Chapter 5
Pharmaceutical and Biomedical Applications of Magnetic Iron-Oxide Nanoparticles

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Abstract   In the past few years, due to the rapid development of the advances in the pharmaceutical and biomedical field, the magnetic iron-oxide nanoparticles have received considerable attention for their attractive properties. Magnetic nanoparticles are perfect candidates for use in diagnosis and disease treatment because they have properties as superparamagnetic behavior, a high superficial area that allows functionalizing, biocompatibility, nanometric size (10–100 nm), low toxicity, possibility of in vivo manipulation by a low external magnetic field, and placement in a specific place. The key point of magnetic iron-oxide nanomaterials is to develop effective synthesis techniques that allow particles to have with a uniform size, high magnetic saturation, and stability, preventing aggregation and oxidation with air since these result in the loss of its magnetic properties. This chapter presents a review of various strategies to synthesis of magnetic nanoparticles and their use in pharmaceutical and biomedical field.

Keywords Magnetic iron-oxide nanoparticles • Synthesis techniques • Pharmacological activity • Biomedical application

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5.1   Introduction

At present, magnetism plays an important role in the study and manufacture of nanostructured and magnetic materials (Abolfazl et al. 2012). In order to make nanostructured materials, it is necessary to manipulate objects with a similar size to groupings of molecules and even molecules and atoms; the diameter of these materials is smaller than 1,000 nanometers (nm). The purpose of manipulating these materials in nanometric scale, must to the possibility of creating devices and systems with new properties allowing specific functions that represent nature behaviors (Martín et al. 2003; Abolfazl et al. 2012).

The use of magnetic iron-oxide nanoparticles (IONPs) offers advantages due to the chemical, physical, and pharmacological properties. These properties include magnetic behavior, chemical composition, the structure of the crystal, granulometric uniformity, properties related to adsorption processes, surface structure, and solubility (Raz et al. 2012). Among the magnetic nanostructured materials, magnetite (Fe_3O_4) and maghemite (Fe_2O_3) are commonly used due to their strong magnetic properties and low toxicity, which motivate their application in the field of biotechnology and medicine (Reddy et al. 2012; Wu et al. 2015).

In the past few years, due to the rapid development of the nanotechnology and magnetic nanostructured materials in biotechnology and medicine areas, magnetic particles of nanometric sizes have received considerable attention (Curtis and Wilkinson 2001; Pankhurst et al. 2003; Tartaj et al. 2003). These particles may have sizes that are comparable to virus (20–500 nm), proteins (5–50 nm), or genes (2 nm to wide it and 10–100 nm along). Moreover, it is possible to control using an external magnetic field and has a great surface area that can be modified to attach biological species via chemical interactions (Tartaj et al. 2005).

For example, in the medicine field, drugs' guided transport to a specific site has been studied by the application of an external magnetic field, and this has been achieved with a minimum amount of magnetic particles obtaining that magnetic drugs are safe and effective (Reddy et al. 2012). The transport guided of biologically active substances to a specific organ allows creating an optimal therapeutic concentration of the drug in the desired part of the organism while maintaining the injection total dose at low levels (Kuznetsov et al. 1999; Koneracká et al. 2002). The use of biocompatible magnetic particle as carrying drugs seems to be a promising technique (Lübbe et al. 1999). The superparamagnetic properties of fine magnetic particles have great importance from a practical point of view because it means that these magnetic particles can be located in a convenient position, transported to specific places, and controlled in desirable parts of organs or blood vessels with the assistance of an external magnetic field (Koneracká et al. 2002).

Some of the advantages of these magnetic materials in this area are (1) the size of the particle because of tolerated small size in order to improve the tissular diffusion, allow lower sedimentation rates, and obtain high effective surface areas. (2) The superficial characteristics allow the particles to be easily functionalized and encapsulated with various compounds (biomolecules, inorganic and organic materials, polymers, surfactants). Consequently, the particles are more resistant to

degradation, and their biocompatibility and stability are increased. (3) The good magnetic response makes possible that the concentration of the nanomagnets decreases in the blood and therefore decreases the collateral effects (Reddy et al. 2012; Wu et al. 2015).

The magnetic separation is a technological advancement recently developed and used in the bioseparation area (Marszałł 2011). For example, magnetic particles can be used for immobilization of molecules via binding to form a magnetic biocatalyst that can be separated from the solution by an external magnetic field gradient. Recently, this magnetic property of the particles allows using in the immobilization of proteins, peptides, and enzymes (Bagheri et al. 2016; Gao et al. 2016), microorganism detection (Shi et al. 2014; Du et al. 2016; Yin et al. 2016), bioseparation (Paulus et al. 2015; Gu et al. 2016), immunoassays (Ahn et al. 2016; Vidal et al. 2016), pathogen detection (Brandão et al. 2015; Chen et al. 2015), controlled release drugs (Hyun 2015; Müller et al. 2017), biosensors (Xu and Wang 2012; Jamshaid et al. 2016), cellular classification (Thornhill et al. 1994; Carinelli et al. 2015), adsorption and purification of proteins (Mirahmadi-Zare et al. 2016), diagnostic magnetic resonance imaging (MRI) (Valdora et al. 2016), magnetic fluid hyperthermia therapy (Yang et al. 2015; Farzin et al. 2017), and separation of nucleic acid (Sun et al. 2014; Ali et al. 2016), among others.

On the other hand, in separation processes (in vitro), magnetic particles must be stable units composed of a high concentration of superparamagnetic nanoparticles (Medeiros et al. 2011). The main difficulty in the synthesis of these ultrafine particles is to control the size of the particles on a nanometric scale. This difficulty is the result of the high superficial energy of these systems. The interface tension acts as force guides for the spontaneous reduction of the superficial area by growth during the initial precipitation step and during aging (Sugimoto 1987). Therefore, the search for easy and flexible routes to synthesize and to produce magnetic iron-oxide nanoparticles with the acceptable size distribution, with desired size, and with high dispersibility, without having particle aggregate and low reactivity with the air, is of extreme importance to understand the potentials that are these materials in biomedicine and biotechnology (Tartaj et al. 2005).

5.2 Synthesis of Magnetic Iron-Oxide Nanoparticles (IONPs)

The synthetic methods used to synthesize magnetic IONPs are based on aqueous and nonaqueous routes on coprecipitation (Wu et al. 2008), thermal decomposition (Sun and Zeng 2002), hydrothermal and solvothermal syntheses (Wu et al. 2008), sol-gel synthesis (Dong and Zhu 2002), microemulsion (López Pérez et al. 1997), ultrasound irradiation (Ali et al. 2016), and biological synthesis (Zhu and Chen 2014) approaches using microorganisms.

The actual challenge in the area is synthesized to lead and improve its magnetic properties while keeping their small size, which is complex due to the colloidal nature of IONPs. A high biocompatibility and stability are also required to extend
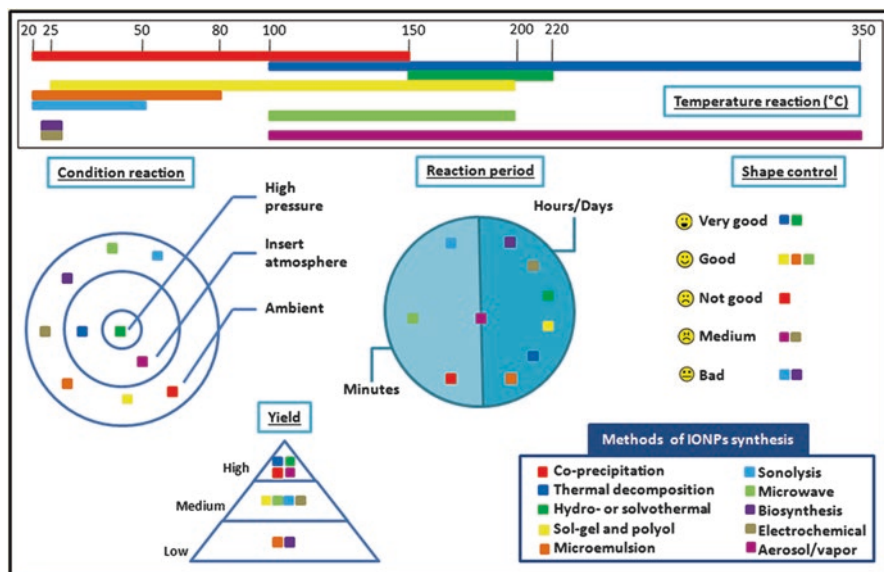
Fig. 5.1 Summary comparison of the synthetic methods for the production of IONPs

the possibility of its applications. Figure 5.1 summarizes a comparison of different reaction characteristics between the main methodologies used in the synthesis of magnetic IONPs according to Wu et al. (2015).

