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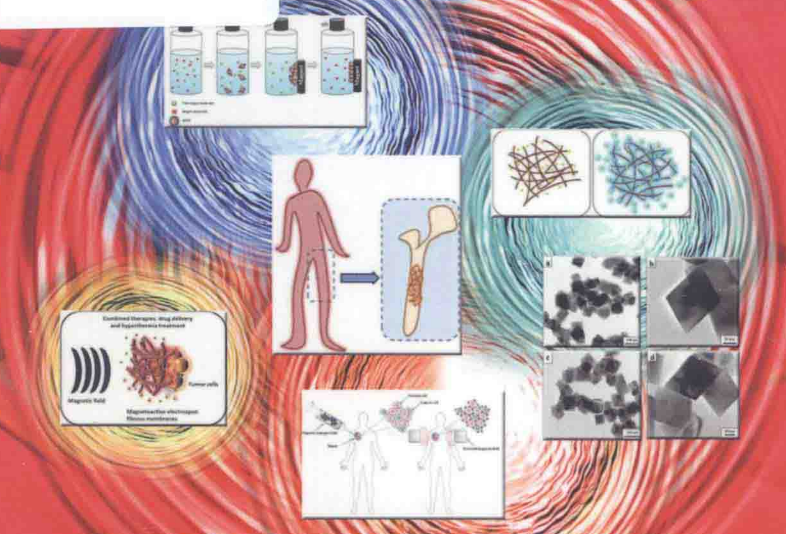

Nora P. Sabbas
Editor

Magnetic Nanoparticles

Synthesis, Physicochemical Properties and Role in Biomedicine

NOVA

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MAGNETIC NANOPARTICLES

SYNTHESIS, PHYSICOCHEMICAL PROPERTIES AND ROLE IN BIOMEDICINE

NORA P. SABBAS
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PREFACE

Magnetic nanoparticles (MNPs) are one of the materials of great interest for presenting a unique combination of relevant properties such as high surface area, magnetic behavior and low toxicity, which can find potential use in different processes and applications in areas such as catalysis, data storage, water treatment, drug delivery system, DNA separation, tissue engineering, sensors, hyperthermia, ferrofluids, and as contrast agents in nuclear magnetic resonance (NMR) imaging. This book provides further information on how magnetic nanoparticles are synthesized, their physicochemical properties and the roles MNPs play in biomedicine.

Chapter 1 - Magnetic nanoparticles (MNPs) are one of the materials of great interest for presenting a unique combination of relevant properties such as high surface area, magnetic behavior and low toxicity, which can find potential use in different processes and applications in areas as catalysis, data storage, water treatment, drug delivery system, DNA separation, tissue engineering, sensors, hyperthermia, ferrofluids, and as contrast agents in nuclear magnetic resonance (NMR) imaging. Modification of the particle surface induces changes in some properties such as high magnetization values and stable water dispersion and recent advances in nanotechnology have improved the range of use of MNPs in diagnosis and therapy.

Among the biological uses of MNPs, the author can highlight the biomedical imaging and therapeutic applications. Chemical modifications of the MNPs surface might result in non-toxic and biocompatible nanoparticles for biomedical applications like the development of new targeted nanoparticles for drug delivery systems for specific tissues. As previously mentioned, MNPs are used as a targeted carrier to be available for drug delivery to the specific site under the influence of a guiding magnet for treatment of diseases.

Furthermore, MNPs offer excellent prospects for chemical and biological sensing. In the case of bioanalytical applications, MNPs can be adopted as nanoparticle-modified transducers for use as sensors and biomolecule-nanoparticle conjugates as labels for biosensing and bioassays. In the present review the author will discuss current uses of MNPs in biomedicine and nanomedicine.

Chapter 2 - Carbon–coated magnetite nanoparticles (NPs) were synthetized by the mechanochemical method with hematite as precursor and amorphous carbon as inorganic reductor. After 18 hours of milling in an inert atmosphere, a nanocomposite material of magnetite and carbon was obtained.

