific application. Experimental evidence shows that magnetic nanoparticles are more efficient than their massive counterparts, in addition with the peculiar properties of nanoparticles (fluid dispersion, small dimensions) it opens the possibility of new applications as magnetic fluid hyperthermia for cancer therapy and special polymer welding. Fluid Hyperthermia by biocompatible nanodevices can act as a therapeutic agent by itself or combined with pharmacologically active molecules and early results made by Jordan [Jordan et al. 1999] show that this approach is feasible and could lead to innovative therapies of cancer but despite these interesting preliminary results many aspects are still to be cleared.

Cobalt ferrite nanoparticles synthesis has been reported on laboratory scale in the literature (Cushing et Al. 2004) but its use in medicine, even if forecasted, has not been possible because of

numerous problems such as the not accessible surface, due to the presence of surfactants, the aggregation in solution and the huge amount of cobalt release in aqueous solutions.

To overcome all this problems we developed a patented synthesis to produce magnetic nanoparticles on an industrial scale based on the polyol-mediated method (Baldi et Al. 2002).

In this paper we will present this synthetic strategy able to produce a stable dispersion of magnetic nanoparticles of cobalt ferrite, the employment of a further synthetic procedure to increase their size and hyperthermic behaviour.

2 Experimental

2.1 Synthesis

Cobalt ferrite nanoparticles (1) were synthesised with the following polyol-mediated method: cobalt and iron acetates (89.6 and 179.2 mmol, respectively) were solubilised in 645g of Diethylen glycol at 110°C for one hour. The solution was successively heated to 180°C with a heating rate of 2°C/min and then kept at 180°C for three hours. After this growing period the dispersion has been air cooled to room temperature and stored. A second series of ferrite particles with larger average size, (2-6), was prepared as follows: we synthesised cobalt ferrite nanoparticles, (2), as described above using half concentrations with respect to (1) (the final concentration of cobalt ferrite was 1.5% w/w) as initial seed. After the first synthesis, suitable quantities of solvent and precursors were added at room temperature to keep the final magnetic material concentration at 3% w/w and the heating cycle was repeated (1 hour at 110°C and 3hours at 180°C) in order to obtain larger particles (sample 3). Repeating the same procedure three times, using each time particles prepared in the previous step as initial seeds, yielded samples (4), (5) and (6).

2.1 Results and Discussion

The XRD pattern (figure 1) of the dried sample (1) matches the one expected for the inverse spinel phase characteristic of cobalt ferrite. The average crystallite size was estimated from the X-ray diffraction line broadening measurement by using the Scherrer formula, analysis of the (311) peak gave a mean diameter of 5.5nm.

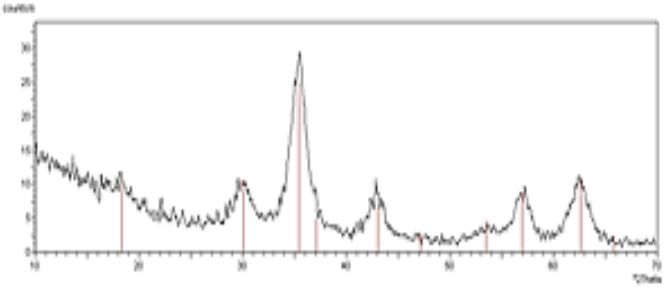

Figure 1 X-ray diffraction spectra of sample 1

Dynamic Light Scattering measurement of samples (1) in distilled water (figure 2) revealed a uniform dispersion of nanoparticles (PDI< 0.1) with average diameter of 13,2 nm. DLS measurements on (1) over a two years' period did not show any significant alteration of the dispersion stability. This can be addressed, according to the DLVO theory, to the low ionic strength and consequently low dielectric constant of the final dispersion that determines a thick electrical double layer that increases the repulsive forces between the charged particles preventing agglomeration.

According to reference 7 the volume average diameter can be converted to the number averaged diameter that is usually obtained by XRD and electron microscopy image analysis. Operating this procedure on DLS results gives an average diameter of 5,56nm that is in perfect agreement with XRD observations.