5.2.1 Coprecipitation

The coprecipitation is the simplest and most conventional method and consists of mixing ferric and ferrous ions in a 2:1 molar ratio (Fe^{3+}/Fe^{2+}) resulting in magnetite (Fe_3O_4) nucleus growth at very basic solutions (pH >11) at room or elevated temperature, as the reaction mechanism below:

$$Fe^{2+} + 2Fe^{3+} + 8OH^- \leftrightarrow Fe(OH)_2 + 2Fe(OH)_3 \rightarrow Fe_3O_4 \downarrow + 4H_2O$$
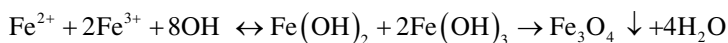
Magnetite (Fe_3O_4) may also be transformed into maghemite (γ-Fe_2O_3) depending on reaction conditions. Massart (1981) described for the first time the method for peptizing magnetite both in alkaline and acidic media. Coprecipitation method has been used to nanoparticle (NP) production, generally associated with different techniques to making magnetic Fe_3O_4 NPs, and, as these particles generated by this method present a wide size distribution, a secondary size selection sometimes is required (Wu et al. 2008).

5.2.2   High-Temperature Thermal Decomposition

The nonaqueous thermal decomposition has been adopted to try to control the particle size and distribution of IONPs formed. The IONPs obtained from high-temperature thermal decomposition display superior properties since they present narrow size distribution and high crystallinity in comparison to coprecipitation, where the particles obtained exhibit low crystallinity once the reactions are carried out at room temperature (Sun and Zeng 2002).

Thermal decomposition approaches include (a) hot-injection method (Tian et al. 2011), where the precursors of IONPs are injected into a hot reaction mixture, and (b) conventional method (Wu et al. 2015), where a reaction mixture is prepared at room temperature and then heated in a closed or open reaction vessel. Both methods are based on the decomposition of different ferric sources as described in Table 5.1.

Organic molecules are also used as reaction stabilizers to obtain monodisperse IONPs. Compounds as oleic acid or ether derivatives can affect the nucleation process decreasing the time spent to growing nanocrystals growth time, favoring the formation of small spherical IONPs (≤30 nm) (Demortiere et al. 2011). The use of specific solvents could contribute for the preparation of strongly faceted iron-oxide nanocrystals with nanocube or octahedron structures (Shavel and Liz-Marzan 2009).

5.2.3   Hydrothermal and Solvothermal Synthesis

Many techniques of crystallization using high-temperature solution (130–250 °C) under high vapor pressure (0.3–4.0 MPa) have been described. The hydrothermal method allows a crystal growth through different crystalline phases resulting in IONPs with controlled size and shape (Sun et al. 2009; Gao et al. 2010; Xu and Zhu 2011).

Table 5.1 Common ferric salts used in high-temperature thermal decomposition reactions

Ferric salts	Temperature requirement (K)	Reference
$Fe(CO)_5$	300	Woo et al. (2004)
$Fe_3(CO)_{12}$	100	Maity et al. (2009)
Fe(acetylacetonate)$_3$	200	Wang et al. (2012)
Fe(N-nitrosophenylhydroxylamine)$_3$	300	Rockenberger et al. (1999)
$Fe_4[Fe(CN)_6 14H_2O]$ (Prussian blue)	300–600	Hu et al. (2012)
$[Fe(CON_2H_4)_6](NO_3)_3$ (Fe-urea)	470	Asuha et al. (2009)
$Fe(C_5H_5)_2$ (Ferrocene)	770–970	Amara and Margel (2011)
$C_{54}H_{99}FeO_6$ (iron oleate)	650	Bronstein et al. (2007)
$FeCl_3$	650	Park et al. (2004)

The synthesis for γ-Fe$_2$O$_3$ involves a controlled oxidation of Fe$_3$O$_4$ and direct mineralization of Fe^{3+} ions and ensures a better crystallinity of single crystal particles of IONPs (α-Fe$_2$O$_3$, γ-Fe$_2$O$_3$, and Fe$_3$O$_4$) (Daou et al. 2006). In the hydrothermal (aqueous) and solvothermal (nonaqueous) processes, Fe^{3+} is used as the iron source and acetate, and urea and sodium citrate are mixed in ethylene glycol, resulting in a homogeneous dispersion which is transferred to a Teflon-lined stainless steel autoclave and sealed to heat at about 200 °C for 8–24 h (Hu et al. 2009; Lin et al. 2012).

The solvothermal method (Walton 2002) is used to synthesize IONPs containing ionic conductivity, magnetism, giant magnetoresistance, low thermal expansion, and ferroelectricity, properties that make it advantageous in comparison to the traditional ceramic synthetic routes.

5.2.4 Sol-Gel Method

The sol-gel method uses a colloidal solution as a stable dispersion precursor for an agglomeration of colloidal or sub-colloidal particles to form the IONPs through at least a two-step phase: Fe(OH)$_3$→β-FeOOH→γ-Fe$_2$O$_3$. In sol systems, these particles interact by van der Waals forces or hydrogen bonds forming linking polymer chains. In gel systems, interactions are of a covalent nature collaborates to an irreversible process (Qi et al. 2011; Lemine et al. 2012).

The precursors of hydrolysis and polycondensation reactions include iron alkoxides and iron salts, and the reaction is performed at room temperature following by heating to obtain the IONPs in a final crystalline state (Dong and Zhu 2002; Pandey and Mishra 2011).

5.2.5 Polyol Method

The polyol method consists of an inverse sol-gel method, since the sol-gel uses an oxidation and polyol uses a reduction reaction. In this method, polyols act as solvents and reducing agents, as well as stabilizers, controlling particle growth and preventing interparticle aggregation (Lemine et al. 2012). In polyol synthesis, the iron precursor compound is stirred in suspension and heated to a given temperature of the boiling point of the polyol, generating different IONP sizes according to polyol nature (Caruntu et al. 2007; Shen et al. 2009).

As the surface of IONPs produced by both methods contains many hydrophilic ligands, the nanoparticles can be easily dispersed in aqueous solution and other polar solvents (Fig. 5.2). These IONPs present also a higher crystallinity and saturation magnetization obtained under high reaction temperature (Wu et al. 2015).
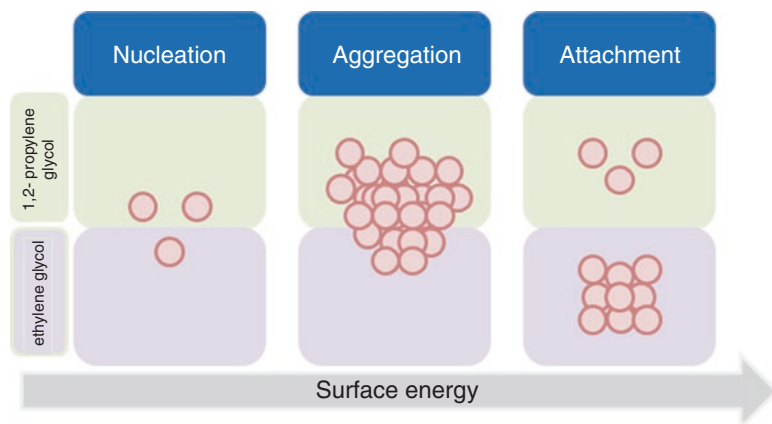
Fig. 5.2 Synthesis of iron-oxide NPs using two different polyols (Adapted from Dhand et al. 2015)

5.3 Microemulsion

In the microemulsion method, a monolayer of surfactant molecules forms an interface between the oil and water, with the hydrophobic tails from surfactant molecules dissolved in the oil phase and the hydrophilic head groups in the aqueous phase, or vice versa, at room temperature. The aggregates formed are called as reverse micelles, which can be formed in the presence or absence of water (López Pérez et al. 1997).

The aqueous phase may contain metal salts and/or other ingredients, and the hydrophobic phase can be a complex mixture of different hydrocarbons and olefins. The proportion of these components and the hydrophilic-lipophilic balance value of the surfactant used may result in the formation of IONPs in different systems as oil-in-water (O/W), water-in-oil (W/O), bicontinuous, and supercritical CO_2 microemulsions (Malik et al. 2012).

5.4 Sonolysis

The sonolysis (sonochemical or ultrasound irradiation) method uses high-intensity ultrasound for the production of IONP structures based on bubble/cavity formation and oscillation, growing to a certain size. In this method, the IONPs are synthesized by the sonication of an aqueous Fe^{3+} or Fe^{2+} salt solution combined with different polymers under room temperature. Another advantage of this method is the possibility of the use of volatile organometallic precursors (Hee Kim et al. 2005; Laurent et al. 2008). Sonolysis has been used also in the synthesis of superparamagnetic iron-oxide nanoparticles (SPIONs) having high magnetization and crystallinity (Mahmoudi et al. 2011; Yoffe et al. 2013).