Structural and magnetic properties of the NPs were investigated by X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), energy dispersive X-ray spectroscopy (EDS) and vibrating sample magnetometry. XRD patterns, refined with the Rietveld method, show that magnetite is present in samples milled from 6 hours onward and that after milling for 18 hours and annealing in Ar, the sample contains a single crystalline phase. Magnetization curves for samples with different milling times show saturation magnetization values that range from 34.1 emu/g after 1 h to 78.0 emu/g after 18 h. Coercive fields are about 500 Oe for all samples. TEM studies reveal that the samples are made of amorphous carbon clusters with magnetite NPs of 20 nm.

The obtained NPs, associated to electrochemical transducers, show an improved enhancement of the charge transfer for redox processes involving different bioanalytes. Thus, these NPs offer unique properties as a catalyst in biosensing strategies for the electrochemical detection of high-impact markers and the development of theranostics smart-devices for biomedical applications.

Chapter 3 - One of the most rapidly growing and exciting applications of nanotechnology in biomedical research is the development of biocompatible magnetic nanoparticles (NPs) for use in powerful and highly complementary bio-imaging modalities. Biocompatible magnetic NPs should be effective as contrast agents (CAs) in magnetic resonance imaging (MRI), and the unique physical properties of magnetic NPs as well as their conjugation with dyes and/or radioactive elements could lead to the development of the multimodal bio-imaging probes for use in MRI/optical imaging, PET/MRI, and MRI/optical/therapy. Multimodal bio-imaging is quite attractive for the early and precise diagnosis of disease, leading to theranostics, since it combines the advantages of, and provides complementary information from, several imaging modalities.

The metabolism of magnetic NPs strongly depends on their size, but also on individual surface characteristics, like charge, morphology and surface chemistry. Accordingly, the creation of novel magnetic NPs for multimodal bio-imaging can be realized only with the fusion of multiple disciplines, including chemistry, material science, biology, and engineering.

In this chapter, recent advances in the use of magnetic NPs, represented by iron oxide NPs, manganese oxide NPs, and gadolinium oxide NPs, for multimodal bio-imaging are highlighted and summarized.

Chapter 4 - Superparamagnetic iron oxide nanoparticle (SPION) has attracted a great deal of attention in the fields of medicine and biology due to its non-toxicity, large specific surface area, amenability to various surface fuctionalization, and unique magnetic properties. For biomedical applications, the author synthesized two kinds of SPIONs by co-precipitation and polyol methods, designated as *C*- and *P*-SPIONs, respectively. To increase their solubility and stability in an aqueous solution, both of the SPIONs were functionalized with hyperbranched polyglycerol (PG) through ring-opening polymerization of glycidol. Scanning transmission electron microscopy (STEM) and dynamic light scattering (DLS) measurements revealed that the *P*-SPION provided individual nanoparticles without aggregation after the PG fuctionalization. This *P*-SPION-PG was highly soluble not only in pure water (> 40 mg/mL), but also in a phosphate buffer solution (> 25 mg/mL). Such high solubility enabled separation of *P*-SPION-PG according to their size by size exclusion chromatography (SEC). The size-separated *P*-SPION-PG shows a gradual increase in transverse relaxivity (r_2) with increasing particle size. The hydroxyl group in PG also serves as a scaffold for further surface functionalization. For targeted cell labeling, the author functionalized *P*-SPION-PG through multi-step organic transformations (-OH → -OTs (tosylate) → -N_3 → -RGD) including click chemistry as a key step to impart targeting specificity by immobilization of cyclic RGD peptide on the surface. The targeting effect was demonstrated by the cell experiments; *P*-SPION-PG-RGD was taken up by the cells overexpressing $\alpha_v\beta_3$-integrin such as U87MG and A549. In addition, near-infrared (NIR) fluorescence dye (IRdye 800CW) was immobilized on the surface of *P*-SPION-PG through amide linkage. The resulting *P*-SPION-PG-IRdye showed good solubility in phosphate buffered saline (PBS) and strong fluorescence in NIR region, which may find application in optical/MR bimodal imaging.