In figure 3 a SEM image of the dispersion of (1) in ethanol deposited over a Cu grid, is shown. The sample consists of a uniform dispersion of spherical particles with a narrow size distribution and a mean diameter, of 6.4nm. The obtained value is close to that obtained from XRD measurements indicating a high crystalline degree of all the particles.

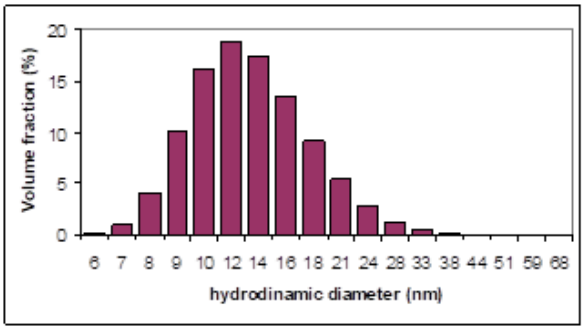

Figure 2. DLS measurement of sample in water

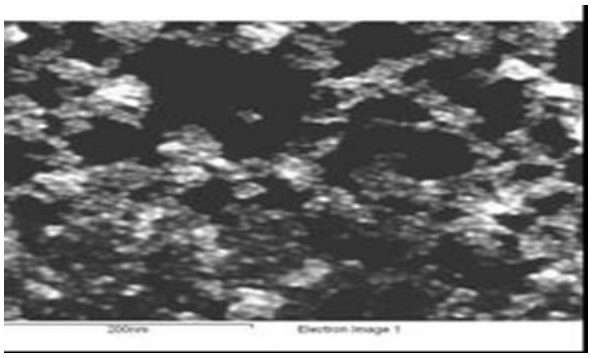

Figure 3. SEM micrographs of a liquid dispersion

It must be noted that, due to the dispersion stability and to the easy handling of liquids with respect to powders, this synthetic strategy can be easily scaled up. We have already realised a pilot implant capable to produce 20 L a day of cobalt ferrite dispersion at 3% w/w without significantly modifying nanoparticles characteristics (i.e. dimensions, polydispersity and magnetic properties). It should be noted that the particles are not covered without any capping agent and then are ready for successive chemical modifications (i.e. surface binding) in order to produce more complex biomedical devices (Baldi et Al. 2007a).

A similar structural and morphological characterisation was performed on the other samples produced with the seed approach (2-6). The main structural features obtained are listed in table 1.

Sample	Fe/Co	D_{XRD} (nm)	D_{DLS} (nm)	PDI
1	2.20	5.5	21.5	0,19
2	2.24	5.01	7,6	0,19
3	2.15	5,91	9,2	0,18
4	2.26	6,05	13,6	0,19
5	2.20	6,21	16,2	0,23
6	2.18	6.72	22,3	0,21

The data show that the proposed synthetic method is effective for producing high crystalline cobalt ferrite nanoparticles with increasing crystal sizes in the 5-7 nm. For all samples the observed Co/Fe molar ratio is constant and close to that of stoichiometric $CoFe_2O_4$. A large increase of the hydrodynamic diameter resulted from DLS measurements, such an increase can be addressed to a strong agglomeration during the steps following the first one. Probably the low quantity of water available together with the magnetic interactions and high temperature conditions produce strongly agglomerated particles as evident from fig 4. This agglomerates of nanoscopic dimensions for stable liquid dispersion over one year.

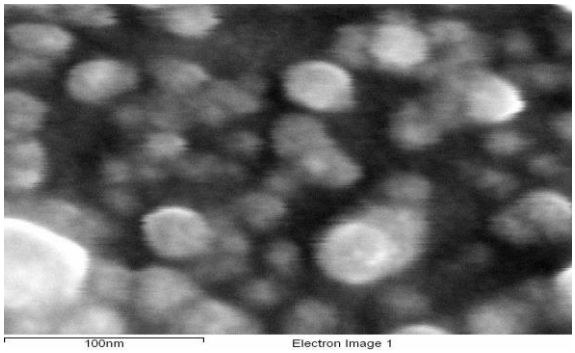

Figure 4 SEM image of cobalt ferrite samples after subsequent synthesis steps

2.3 Hyperthermic properties

Hyperthermic experiments were carried out at 298K irradiating with an electromagnetic field generated by an induction coil working at 167 kHz and with a field intensity of 21 kA/m for 30 seconds. The nanoparticles concentration was 3%w/w for all the samples blocked in a solid matrix. In this experiments the temperature increase has been recorded by a FLIR E65 thermocamera. The heat generated has been calculated as