5.5 Microwave-Assisted Synthesis

The microwave-assisted synthesis is based on the intense internal heating of the molecules under microwave radiation excitation, caused by the strong agitation in phase with the electrical field excitation. This method has been utilized since the late 1980s in the preparation of organometallics and can reduce the processing time and energy cost. The method has been used to prepare magnetic IONPs increasing yields and reproducibility (Hu et al. 2007; Ai et al. 2010; Qiu et al. 2011; Wu et al. 2011; Zhu and Chen 2014).

This method has been successfully employed in the improvement of IONPs applied in hyperthermia therapy as a direct or adjunct treatment for cancer (Blanco-Andujar et al. 2015). In this study, the authors reported the effect of the synthesis conditions on the properties of IONPs obtained by a coprecipitation method in a microwave reactor and also the beneficial effects of the microwave route with regard to the citric acid coatings that were produced.

Preparation of ferrite magnetic nanoparticles of different particle sizes by controlling the reaction temperature using microwave-assisted synthesis was reported with a temperature variation between 45 and 85 °C. These IONPs exhibited superparamagnetic behavior at room temperature, and their size could be varied by controlling the reaction temperature inside a microwave reactor (Kalyani et al. 2015).

5.6 Biosynthesis

Biosynthesis of IONPs is based on reduction and oxidation reactions catalyzed by microbial enzymes or plant phytochemicals. In this method, the special ability of Gram-negative magnetotactic bacteria in biomineralize magnetosomes is exploited in the obtainment of IONPs with uncontrolled shapes (Yan et al. 2012). The magnetosomes consist of intracellular crystals with high levels of purity and crystallinity of magnetic iron mineral, such as magnetite (Fe_3O_4), which can oxidize into maghemite (γ-Fe_2O_3), or greigite (Fe_3S_4) (Alphandéry 2014).

The magnetosomes present a great advantage in biomedical applications once the biomembrane surrounding the crystals is composed of lipids and proteins, and these functional groups make them suitable for use in living organisms (Prabhau and Kowshik 2016).

It is known that the key functions of magnetosome biogenesis are encoded by about 30 genes and, recently, a non-magnetotactic bacterium was capable of expressing these genes and encoding the magnetosome biogenesis pathway (Uebe and Schuler 2016).

Due to its ferrimagnetism propriety, bacterial magnetite magnetosomes have been used in the immobilization of bioactive substances such as glucose oxidase and uricase enzymes (Matsunaga and Kamiya 1987), antibodies for fluoroimmunoassays (Bazylinski and Schübbe 2007), and immunoassays (Tang et al. 2012).

5.7   Electrochemical

The electrochemical method generates IONPs with high purity and controlled particle size by adjusting the current or the potential applied to the reaction system. In a galvanostatic synthesis, the cell potential deviates by decreasing the reactant activity, and the reaction is suitable to supply a pure single-phase product by chosen potential. On the other hand, in a potentiostatic synthesis, a linear increasing of the cell potential from an initial to a final value if the reaction occurs in an intermediate value first carries out a linear voltammetry (Ramimoghadam et al. 2014).

In this method, IONPs are synthesized by an anodic polarization of iron in the transpassive range of the potential generating mainly maghemite (γ-Fe_2O_3) with a certain addition of magnetite (Fe_3O_4) in neutral pH (~7) (Starowicz et al. 2011; Ramimoghadam et al. 2014). In comparison to other abiotic methods as thermal decomposition, the electrochemical method produced the largest iron oxide in terms of mean particle size (Jung et al. 2007). IONPs have been synthesized within the pores of mesoporous silica (MS) microspheres by an electrochemical method to produce particles with a diameter of 20 nm inside the pore of MS spheres (Liberman et al. 2014).

5.8   Flow Injection Synthesis

The flow injection synthesis (FIS) is a modified coprecipitation method based on flow injection where different precursors can be added by pumping with a controllable flow rate in a capillary reactor under laminar flow. The advantage is the high reproducibility and high mixing homogeneity in a continuous synthesis reaction (Mohapatra and Anand 2010; Ramimoghadam et al. 2014).

A novel technique based on a flow injection was developed using continuous or segmented mixing of reagents under laminar flow regime in a capillary reactor. The obtained IONPs had a narrow size distribution in the range 2–7 nm. It was observed that the variation of reagent concentrations and the flow rates allowed the manipulation of the particle size and narrow down the particle size distribution without decreasing the quality of the particles (Salazar-Alvarez et al. 2006).

5.9   Aerosol/Vapor

The aerosol method consists of using of spray and laser pyrolysis techniques for the continuously controlled production of IONPs. In spray pyrolysis, ultrafine particles are aggregated into larger particles and are obtained from evaporation of ferric salts, drying, and pyrolysis reaction of liquid drops (a reducing agent in organic solvent) inside a high-temperature atmosphere. In laser pyrolysis, ultrafine

particles are less aggregated and are obtained from a heating a flowing mixture of gasses with a continuous wave CO_2 laser, which initiates and sustains a chemical reaction (Wu et al. 2008, 2015).

5.10 Pharmaceutical Application of Iron-Oxide Nanoparticles (IONPs)

The main disadvantage of most chemotherapeutic agents is its side effects since these are non-specific compounds. For example, most of the anticancer drugs have characteristics such as hydrophobicity, low water solubility, high clearance, short residence time, and some systemic side effects (Akash and Rehman 2015).

As a way to bypass these negative effects, mainly avoid side effects, the use of magnetic iron-oxide nanoparticles (IONPs) as carriers to target-specific drug delivery has been studied. Exploring the attraction of IONP carriers to an external magnetic field could increase delivery of a drug in a specific site. Such particles can be also used to form complexes with other materials. Besides, those systems formed by magnetic nanoparticles have also been evaluated to be used as theranostic, that is, materials that combine therapeutic and diagnostic functions in a nanostructured complex (Zhou et al. 2016).

In general, the use of target-specific drug delivery involves binding of a drug to biocompatible IONP carrier, injection of magnetic target carries (MTC) as a colloidal suspension, application of magnetic field gradient to MTC be direct to the specific site, and release of drug from MTC (Sun et al. 2008).

Magnetic delivery of drugs or magnetic drug targeting (MDT) is a technique that adds drugs in nano-/micro-magnetic particles and then applies an external magnetic field to direct and concentrate these particles in disease sites such as solid tumors, infection regions, or blood clots. Magnetic drug targeting allows its dosage to be increased without side effects in healthy tissues (Do et al. 2015).

Molecular transport employing nanoparticles has been used as a strategy to improve the drug delivery and reduce its toxicity in different areas including cardiology, hemostasis, ophthalmology, and oncology. Magnetic nanoparticles have been developed because of their ability to respond to magnetic fields, including magnetic hyperthermia, their controllable movements, and their utilization as contrast agents in magnetic resonance imaging (Bhandari et al. 2016; Do et al. 2016; Zhou et al. 2016).

As reported by Bixner and Reimhult (2016), combining magnetic nanoparticles with the liposome drug delivery technology could be a reasonable pharmaceutical formulation technology alternative. Among the main advantages, one might point out hydrolytic degradation in nontoxic ions, high compatibility with in vivo applications, and the low susceptibility of tissue to magnetic fields, favoring their use to direct the drug delivery and in diagnostic bioimaging techniques (Liu et al. 2013; Amjad et al. 2015).

There are many types of target-specific drug delivery employing IONPs, most of them with patents disclosed, as reported by Daniel-da-Silva et al. (2013). Here, some examples of these systems are presented. Tehrani et al. (2014) related the use of an electromagnetic system, composed by six electromagnets powered by currents, for directing magnetic nanoparticles in blood vessels, which presented reduction of cost and lower power consumption as advantages.

The use of IONPs also has been studied to deliver diclofenac, a drug used for the treatment of inflammatory diseases. According to Agotegaray et al. (2014), chitosan-linked magnetic nanocarriers have been studied to target diclofenac delivery, with a satisfactory efficiency of drug loading in vitro assays. The authors affirmed that system would be suitable for in vivo assays. Posteriorly, Agotegaray et al. (2016) evaluated the effects of these magnetic IONPs on rat aortic endothelial cells. Results demonstrated that even after different doses (1, 10, and 100 μg/ml), endothelial cell metabolism was not affected by IONPs and these nanoparticles neither induced cytotoxicity in the cells nor accumulated in the organs. According to the authors, chitosan-linked magnetic IONPs could be a successful alternative to personalized treatments with site-specific drug delivery.

