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Research Paper

IRON OXIDE NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

Aadarsh Mishra*

*Corresponding Author: ***Aadarsh Mishra,*** ✉ *aadarshm9@gmail.com*

Superparamagnetic iron oxide nanoparticles (SPION) with appropriate surface chemistry have been widely used experimentally for numerous in vivo applications such as magnetic resonance imaging contrast enhancement, tissue repair, immunoassay, detoxification of biological fluids, hyperthermia, drug delivery and in cell separation, etc. All these biomedical and bioengineering applications require that these nanoparticles have high magnetization values and size smaller than 100 nm with overall narrow particle size distribution, so that the particles have uniform physical and chemical properties. In addition, these applications need special surface coating of the magnetic particles, which has to be not only non-toxic and biocompatible but also allow a targetable delivery with particle localization in a specific area. To this end, most work in this field has been done in improving the biocompatibility of the materials, but only a few scientific investigations and developments have been carried out in improving the quality of magnetic particles, their size distribution, their shape and surface in addition to characterizing them to get a protocol for the quality control of these particles. Nature of surface coatings and their subsequent geometric arrangement on the nanoparticles determine not only the overall size of the colloid but also play a significant role in biokinetics and biodistribution of nanoparticles in the body. The types of specific coating, or derivatization, for these nanoparticles depend on the end application and should be chosen by keeping a particular application in mind, whether it be aimed at inflammation response or anti-cancer agents. Magnetic nanoparticles can bind to drugs, proteins, enzymes, antibodies, ornucleotides and can be directed to an organ, tissue, or tumour using an external magnetic field or can be heated in alternating magnetic fields for use in hyperthermia. This review discusses the synthetic chemistry, fluid stabilization and surface modification of superparamagnetic iron oxide nanoparticles, as well as their use for above biomedical applications.

Keywords: Magnetic nanoparticles, MRI, Drug deliverym Surface modification, Hyperthermia

INTRODUCTION

In the last decade, nanotechnology has developed to such an extent that it has become possible to fabricate, characterize and specially tailor the functional properties of nanoparticles for biomedical applications and diagnostics. As intermediates between the molecular and the solid states, inorganic

[1] Department of Mechanical Engineering, Manipal Institute of Technology.

nanoparticles combine chemical accessibility in solution with physical properties of the bulk phase . They are thus ideal elements for the construction of nanostructured materials and devises with adjustable physical and chemical properties. The application of small iron oxide particles in in vitro diagnostics has been practised for nearly 40 years. In the last decade, increased investigations with several types of iron oxides have been carried out in the field of nanosized magnetic particles (mostly maghemite, γ-Fe2O3, or magnetite, Fe3O4, single domains of about 4-15 nm in diameter), among which magnetite is a very promising candidate since its biocompatibility has already proven. Magnetite, Fe3O4, is a common magnetic iron oxide that has a cubic inverse spinel structure with oxygen forming an fcc closed packing and Fe cations occupying interstitial tetrahedral sites and octahedral sites. The electrons can hop between Fe2+ and Fe3+ ions in the octahedral sites at room temperature, rendering magnetite an important class of half-metallic materials. With proper surface coating, these magnetic nanoparticles can be dispersed into suitable solvents, forming homogeneous suspensions, called ferro- fluids. Such a suspension can interact with an external magnetic field and be positioned to a specific area, facilitating magnetic reso- nance imaging for medical diagnosis and AC magnetic field-assisted cancer therapy. Nanosized particles have physical and chemical properties that are characteristic of neither the atom nor the bulk counterparts. Quantum size effects and the large surface area of magnetic nanoparticles dramatically change some of the magnetic properties and exhibit superparamagnetic phenomena and quantum tunnelling of magnetization, because each particle can be considered as a single magnetic domain.