$$Q_i = m_i \cdot c_s \cdot \Delta T_i$$

Where m is the mass in grams of the different species (solvent, particles, sample holder), c_s their specific heat in J/K*g and Ti is the temperature increase. The efficiency can be determined by the following equation:

$$P = \frac{\sum_i Q_i}{m_M \Delta t}$$

Where m_M is the total amount of metal in the sample, Δt the time of irradiation.

The results, shown in figure 6, indicate an efficiency increase with particle size and synthesis steps. It must be noted that these value are obtained in mechanically blocked samples and not in fluids as often reported. The maximum values reported are rather high and comparable to the values found in literature (Fortin et Al. 2007).

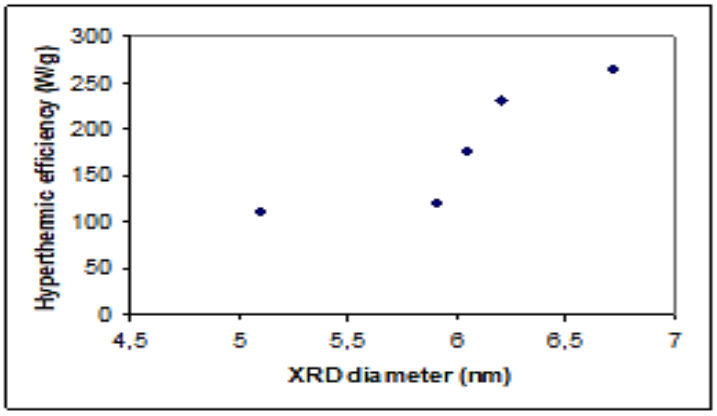

Figure 6 Hyperthermic efficiency of cobalt ferrite nanoparticles in function of) the XRD diameter

According to the theory of magnetic hyperthermia (Rosenweig 2002) the power dissipation can be expressed by the following formula:

$$P=\mu_0\pi\chi_o''fH_0^2$$

Where μ_0 is the permeability in the free space, χ_o''' is the out of phase component of the magnetization, f is the irradiating frequency and H_0 is the intensity of the oscillating field.

The χ_o'' component can also be expressed as:

$$\chi_o'' = \chi_o \chi''$$

Since we presume only small differences in χ'' due to the large relaxation peaks and we observed small variations of saturation magnetisation (Baldi et al. 2007b), we suggest that the increase of the hyperthermic efficiency should be addressed to the increasing average volume that increases χ_o according to Langevin theory as previously stated.

The relaxation pathway dominating the hyperthermic process can be either magnetic or mechanic. As our samples are mechanically blocked the only possible relaxation process is the magnetic one.

3 Conclusions

A novel method to prepare spherical shaped, highly monodisperse, spinel ferrite $CoFe_2O_4$ nanoparticles, in the form of stable dispersion is presented. The technique is based on the polyol synthesis and can be repeated in subsequent steps, using each time ferrite particles as seed, to finely tune the average size of the particles in the 5 – 7 nm range. This latter effect also produces a large increase in hyperthermic efficiency that represents the most important characteristic of the material. Fine tuning of nanoparticle size leads to an increase in material hyperthermic efficiency that is critical for both producing higher local temperatures and also reducing the quantities of the material needed to achieve a target temperature, of paramount importance in biomedical applications. For biomedical applications a biocompatible coverage of the particles has to be provided in order to avoid immuno-defensive system, moreover successive anchoring of targeting moieties can direct the particles to a specified target as a following step. In this sense we have already developed new biocompatible hyperthermic nanoparticles in order to provide an alternative strategy in the cure of cancer.

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