Georgiadou et al. (2016) prepared $CoFe_2O_4$ IONPs as carriers for the naproxen (NAP), a nonsteroidal anti-inflammatory drug, and its biological behavior was evaluated in vitro in rat serum and in vivo in mice. The authors observed that the use of magnetic IONPs-NAP carriers avoided the undesirable drug release and their accumulation at the inflammation site, possibly because of the increased vascular permeability of the inflamed muscle.

Hybrid beads composed of magnetic nanoparticles and alginate (Alg-IONPs) were synthesized and evaluated as a carrier for dopamine release, in the absence and the presence of an external magnetic field. The results suggested that Alg-IONP beads presented potential utility for loading of dopamine and its controlled release in the presence of external magnetic field (Kondaveeti et al. 2016).

Stocke et al. (2015) reported the use of a spray drying formulated with magnetic nanocomposite microparticles (MnMs) composed by IONPs and D-mannitol. According to the authors, these materials presented moderate cytotoxicity in vitro studies on a human lung cell line and have potential applications for thermal treatment of the lungs through targeted pulmonary inhalation aerosol delivery of IONPs.

The combination of magnetic IONPs (Fe_3O_4) with amino acids (L-lysine and L-arginine) to the construction of fluorescent magnetic nanoparticles was also reported that could be biocompatible and nontoxic to be used in biological systems (Ebrahiminezhad et al. 2013).

There are many works related to the use of magnetic IONPs for the treatment of diseases of central nervous system (CNS) and cancer. Do et al. (2016) reported that magnetic nanoparticles (MNPs) could be directed by external magnetic forces to cross the blood-brain barrier and delivery drugs to a disease region.

Akash and Rehman (2015) reported the use of polymeric-based targeted particulate carrier system, which has been showed efficient in delivering anticancer encapsulated drug directly at the desired action site avoiding interaction of encapsulated

drug to normal cells. According to the authors, the use of pluronic F127 (PF127) conjugated with MNPs could result in increased stability of incorporated hydrophobic drugs with higher cytotoxicity in vitro, improvement of cell assimilation of anticancer drugs, and higher specific distribution with minimum toxicity.

Montha et al. (2016) described that poly-lactide-co-glycolic acid-coated chitosan stabilized (Mn, Zn) ferrite nanoparticles could be used as an efficient carrier of the doxorubicin (anticancer drug) because the carrier presented biological activity and pH-responsive controlled release, i.e., low pH around the tumor (pH 4.0) favored drug release.

Chen et al. (2016) studied a cis-diamminedichloridoplatinum(II) (CDDP), also known as cisplatin, loaded magnetic nanoparticle system as an intelligent drug delivery system that target malignant tumors of the head and neck, particularly nasopharyngeal cancer. This system showed stable and exhibited magnetic responsiveness, which released CDDP in a low pH environment.

Farjadian et al. (2016) evaluated the production of hydroxyl-modified magnetite as a nanocarrier for methotrexate conjugation (an anticancer drug). The in vitro cell assays in the presence of free methotrexate and conjugated form showed an excellent anticancer effect of magnetic IONPs when compared with the soluble drug.

Another anticancer chemotherapy medicine, docetaxel, had its targeted delivery evaluated employing magnetic IONPs prepared with poly-N-5-acrylamido isophthalic acid grafted on to Fe_3O_4 magnetic nanoparticles and conjugated with β-cyclodextrin and tumor-targeting folic acid to increase the site-specific intracellular delivery (Tarasi et al. 2016). The effect of magnetic IONPs on the cell viability was evaluated for the human embryonic kidney normal cell line and in different cancerous cell lines. According to authors, the new magnetically nano-drug delivery system did not show any apparent cytotoxic effect and besides reduced the growth of cancerous cell lines.

Tariq et al. (2016) studied the effect of surface decoration on pharmacokinetic and pharmacodynamic profile of epirubicin (EPI), an anthracycline drug used for chemotherapy, which elicits poor oral bioavailability. EPI-loaded poly-lactide-co-glycolic acid nanoparticles (PLGA-NPs) were prepared, and their superficies were decorated with polyethylene glycol (EPI-PNPs) and mannosamine (EPI-MNPs). Cytotoxicity studies were performed against human breast adenocarcinoma cell lines. The results showed that epirubicin linked to the nanocarriers had superior in vitro and in vivo activities than free epirubicin solution. Besides, EPI-MNPs showed better pharmacokinetic and pharmacodynamic profile when compared with EPI-PNPs.

Kaushik et al. (2016) explored a noninvasive magnetically guided central nervous system (CNS) delivery of magnetoelectric nanocarriers (MENCs) for on-demand controlled release of anti-HIV drugs as a potential therapy against NeuroAIDS (a neurodegenerative disorder), using in vitro model and in vivo assays (adult mice). The results demonstrated that delivered MENCs were uniformly distributed inside the brain and were nontoxic to the brain and other major organs, such as the kidney, lung, liver, and spleen, and did not affect hepatic, kidney, and neurobehavioral functioning. The authors considered blood-brain barrier (BBB)

delivery method as noninvasive and completely safe for in vivo application and the nanocarriers as potential to deliver therapeutic agents across the BBB to treat CNS diseases such as Alzheimer's, brain tumors, and NeuroAIDS.

5.11 Biomedical Application

The development of magnetic nanoparticles (MNPs) has opened many opportunities for potential biomedical applications. The main reason MNPs are increasingly being tested for such applications is their size itself: MNPs are smaller than cells, but their size is comparable to those of viruses, proteins, or genes. Consequently, many potential applications are related to considerably localized action in biological systems (e.g., within cells). Additionally, their magnetic properties provide the possibility of manipulation by an external field, improving the property of locally interacting with biological systems and reducing side effects, caused by unintentional interaction with other biological entities (Nikiforov and Filinova 2009).

Reported biomedical applications of MNPs include its usage as alternative contrast agents in magnetic resonance imaging (MRI), due to their low toxicity, better colloidal stability, and magnetic properties. Other properties of MNPs, such as the possibility of functionalization, surface modification, and the potential use of heat sources, provide other applications.

For biomedical applications, additional procedures for the preparation of MNPs are required to increase their biocompatibility. Due to the importance of such procedures, this section begins with general considerations about biocompatibility of MNPs. Afterward, each discussion of the biomedical and pharmaceutical application of MNPs is started by a brief description of the basic principles of each application, followed by a discussion of recently published papers on the subject.

5.12 Biocompatibility of MNPs and Its Relation to Surface Modification

The concept of biocompatibility is more commonly related to medical devices, which are intended to remain inside the body for a long time (e.g., implants, pacemakers, etc.). Even though MNPs are not intended for such applications a priori, their application in any treatment or diagnosis procedure must minimize or eliminate possible side effects while performing the intended function; thus they must present biocompatibility. MNP biocompatibility is related to the different paths they can be eliminated from the body, which is in turn related to their physical and chemical properties. In order to interact with its target, MNPs should undergo a coating process, yielding a core-shell structure for MNPs. Different coating layers result in different MNPs for different applications. As expected, MNP biocompatibility is related to their physical and chemical properties, which are related to their synthetic route.

In addition to the general requirements for an effective performance of MNPs on applications (as aforementioned in this chapter), MNPs should present additional properties for biomedical applications, which can be attained by the choice of a suitable coating. Different coating materials for MNPs are compared and contrasted by Gupta et al. (2007) and by Gun'ko and Brougham (2009). Common considerations are (a) preventing the degradation of MNPs or particle agglomeration in physiological conditions, such as intravenous media; (b) reducing MNP toxicity, even though non-coated iron-oxide MNPs present IC50 (19.1 mm (red), 4.8 mm (yellow), 3 mm (green) CdTe quantum dots) suitable for biomedical applications (Lewinski et al. 2008); (c) the necessity (or not) of opsonization of MNPs, i.e., adsorption of serum proteins onto the nanoparticles, which is the first step required by the major defense system (reticuloendothelial system, RES) to perform phagocytosis; and (d) increasing specificity to certain cells by attaching, e.g., antibodies, hormones, etc., to its surface (Gupta and Gupta 2005; Hola et al. 2015).

5.13   Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is an in vivo imaging procedure, which provides detailed images of soft tissues. One of its main advantages over other imaging diagnostic methods (such as X-ray or ultrasound techniques) is that the contrast between different tissues is a consequence of the physicochemical environment of water and also due to local biochemical and metabolic activity in each tissue, being thus much more sensitive to tissue composition. Consequently, MRI allows a more detailed tissue analysis. Another important advantage of MRI is that both spatial and temporal analyses might be carried out, hence being capable of providing dynamic imaging (Gun'ko and Brougham 2009; Qiao et al. 2009).