EXPERIMENTAL

Physical methods such as gas phase deposition and electron beam lithography are elaborate procedures that suffer from the inability to control the size of particles in the nanometer size range. The wet chemical routes to magnetic nanoparticles are simpler, more tractable and more efficient with appreciable control over size, composition and sometimes even the shape of the nanoparticles. Iron oxides (either Fe_3O_4 or γ-Fe_2O_3) can be synthesized through the co-precipitation of Fe^{2+} and Fe^{3+} aqueous salt solutions by addition of a base. The control of size, shape and composition of nanoparticles depends on the type of salts used (e.g. chlorides, sulphates, nitrates, perchlorates, etc.), Fe^{2+} and Fe^{3+} ratio, pH and ionic strength of the media. Conventionally, magnetite is prepared by adding a base to an aqueous mixture of Fe^{2+} and Fe^{3+} chloride at a 1:2 molar ratio. The precipitated magnetite is black in colour. The overall reaction may be written as follows:

equation

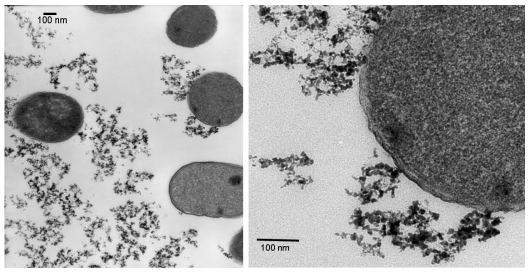
$Fe^{2+}+2Fe^{3}++8OH^{-} \rightarrow Fe_3O_4+4H_2O.$

According to the thermodynamics of this reaction, a complete precipitation of Fe3O4 should be expected between pH 8 and 13, while maintaining a molar ratio of Fe3+:Fe2+ is 2:1 under a non-oxidizing oxygen-free environment. Otherwise, Fe3O4 might also be oxidized as

Equation

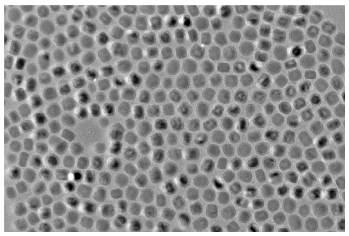
$Fe3O4+0.25O2+4.5H2O \rightarrow 3Fe(OH)3$

Figure 1: Transmission Electron Microscope Image of Cross Sections of E. Coli Grown with Composite Iron Oxide Nanoparticles



Magnetite particles obtained under different synthetic conditions may display large diff- erences regarding their magnetic properties. These differences are attributed to changes in structural disorder, creation of antiphase boundaries, or the existence of a magnetically dead layer at the particle surface. The sa- turation magnetization (Ms) values found in nanostructured materials are usually smaller than the corresponding bulk phases, provided that no change in ionic confi-gurations occurs. Accordingly, experimental values for Ms (i.e. magnetic saturation) in magnetite nano- particles have been reported to span the 28-45 emu/g range, lower than the bulk mag- netite value; 90 emu/g. Many studies have been reported on the origin of the observed reduction in magnetization in fine magnetic particles. The first studies on the decrease in magnetization performed in γ-Fe2O3 showed that this reduction is due to the existence of noncollinear spins at the surface, making the same mechanism appealing for Fe3O4.

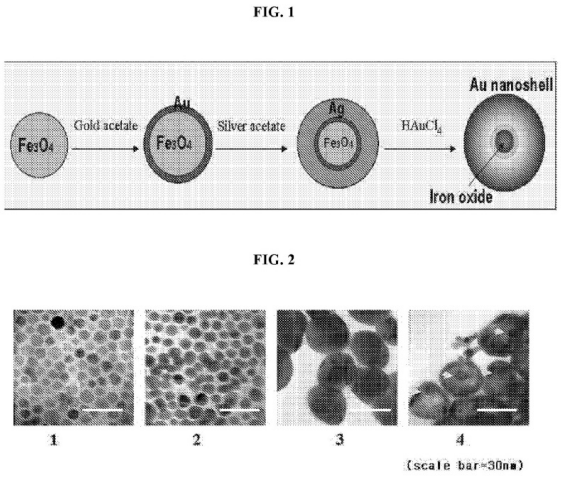
Figure 2: Strongly Magnetic Iron/Iron Oxide Core-Shell Nanoparticles



Also, in magnetite fine particles, have reported a linear correlation between saturation magnetization and particle size, suggesting that defects at the particle surface can influence the magnetic properties. The surface curvature of the nanoparticle was much larger for smaller particle size, which encouraged disordered crystal orientation on the surface and thus resulted in significantly decreased Ms in smaller nanoparticles.