Chapter 5 - Magnetic nanoparticles and nanocomposites have been special focus of high research interest due to their high magnetic moment and bio-affinity surface properties and promising applications in nanoscience, nanotechnology and bio-applications. These properties can be obtained by synthesizing various magnetic nanoparticles and core-shell type magnetic nanocomposites. In this research, the author synthesized high magnetization superparamagnetic nanoparticles and core-shell nanocomposites by chemical and sonochemical method for using as carriers/labels in bio-sensing purpose.

Iron oxide magnetic nanoparticles (NPs) have been synthesized by sonochemical method using inexpensive and non-toxic metal salts as reactants. Transmission electron microscopy (TEM) data demonstrated that the particles were narrow range in size distribution with 11 nm average particle size and spherical in shape. The magnetization curve from vibrating sample magnetometer (VSM) measurement shows that as-synthesized NPs were nearly superparamagnetic in magnetic properties with very low coercivity, and magnetization values were 80 emu/g.

Monodisperse magnetite nanocubes with uniform particle size of about 80 nm have been synthesized in aqueous medium by sonochemical method. The magnetic characterization of the NPs reveals saturation magnetization of 91 emu/g at 5 K for as-synthesized sample and 94.8 emu/g for the sample which annealed at the temperature of 600 °C in a vacuum chamber. However, the saturation magnetization has been observed to decrease with further increase in annealing temperature and this has been attributed to the presence of a thin magnetic dead layer at the surface caused by shape anisotropy distortion and broken exchange bonds, and spin canting on the surface of the particles in addition to formation of a small amount of maghemite phase.

Highly crystalline and monodisperse cobalt ferrite ($CoFe_2O_4$) nanoparticles have been synthesized via rapid one-pot sonochemical techniques and without subsequent calcination. The size of $CoFe_2O_4$ nanoparticle was controlled in the range from 20 to 110 nm based on the solvent medium used in the synthesis process. Furthermore, the evolution from spherical to cubic morphology of cobalt ferrite is achieved by simply changing the solvent medium from aqueous to alcoholic medium. High saturation magnetization (Ms) and high coercivity (Hc) values of 87 emu/g and 1610 Oe, respectively were obtained for the $CoFe_2O_4$ NPs.

For synthesis of core-shell type of silica coated iron oxide magnetic (Fe_3O_4@SiO_2 core-shell) NPs, sono-chemical approach was applied using inexpensive and non-toxic chemicals. TEM data demonstrated that the thickness of silica coating on iron oxide magnetic NPs 10-15 nm in average. The magnetization curve from VSM measurement shows that the magnetization has also been decreased of as synthesized silica coated iron oxide NPs compared to freshly prepared bare iron oxide magnetic NPs, which is also a evidence of synthesizing of $Fe_3O_4@SiO_2$ core-shell NPs.

Besides the synthesis of metal oxide core-shell NPs, high magnetization FeCo nanoparticles with different Fe/Co ratios have been successfully synthesized by surfactant free simple modified polyol method. In this process, polyethylene glycol was used as a solvent media and it has been found to play a key role to act as a reducing agent as well as a stabilizer simultaneously. TEM data suggest that the annealed FeCo nanoparticles are of 50–90 nm in size. The physical Property Measurement System (PPMS) reveals that the $Fe_{60}Co_{40}$ composition among all the samples exhibit highest saturation magnetization of 230.14 emu/g at 5K.

In another study, high magnetic monodisperse NiFe NPs with different compositions have been successfully synthesized polyol method. TEM images displayed formation of a thin oxide layer around the nanoparticles, and confirmed by detection of some oxygen element using EDS measurement. The magnetic properties of the synthesized NiFe NPs samples were measured VSM at room temperature, and the saturation magnetization value was found to be iron content dependent.