The physical basis for MRI is the reduction of magnetic relaxation times by MRI contrast agents: hydrogen protons (mainly those from water) tend to align themselves with an external magnetic field. When another radio-frequency pulse sequence is applied to the external magnetic field, a magnetic moment is created onto particles. When the pulse sequence ends, the protons tend to align themselves again to the previous magnetic field. This process of protons returning to the original position is known as magnetic relaxation. Relaxation occurs by either longitudinal (T1-recovery time) or transversal (T2-decay time) relaxation. Reduction in T1 relaxation times is observed for positive contrasts, whereas reduction in T2 relaxation times is observed for negative contrasts. More details of fundamental aspects of magnetic relaxation are found elsewhere (Aharoni 1992).

The most commonly used MRI contrast agents are based on gadolinium chelates, such as Gd-DTPA (gadolinium-diethylenetriaminepentaacetic acid). However, MNPs are more efficient in promoting relaxation (Kim 2009), by reducing relaxation times in water even at nanomolar concentrations. Additionally, the possibility of physical and chemical modification of MNPs enables the customization of their properties, according to the applications (Gun'ko and Brougham 2009).

Iron oxide-based MNPs for MRI applications are classified according to their hydrodynamic size. Particles with hydrodynamic size larger than 40 nm are quickly opsonized and uptaken by the reticuloendothelial system (as aforementioned in Sect. 4.1) and are then processed, e.g., in the liver or spleen, in order to eliminate MNPs from the body. Such materials are classified as small particles of iron oxide (SPIOs) and are suitable for liver MRI applications. On the other hand, particles smaller than 40 nm (typically smaller than 10 nm, known as ultrasmall particles of iron oxide – USPIOs) are more difficult to opsonize; hence USPIOs have longer blood circulation times and have the tendency of accumulation within lymph nodes. Such property renders suitability for the detection of lymph nodes metastases by MRI (Qiao et al. 2009).

Novel applications of MNPs for tumor imaging commonly involve the addition of antibodies to MNP surfaces, increasing their specificity to the affected region. For instance, Tse et al. (2015) evaluated the potential MNPs conjugated with an antibody to an extracellular epitope of prostate-specific membrane antigen. In comparison to MNPs without the attached antibody, preclinical imaging of prostate cancer was improved with MNPs coated with antibodies. The prepared MNPs were proven to be nontoxic to prostate cells.

An MRI contrast agent for unstable atherosclerotic plaques was developed by Meier et al. (2015). The researchers developed magnetoliposomes linked to an antibody, which targets activated receptors of platelets. The specific binding to such receptors was confirmed ex vivo and presents an opportunity for further development of a contrast agent for early detection of unstable atherosclerotic plaques.

There has been a tendency of including both antibodies and specific drugs onto MNP coatings, in the context of the theranostics, a new research area which deals with simultaneous therapy and diagnosis of tumors. Consequently, both drug delivery and MR imaging might be carried out simultaneously, allowing an early detection and treatment of degenerative diseases.

5.14   Magnetic Fluid Hyperthermia

In the context of this chapter, hyperthermia or thermotherapy is a treatment of malignant diseases based on the increase of the temperature. Hyperthermia is a medical procedure recognized by the US National Cancer Institute for the treatment of tumors, despite being still under study in clinical trials. In general, such clinical studies are carried out in combination with other forms of cancer therapy, as a complementary treatment to traditional chemotherapy and radiotherapy (Wust et al. 2002).

Magnetic fluid hyperthermia (MFH) consists of the use of MNPs suspended in a biocompatible fluid for local temperature increase. Such temperature increase is based on applying external alternating current magnetic field onto magnetic particles (Nikiforov and Filinova 2009). The external magnetic field causes alignment of magnetic spins, thus reducing magnetic entropy. If the magnetic field is

adiabatically removed, magnetic spins tend to their previous random orientation (magnetic relaxation). Hence entropy is generated and temperature is increased (Shull et al. 1992). An alternating magnetic field at frequencies of several hundreds of MHz repeats the cycle of orientation and randomness of magnetic spins and is responsible for the temperature increase on which MFH is based.

Heat is generated locally in MFH treatments by, e.g., implanted RF electrodes, causing concentrated thermal damage on a pathological tissue (e.g., tumor cells). Considering the local effect of MFH, side effects are reduced in comparison to other common treatments such as chemotherapy or radiotherapy (Laurent et al. 2011).

Since the first applications of MFH, many papers on the subject have been published. In fact, the International Journal of Hyperthermia is the official journal of the Society of Thermal Medicine, the European Society for Hyperthermic Oncology, and the Japanese Society for Thermal Medicine. Many articles have been published in the Journal since its first issue in 1985, coping with clinical and biological studies (either in vivo, ex vivo, or in vitro studies), including procedures for production of hyperthermia, modeling analysis, and calibration and control of hyperthermia equipment.

Di Corato et al. (2015) combined MFH and photodynamic therapy for the treatment of tumors (human adenocarcinoma cells grown in vitro and epidermoid carcinoma cells grown in vitro or inoculated in mice) by using photoresponsive magnetoliposomes. The photoresponsive magnetoliposomes were synthesized by alkaline coprecipitation of iron salts (magnetic core), followed by a reverse-phase evaporation method, i.e., an addition of the magnetic suspension (MNPs suspended in buffer) into an emulsion, sonication, and evaporation of organic solvents. Each treatment – either photodynamic therapy or MFH – yielded similar tumor cell death rates in vitro and in vivo when performed separately, whereas the combined MFH-photodynamic therapy was able to completely eradicate the tumor.

A slightly different procedure for the synthesis of MNPs was carried out by Munoz de Escalona et al. (2016). Solid lipid nanoparticles were formulated by the authors by synthesizing magnetic nanoparticles embedded within a lipidic (glyceryl trimyristate) solid matrix. Human HT29 colon adenocarcinoma cells were submitted to MFH in vitro, and the particles presented promising hyperthermia characteristics.

5.15   Conclusion

There are numerous applications for magnetics iron-oxide nanoparticles (IONPs) in pharmaceutical and biomedical areas. The development of new methodologies for the improvement of the synthesis techniques of these IONPs will allow progressing in their utilization. Magnetic nanoparticles allow functionalization with various biomolecules without losing their magnetic properties or change in the original structure, and it is possible to prevent the formation of aggregates and biodegradation. These features are useful for their application, for example, in magnetic resonance

contrast media and therapeutic agents in cancer and neurodegenerative disorder treatments, magnetic fluid hyperthermia, and drug and gene delivery, without side effects. The field of iron-oxide nanoparticles has grown rapidly. Many types of researchers have realized, and the results demonstrated that monitoring of the medication could be possible by magnetic resonance imaging and finally, drug delivery in the specific area without affecting other tissue and/or organ, reducing dosages and increasing rapid action.

References

Abolfazl A, Mohamad S, Soodabeh D. Magnetic nanoparticles: preparation, physical properties, and applications in biomedicine. Nanoscale Res Lett. 2012;7:144–1.

Agotegaray M, Palma S, Lassalle V. Novel chitosan coated magnetic nanocarriers for the targeted Diclofenac delivery. J Nanosci Nanotechnol. 2014;14:3343–7.

Agotegaray M, Campelo A, Zysler R, Gumilar F, Bras C, Minetti A, Massheimer V, Lassalle V. Influence of chitosan coating on magnetic nanoparticles in endothelial cells and acute tissue biodistribution. J Biomater Sci Polym Ed. 2016;27:1069–85.

Aharoni A. Magnetic properties of fine particles, Chap. 1. Relaxation processes. Amsterdam: Elsevier; 1992.

Ahn S, Cho J, Kim SI, Yim J, Lee S-G, Kim J-H. Characterization of circulating antibodies with affinity to an epitope used in antibody-conjugated magnetic immunoassays from a case of falsely elevated cyclosporine A. Clin Chim Acta. 2016;458:35–9.

Ai Z, Deng K, Wan Q, Zhang L, Lee S. Facile microwave-assisted synthesis and magnetic and gas sensing properties of Fe3O4 nanoroses. J Phys Chem C. 2010;114:6237–42.

Akash MS, Rehman K. Recent progress in biomedical applications of Pluronic (PF127): pharmaceutical perspectives. J Control Release. 2015;209:120–38.

Ali ME, Rahman MM, Dhahi TS, Kashif M, Sarkar MS, Basirun WJ, Hamid SBA, Bhargava SK. Reference module in materials science and materials engineering, Chap. 10. Nanostructured materials. Amsterdam: Elsevier; 2016.

Alphandéry E. Applications of magnetosomes synthesized by magnetotactic bacteria in medicine. Front Bioeng Biotechnol. 2014;2:5.