The disadvantage of these bulk solution synthesis is that the pH value of the reaction mixture has to be adjusted in both the synthesis and purification steps. As a result, the production of significant quantities of narrowly dispersed, nanometer sized mag-netic particles remains a significant challenge through these methods. The critical difficulty is that these particles form aggregates and grow to minimize the overall surface free energy, so that free precipitation is not a viable technique.

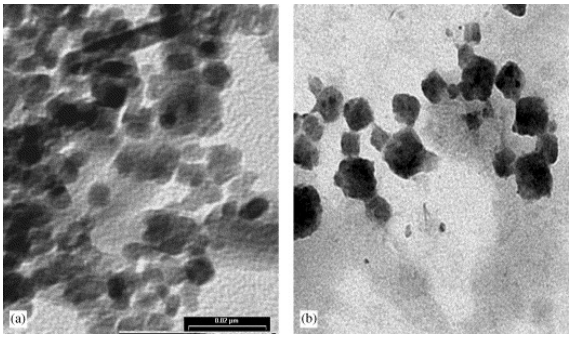
Figure 1 & 2: Electron Microscope Photographs of Iron Oxide Nanoparticles



Advancement in the use of magnetic particles for biomedical applications depends on the new synthetic methods with better control of the size distribution, magnetic properties and the particle surface characteristics. Orga-

nized assemblies or complex structures have been used as reactors to obtain ultrafine magnetic iron oxide particles. Stable aqueous magnetic suspensions can also be fabricated using various saturated and unsaturated fatty acids as primary and secondary surfactants. In practice, however, little control can actually be exercised over the size and size distribution of the nanostructures and, moreover, only small quantities of iron oxide can be obtained, owing to the constraints of low reagent concentrations necessitated by this synthetic procedure. A variety of other methods based on the principle of precipitation in highly constrained domains have been developed; these include sol-gel preparation, polymer matrix-mediated synthesis, precipitation using microemulsions and vesicles. Small quantities of these materials have been produced in apoferritin cages and laboratory-grown bacteria.

Figure 3: Transmission Electron Microscopy Pictures of Magnetic Particles Prepared in (a) Bulk Solutions and (b) in w/o Microemulsions



RESULTS

The concept of drug delivery using magnetic nanoparticles greatly benefit from the fact that nanotechnology has developed to a stage that it makes possible not only to produce magnetic nanoparticles in a very narrow size distribution range with superparamagnetic properties but also to engineer particle surfaces to provide site-specific delivery of drugs. Magnetite due to its strong magnetic properties was used first in biology and then in medicine for the magnetic separation of biological products and cells as well as magnetic guidance of particle systems for site-specific drug delivery. The size, charge, and surface chemistry of magnetic particles could strongly influence their biodistribution. Another important point is that the magnetic properties depend strongly on the size of the magnetic particles. In the last decade, the activities in the clinical applications of magnetic carriers and magnetic particles have been very high, because the needs of better diagnostics procedures on one side and better treatment modalities are, on the other hand, strongly increasing.The most relevant biomedical applications for these particles may be targeted at healthcare for the aged peoples and in particular at diseases of the musculoskeletal system. Many of these diseases are characterized by severe inflammation, disability and pain and the better control of inflammation is an important goal to which magnetic nanoparticles may contribute to a great extent. Precise delivery of anti-inflammatory drugs to the exact area of inflammation is a desirable end since this could lead to reduced drug dosages, elimination of side effects on the other healthy tissues and increased rapidity of action.

CONCLUSION

Application of external magnetic fields to the area of inflammation, e.g. a joint, while the particles are to be targeted may provide an important component of such treatments. If successful, this type of treatment could be used to treat autoimmune diseases, direct immunosuppressive drugs to where they are needed in transplant patients and patients with tumours. Attachment of specific antibod-

ies to the particles may allow particles to target specific cell types i.e. macrophages having receptors expressed on their surfaces. Inflammation could then be modified by using magnetic fields to focus the macrophages or divert them away from tissue if appropriate. This kind of application also includes other biological applications, e.g. cell separation, in which the improvement of the success rate is of importance for the classification and further surely handling of cells. Successful development in this area will aid the growth of the biomedical industry as well as improving the quality of life in the population.

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