Chapter 6 - Materials capable of responding to external stimuli including pH, temperature, magnetic and electric field, undergoing conformational changes are considered to be one of the most exciting and emerging classes of advanced materials receiving considerable scientific interest especially in the biomedical field. Stimuli-responsive polymers in the form of micro- or nanofibers have received great attention during the last 10 years and have been exploited in a diverse range of biomedical applications such as drug delivery, tissue engineering, bioseparation and biosensing. One of the most popular and versatile fiber fabrication methods used for the production of fibers is electrospinning. Its simplicity, cost-effectiveness and applicability not only to pristine synthetic and natural polymers but also to composites, enables the development of polymer-based fibrous nanocomposites *via* the combination of polymers with inorganic nanofillers. Among such nanoadditives, magnetic nanoparticles capable of interacting with an externally applied magnetic field, are particularly attractive owing to their potential biomedical applications including magnetically-triggered drug delivery, magnetic cell seeding, magnetic bioseparation, hyperthermia cancer treatment and contrast enhancement in magnetic resonance imaging. In this chapter, an introductory section on electrospinning and on different parameters influencing this process is initially provided. The different fabrication routes for generating electrospun magnetoactive polymer-based (nano)fibrous materials are briefly discussed and finally the applicability of these materials in the biomedical field including tissue engineering, drug delivery, hypethermia treatment and biosensing is reviewed.

Chapter 7 - Interest to the nanomedicine has increased dramatically during past years. Since nanotechnology has the potential to have a revolutionary impact on cancer diagnosis and therapy, is there a major challenge to produce magnetic nanoparticles (MNPs) suitable for biomedical applications. In this review the main theoretical views on the properties, synthesis, characterization, functionalization, and bioapplication of MNPs in the current context of science are considered. This review examines some of the recent developments in MNPs technology and provides a brief background of their applications and results of *in-vitro* and *in-vivo*, animal and clinical experiments of targeted drug delivery. Finally, some of the recent biological, medical and scientific applications of MNPs are briefly reviewed, and some future trends and perspectives in these research areas will be outlined.

CONTENTS

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Chapter 1

Biomedical Applications of Magnetic Nanoparticles: An Overview

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1. Abstract

Magnetic nanoparticles (MNPs) are one of the materials of great interest for presenting a unique combination of relevant properties such as high surface area, magnetic behavior and low toxicity, which can find potential use in different processes and applications in areas as catalysis (Lu et al., 2007), data storage (Frey et al., 2009), water treatment (Meng et al., 2011), drug delivery system (Anirudhan et al., 2013b), DNA separation (Chiang et al., 2005), tissue engineering (Ito and Honda, 2007), sensors (Baby and Ramaprabhu, 2010), hyperthermia (Alphandéry et al., 2012), ferrofluids (Hee Kim et al., 2005), and as contrast agents in nuclear magnetic resonance (NMR) imaging (Choi et al., 2004). Modification of the particle surface induces changes in some properties such as high magnetization values and stable water dispersion and recent advances in nanotechnology have improved the range of use of MNPs in diagnosis and therapy.

Among the biological uses of MNPs, we can highlight the biomedical imaging and therapeutic applications. Chemical modifications of the MNPs surface might result in non-toxic and biocompatible nanoparticles for biomedical applications like the development of new targeted nanoparticles for drug delivery systems for specific tissues. As previously mentioned, MNPs are used as a targeted carrier to be available for drug delivery to the specific site under the influence of a guiding magnet for treatment of diseases. Furthermore, MNPs offer excellent prospects for chemical and biological sensing. In the case of bioanalytical applications, MNPs can be adopted as nanoparticle-modified transducers for use as sensors and biomolecule-nanoparticle conjugates as labels for biosensing and bioassays. In the present review we will discuss current uses of MNPs in biomedicine and nanomedicine.

Keywords: Magnetic nanoparticles, biomolecules, biomedicine, therapy, diagnosis

2. Magnetic Nanoparticles

In recent years, the nanotechnology has been of great interest in Physics, Chemistry, Science and Engineering of Materials, and Biotechnology, because it is bringing technological breakthroughs (Charles P. Poole and Owens, 2003). Nanotechnology involves the control and manipulation of materials with at least one dimension smaller than 100 nanometers; when the matter is in the nanometric scale has different properties in relation to bulk materials (Charles P. Poole and Owens, 2003).

MNPs are one of the materials of main interest in this area due to their properties as high surface area to volume ratio, magnetic behavior and low toxicity. Thus, diverse applications are discussed in the subsequent topics to introduce the reader to the use of MNPs in biomedicine.