Amara D, Margel S. Solventless thermal decomposition of ferrocene as a new approach for the synthesis of porous superparamagnetic and ferromagnetic composite microspheres of narrow size distribution. J Mater Chem. 2011;21:15764–72.

Amjad MS, Sadiq N, Qureshi H, Fareed G, Sabir S. Nano particles: an emerging tool in biomedicine. Asian Pac J Trop Dis. 2015;5:767–71.

Asuha S, Zhao S, Wu HY, Song L, Tegus O. One step synthesis of maghemite nanoparticles by direct thermal decomposition of Fe–urea complex and their properties. J Alloys Compd. 2009;472:L23–5.

Bagheri H, Ranjbari E, Amiri-Aref M, Hajian A, Ardakani YH, Amidi S. Modified fractal iron oxide magnetic nanostructure: a novel and high performance platform for redox protein immobilization, direct electrochemistry and bioelectrocatalysis application. Biosens Bioelectron. 2016;85:814–21.

Bazylinski DA, Schübbe S. Controlled biomineralization by and applications of magnetotactic bacteria. Adv Appl Microbiol. 2007;62:21–62.

Bhandari R, Gupta P, Dziubla T, Hilt JZ. Single step synthesis, characterization and applications of curcumin functionalized iron oxide magnetic nanoparticles. Mater Sci Eng C Mater Biol Appl. 2016;67:59–64.

Bixner O, Reimhult E. Controlled magnetosomes: embedding of magnetic nanoparticles into membranes of monodisperse lipid vesicles. J Colloid Interface Sci. 2016;466:62–71.

Blanco-Andujar C, Ortega D, Southern P, Pankhurst QA, Thanh NT. High performance multi-core iron oxide nanoparticles for magnetic hyperthermia: microwave synthesis, and the role of core-to-core interactions. Nanoscale. 2015;7:1768–75.

Brandão D, Liébana S, Pividori MI. Multiplexed detection of foodborne pathogens based on magnetic particles. New Biotechnol. 2015;32:511–20.

Bronstein LM, Huang X, Retrum J, Schmucker A, Pink M, Stein BD, Dragnea B. Influence of iron Oleate complex structure on iron oxide nanoparticle formation. Chem Mater. 2007;19:3624–32.

Carinelli S, Martí M, Alegret S, Pividori MI. Biomarker detection of global infectious diseases based on magnetic particles. New Biotechnol. 2015;32:521–32.

Caruntu D, Caruntu G, O'Connor CJ. Magnetic properties of variable-sized Fe 3 O 4 nanoparticles synthesized from non-aqueous homogeneous solutions of polyols. J Phys D Appl Phys. 2007;40:5801.

Chen J, Lin Y, Wang Y, Jia L. Cationic polyelectrolyte functionalized magnetic particles assisted highly sensitive pathogens detection in combination with polymerase chain reaction and capillary electrophoresis. J Chromatogr B. 2015;991:59–67.

Chen SJ, Zhang HZ, Wan LC, Jiang SS, Xu YM, Liu F, Zhang T, Ma D, Xie MQ. Preparation and performance of a pH-sensitive cisplatin-loaded magnetic nanomedicine that targets tumor cells via folate receptor mediation. Mol Med Rep. 2016;13:5059–67.

Curtis A, Wilkinson C. Nantotechniques and approaches in biotechnology. Trends Biotechnol. 2001;19:97–101.

Daniel-da-Silva AL, Carvalho RS, Trindade T. Magnetic hydrogel nanocomposites and composite nanoparticles – a review of recent patented works. Recent Pat Nanotechnol. 2013;7:153–66.

Daou TJ, Pourroy G, Bégin-Colin S, Grenèche JM, Ulhaq-Bouillet C, Legaré P, Bernhardt P, Leuvrey C, Rogez G. Hydrothermal synthesis of monodisperse magnetite nanoparticles. Chem Mater. 2006;18:4399–404.

Demortiere A, Panissod P, Pichon BP, Pourroy G, Guillon D, Donnio B, Begin-Colin S. Size-dependent properties of magnetic iron oxide nanocrystals. Nanoscale. 2011;3:225–32.

Dhand C, Dwivedi N, Loh XJ, Jie Ying AN, Verma NK, Beuerman RW, Lakshminarayanan R, Ramakrishna S. Methods and strategies for the synthesis of diverse nanoparticles and their applications: a comprehensive overview. RSC Adv. 2015;5:105003–37.

Di Corato R, Béalle G, Kolosnjaj-Tabi J, Espinosa A, Clément O, Silva AKA, Ménager C, Wilhelm C. Combining magnetic hyperthermia and photodynamic therapy for tumor ablation with photoresponsive magnetic liposomes. ACS Nano. 2015;9:2904–16.

Do TD, Noh Y, Kim MO, Yoon J. An optimized field function scheme for nanoparticle guidance in magnetic drug targeting systems, IEEE/RSJ International Conference on Intelligent Robots and Systems: Hamburg; 2015.

Do TD, Noh Y, Kim MO, Yoon J. In silico magnetic nanocontainers navigation in blood vessels: a feedback control approach. J Nanosci Nanotechnol. 2016;16:6368–73.

Dong W, Zhu C. Use of ethylene oxide in the sol-gel synthesis of [small alpha]-Fe2O3 nanoparticles from Fe(iii) salts. J Mater Chem. 2002;12:1676–83.

Du J, Zhao Y, Yang Z, Xu C, Lu Y, Pan Y, Shi D, Wang Y. Influence of controlled surface functionalization of magnetic nanocomposites on the detection performance of immunochromatographic test. Sensors Actuators B Chem. 2016;237:817–25.

Ebrahiminezhad A, Ghasemi Y, Rasoul-Amini S, Barar J, Davaran S. Preparation of novel magnetic fluorescent nanoparticles using amino acids. Colloid Surf B. 2013;102:534–9.

Farjadian F, Ghasemi S, Mohammadi-Samani S. Hydroxyl-modified magnetite nanoparticles as novel carrier for delivery of methotrexate. Int J Pharm. 2016;504:110–6.

Farzin A, Fathi M, Emadi R. Multifunctional magnetic nanostructured hardystonite scaffold for hyperthermia, drug delivery and tissue engineering applications. Mater Sci Eng C. 2017;70(1):21–31.

Gao G, Liu X, Shi R, Zhou K, Shi Y, Ma R, Takayama-Muromachi E, Qiu G. Shape-controlled synthesis and magnetic properties of monodisperse Fe3O4 nanocubes. Cryst Growth Des. 2010;10:2888–94.

Gao R, Hao Y, Zhang L, Cui X, Liu D, Zhang M, Tang Y, Zheng Y. A facile method for protein imprinting on directly carboxyl-functionalized magnetic nanoparticles using non-covalent template immobilization strategy. Chem Eng J. 2016;284:139–48.

Georgiadou V, Makris G, Papagiannopoulou D, Vourlias G, Dendrinou-Samara C. Octadecylamine-mediated versatile coating of CoFe2O4 NPs for the sustained release of anti-inflammatory drug naproxen and in vivo target selectivity. ACS Appl Mater Interfaces. 2016;8:9345–60.

Gu J-L, Tong H-F, Lin D-Q. Evaluation of magnetic particles modified with a hydrophobic charge-induction ligand for antibody capture. J Chromatogr A. 2016;1460:61–7.

Gun'ko YK, Brougham DF. Nanotechnologies for the life sciences, Chap. Magnetic nanomaterials. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany. 2009.

Gupta AK, Gupta M. Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. Biomaterials. 2005;26:3995–4021.

Gupta AK, Naregalkar RR, Vaidya VD, Gupta M. Recent advances on surface engineering of magnetic iron oxide nanoparticles and their biomedical applications. Nanomedicine-UK. 2007;2:23–39.

Hee Kim E, Sook Lee H, Kook Kwak B, Kim B-K. Synthesis of ferrofluid with magnetic nanoparticles by sonochemical method for MRI contrast agent. J Magn Magn Mater. 2005;289:328–30.

Hola K, Markova Z, Zoppellaro G, Tucek J, Zboril R. Tailored functionalization of iron oxide nanoparticles for MRI, drug delivery, magnetic separation and immobilization of biosubstances. Biotechnol Adv. 2015;33:1162–76.

Hu X, Yu JC, Gong J, Li Q, Li G. α-Fe2O3 nanorings prepared by a microwave-assisted hydrothermal process and their sensing properties. Adv Mater. 2007;19:2324–9.

Hu P, Yu L, Zuo A, Guo C, Yuan F. Fabrication of monodisperse magnetite hollow spheres. J Phys Chem C. 2009;113:900–6.

Hu M, Jiang J-S, Bu F-X, Cheng X-L, Lin C-C, Zeng Y. Hierarchical magnetic iron (iii) oxides prepared by solid-state thermal decomposition of coordination polymers. RSC Adv. 2012;2:4782–6.

Hyun DC. Magnetically-controlled, pulsatile drug release from poly(ε-caprolactone) (PCL) particles with hollow interiors. Polymer. 2015;74:159–65.

Jamshaid T, Neto ETT, Eissa MM, Zine N, Kunita MH, El-Salhi AE, Elaissari A. Magnetic particles: from preparation to lab-on-a-chip, biosensors, microsystems and microfluidics applications. Trends Anal Chem. 2016;79:344–62.

Jung H, Park H, Kim J, Lee J-H, Hur H-G, Myung NV, Choi H. Preparation of biotic and abiotic iron oxide nanoparticles (IOnPs) and their properties and applications in heterogeneous catalytic oxidation. Environ Sci Technol. 2007;41:4741–7.

Kalyani S, Sangeetha J, Philip J. Microwave assisted synthesis of ferrite nanoparticles: effect of reaction temperature on particle size and magnetic properties. J Nanosci Nanotechnol. 2015;15:5768–74.

Kaushik A, Jayant RD, Nikkhah-Moshaie R, Bhardwaj V, Roy U, Huang Z, Ruiz A, Yndart A, Atluri V, El-Hage N, Khalili K, Nair M. Magnetically guided central nervous system delivery and toxicity evaluation of magneto-electric nanocarriers. Sci Rep. 2016;6:25309.

Kim KY. Nanotechnologies for the life sciences, Chap. Magnetic nanomaterials. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany. 2009.

Kondaveeti S, Cornejo DR, Petri DF. Alginate/magnetite hybrid beads for magnetically stimulated release of dopamine. Colloid Surface B. 2016;138:94–101.

Koneracká M, Kopčanský P, Timko M, Ramchand CN. Direct binding procedure of proteins and enzymes to fine magnetic particles. J Magn Magn Mater. 2002;252:409–11.

Kuznetsov AA, Filippov VI, Kuznetsov OA, Gerlivanov VG, Dobrinsky EK, Malashin SI. New ferro-carbon adsorbents for magnetically guided transport of anti-cancer drugs. J Magn Magn Mater. 1999;194:22–30.

Laurent S, Forge D, Port M, Roch A, Robic C, Vander Elst L, Muller RN. Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. Chem Rev. 2008;108:2064–110.

Laurent S, Dutz S, Häfeli UO, Mahmoudi M. Magnetic fluid hyperthermia: focus on superparamagnetic iron oxide nanoparticles. Adv Colloid Interf. 2011;166:8–23.

Lemine OM, Omri K, Zhang B, El Mir L, Sajieddine M, Alyamani A, Bououdina M. Sol–gel synthesis of 8 nm magnetite (Fe3O4) nanoparticles and their magnetic properties. Superlattice Microst. 2012;52:793–9.

Lewinski N, Colvin V, Drezek R. Cytotoxicity of nanoparticles. Small. 2008;4:26–49.

Liberman A, Mendez N, Trogler WC, Kummel AC. Synthesis and surface functionalization of silica nanoparticles for nanomedicine. Surf Sci Rep. 2014;69:132–58.

Lin X, Ji G, Liu Y, Huang Q, Yang Z, Du Y. Formation mechanism and magnetic properties of hollow Fe3O4 nanospheres synthesized without any surfactant. Cryst Eng Comm. 2012;14:8658–63.

Liu G, Gao J, Ai H, Chen X. Applications and potential toxicity of magnetic iron oxide nanoparticles. Small. 2013;9:1533–45.

López Pérez JA, López Quintela MA, Mira J, Rivas J, Charles SW. Advances in the preparation of magnetic nanoparticles by the microemulsion method. J Phys Chem B. 1997;101:8045–7.

Lübbe AS, Bergemann C, Brock J, McClure DG. Physiological aspects in magnetic drug-targeting. J Magn Magn Mater. 1999;194:149–55.

Mahmoudi M, Sant S, Wang B, Laurent S, Sen T. Superparamagnetic iron oxide nanoparticles (SPIONs): development, surface modification and applications in chemotherapy. Adv Drug Deliv Rev. 2011;63:24–46.

Maity D, Choo S-G, Yi J, Ding J, Xue JM. Synthesis of magnetite nanoparticles via a solvent-free thermal decomposition route. J Magn Magn Mater. 2009;321:1256–9.

Malik MA, Wani MY, Hashim MA. Microemulsion method: a novel route to synthesize organic and inorganic nanomaterials: 1st Nano update. Arab J Chem. 2012;5:397–417.

Marszałł MP. Application of magnetic nanoparticles in pharmaceutical sciences. Pharm Res. 2011;28:480–3.

Martín JI, Nogués J, Liu K, Vicent JL, Schuller IK. Ordered magnetic nanostructures: fabrication and properties. J Magn Magn Mater. 2003;256:449–501.

Massart R. Preparation of aqueous magnetic liquids in alkaline and acidic media. IEEE Trans Magn. 1981;17:1247–8.

Matsunaga T, Kamiya S. Use of magnetic particles isolated from magnetotactic bacteria for enzyme immobilization. Appl Microbiol Biotechnol. 1987;26:328–32.

Medeiros SF, Santos AM, Fessi H, Elaissari A. Stimuli-responsive magnetic particles for biomedical applications. Int J Pharm. 2011;403:139–61.

Meier S, Putz G, Massing U, Hagemeyer CE, von Elverfeldt D, Meissner M, Ardipradja K, Barnert S, Peter K, Bode C, Schubert R, von zur Muhlen C. Immuno-magnetoliposomes targeting activated platelets as a potentially human-compatible MRI contrast agent for targeting atherothrombosis. Biomaterials. 2015;53:137–48.

Mirahmadi-Zare SZ, Allafchian A, Aboutalebi F, Shojaei P, Khazaie Y, Dormiani K, Lachinani L, Nasr-Esfahani M-H. Super magnetic nanoparticles NiFe2O4, coated with aluminum–nickel oxide sol-gel lattices to safe, sensitive and selective purification of his-tagged proteins. Protein Expr Purif. 2016;121:52–60.

Mohapatra M, Anand S. Synthesis and applications of nano-structured iron oxides/hydroxides – a review. Int J Eng Sci Technol. 2010;2:127–46.

Montha W, Maneeprakorn W, Buatong N, Tang IM, Pon-On W. Synthesis of doxorubicin-PLGA loaded chitosan stabilized (Mn, Zn)Fe2O4 nanoparticles: biological activity and pH-responsive drug release. Mater Sci Eng C Mater Biol Appl. 2016;59:235–40.

Müller R, Zhou M, Dellith A, Liebert T, Heinze T. Meltable magnetic biocomposites for controlled release. J Magn Magn Mater. 2017; 431(1): 289–93.

Munoz de Escalona M, Saez-Fernandez E, Prados JC, Melguizo C, Arias JL. Magnetic solid lipid nanoparticles in hyperthermia against colon cancer. Int J Pharm. 2016;504:11–9.

Nikiforov VN, Filinova EY. Magnetic nanoparticles, Chap. 10. Wiley-VCH Verlag GmbH & Co. KGaA; 2009.

Pandey S, Mishra SB. Sol–gel derived organic–inorganic hybrid materials: synthesis, characterizations and applications. J Sol-Gel Sci Technol. 2011;59:73–94.

Pankhurst QA, Connolly J, Jones SK, Dobson J. Applications of magnetic nanoparticles in biomedicine. J Phys D Appl Phys. 2003;36:R167.

Park J, An K, Hwang Y, Park J-G, Noh H-J, Kim J-Y, Park J-H, Hwang N-M, Hyeon T. Ultra-large-scale syntheses of monodisperse nanocrystals. Nat Mater. 2004;3:891–5.

Paulus A, Till N, Franzreb M. Controlling the partitioning behavior of magnetic micro-particles via hydrophobization with alkylamines: tailored adsorbents for continuous bioseparation. Appl Surf Sci. 2015;332:631–9.

Prabhau NN, Kowshik M. Magnetosomes: the bionanomagnets and its potential use in biomedical applications. J Nanomed Res. 2016;3:00057.

Qi H, Yan B, Lu W, Li C, Yang Y. A non-alkoxide sol-gel method for the preparation of magnetite (Fe3O4) nanoparticles. Curr Nanosci. 2011;7:381–8.

Qiao R, Yang C, Gao M. Superparamagnetic iron oxide nanoparticles: from preparations to in vivo MRI applications. J Mater Chem. 2009;19:6274–93.

Qiu G, Huang H, Genuino H, Opembe N, Stafford L, Dharmarathna S, Suib SL. Microwave-assisted hydrothermal synthesis of nanosized α-Fe2O3 for catalysts and adsorbents. J Phys Chem C. 2011;115:19626–31.

Ramimoghadam D, Bagheri S, Hamid SBA. Progress in electrochemical synthesis of magnetic iron oxide nanoparticles. J Magn Magn Mater. 2014;368:207–29.

Raz M, Moztarzadeh F, Ansari Hamedani A, Ashuri M, Tahriri M. Controlled synthesis, characterization and magnetic properties of magnetite (Fe3O4) nanoparticles without surfactant under N2 gas at room temperature. Key Eng Mater. 2012;493-494:746–51.

Reddy LH, Arias JL, Nicolas J, Couvreur P. Magnetic nanoparticles: design and characterization, toxicity and biocompatibility, pharmaceutical and biomedical applications. Chem Rev. 2012;112:5818–78.

Rockenberger J, Scher EC, Alivisatos AP. A new nonhydrolytic single-precursor approach to surfactant-capped nanocrystals of transition metal oxides. J Am Chem Soc. 1999;121:11595–6.

Salazar-Alvarez G, Muhammed M, Zagorodni AA. Novel flow injection synthesis of iron oxide nanoparticles with narrow size distribution. Chem Eng Sci. 2006;61:4625–33.

Shavel A, Liz-Marzan LM. Shape control of iron oxide nanoparticles. Phys Chem Chem Phys. 2009;11:3762–6.

Shen YF, Tang J, Nie ZH, Wang YD, Ren Y, Zuo L. Preparation and application of magnetic Fe3O4 nanoparticles for wastewater purification. Sep Purif Technol. 2009;68:312–9.

Shi D, Huang J, Chuai Z, Chen D, Zhu X, Wang H, Peng J, Wu H, Huang Q, Fu W. Isothermal and rapid detection of pathogenic microorganisms using a nano-rolling circle amplification-surface plasmon resonance biosensor. Biosens Bioelectron. 2014;62:280–7.

Shull RD, McMichael RD, Swartzendruber LJ, Bennett LH. Magnetic properties of fine particles., Chap. 19. Amsterdam: Elsevier; 1992.

Starowicz M, Starowicz P, Żukrowski J, Przewoźnik J, Lemański A, Kapusta C, Banaś J. Electrochemical synthesis of magnetic iron oxide nanoparticles with controlled size. J Nanopart Res. 2011;13:7167–76.

Stocke NA, Meenach SA, Arnold SM, Mansour HM, Hilt JZ. Formulation and characterization of inhalable magnetic nanocomposite microparticles (MnMs) for targeted pulmonary delivery via spray drying. Int J Pharm. 2015;479:320–8.

Sugimoto T. Preparation of monodispersed colloidal particles. Adv Colloid Interface. 1987;28:65–108.

Sun S, Zeng H. Size-controlled synthesis of magnetite nanoparticles. J Am Chem Soc. 2002;124:8204–5.

Sun C, Lee JSH, Zhang M. Magnetic nanoparticles in MR imaging and drug delivery. Adv Drug Deliv Rev. 2008;60:1252–65.

Sun X, Zheng C, Zhang F, Yang Y, Wu G, Yu A, Guan N. Size-controlled synthesis of magnetite (Fe3O4) nanoparticles coated with glucose and gluconic acid from a single Fe(III) precursor by a sucrose bifunctional hydrothermal method. J Phys Chem C. 2009;113:16002–8.

Sun N, Deng C, Liu Y, Zhao X, Tang Y, Liu R, Xia Q, Yan W, Ge G. Optimization of influencing factors of nucleic acid adsorption onto silica-coated magnetic particles: application to viral nucleic acid extraction from serum. J Chromatogr A. 2014;1325:31–9.

Tang YS, Wang D, Zhou C, Ma W, Zhang YQ, Liu B, Zhang S. Bacterial magnetic particles as a novel and efficient gene vaccine delivery system. Gene Ther. 2012;19:1187–95.

Tarasi R, Khoobi M, Niknejad H, Ramazani A, Ma'mani L, Bahadorikhalili S, Shafiee A. β-cyclodextrin functionalized poly (5-amidoisophthalicacid) grafted Fe3O4 magnetic nanoparticles: a novel biocompatible nanocomposite for targeted docetaxel delivery. J Magn Magn Mater. 2016;417:451–9.

Tariq M, Alam MA, Singh AT, Panda AK, Talegaonkar S. Surface decorated nanoparticles as surrogate carriers for improved transport and absorption of epirubicin across the gastrointestinal tract: pharmacokinetic and pharmacodynamic investigations. Int J Pharm. 2016;501:18–31.

Tartaj P, Morales MDP, Veintemillas-Verdaguer S, González-Carreño T, Serna CJ. The preparation of magnetic nanoparticles for applications in biomedicine. J Phys D Appl Phys. 2003;36:R182.

Tartaj P, Morales MP, González-Carreño T, Veintemillas-Verdaguer S, Serna CJ. Advances in magnetic nanoparticles for biotechnology applications. J Magn Magn Mater. 2005:290–291, Part 1: 28–34.

Tehrani MD, Kim MO, Yoon J. A novel electromagnetic actuation system for magnetic nanoparticle guidance in blood vessels. IEEE Trans Magn. 2014;50:1–12.

Thornhill RH, Grant Burgess J, Sakaguchi T, Matsunaga T. A morphological classification of bacteria containing bullet-shaped magnetic particles. FEMS Microbiol Lett. 1994;115:169–76.

Tian Q, Tao K, Li W, Sun K. Hot-injection approach for two-stage formed hexagonal NaYF4:Yb,Er nanocrystals. J Phys Chem C. 2011;115:22886–92.

Tse BW, Cowin GJ, Soekmadji C, Jovanovic L, Vasireddy RS, Ling MT, Khatri A, Liu T, Thierry B, Russell PJ. PSMA-targeting iron oxide magnetic nanoparticles enhance MRI of preclinical prostate cancer. Nanomedicine-UK. 2015;10:375–86.

Uebe R, Schuler D. Magnetosome biogenesis in magnetotactic bacteria. Nat Rev Microbiol. 2016;14:621–37.

Valdora F, Cutrona G, Matis S, Morabito F, Massucco C, Emionite L, Boccardo S, Basso L, Recchia AG, Salvi S, Rosa F, Gentile M, Ravina M, Pace D, Castronovo A, Cilli M, Truini M, Calabrese M, Neri A, Neumaier CE, Fais F, Baio G, Ferrarini M. A non-invasive approach to monitor chronic lymphocytic leukemia engraftment in a xenograft mouse model using ultra-small superparamagnetic iron oxide-magnetic resonance imaging (USPIO-MRI). Clin Immunol. 2016;172:52–60.

Vidal JC, Bertolín JR, Bonel L, Asturias L, Arcos-Martínez MJ, Castillo JR. Rapid determination of recent cocaine use with magnetic particles-based enzyme immunoassays in serum, saliva, and urine fluids. J Pharm Biomed. 2016;125:54–61.

Walton RI. Subcritical solvothermal synthesis of condensed inorganic materials. Chem Soc Rev. 2002;31:230–8.

Wang Y, Zhu Z, Xu F, Wei X. One-pot reaction to synthesize superparamagnetic iron oxide nanoparticles by adding phenol as reducing agent and stabilizer. J Nanopart Res. 2012;14:1–7.

Woo K, Hong J, Choi S, Lee H-W, Ahn J-P, Kim CS, Lee SW. Easy synthesis and magnetic properties of iron oxide nanoparticles. Chem Mater. 2004;16:2814–8.

Wu W, He Q, Jiang C. Magnetic iron oxide nanoparticles: synthesis and surface functionalization strategies. Nanoscale Res Lett. 2008;3:397–415.

Wu L, Yao H, Hu B, Yu S-H. Unique lamellar sodium/potassium iron oxide nanosheets: facile microwave-assisted synthesis and magnetic and electrochemical properties. Chem Mater. 2011;23:3946–52.

Wu W, Wu Z, Yu T, Jiang C, Kim W-S. Recent progress on magnetic iron oxide nanoparticles: synthesis, surface functional strategies and biomedical applications. Sci Technol Adv Mater. 2015;16:023501.

Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, Felix R, Schlag PM. Hyperthermia in combined treatment of cancer. Lancet Oncol. 2002;3:487–97.

Xu Y, Wang E. Electrochemical biosensors based on magnetic micro/nano particles. Electrochim Acta. 2012;84:62–73.

Xu J-S, Zhu Y-J. [small alpha]-Fe2O3 hierarchically hollow microspheres self-assembled with nanosheets: surfactant-free solvothermal synthesis, magnetic and photocatalytic properties. Cryst Eng Comm. 2011;13:5162–9.

Yan L, Zhang S, Chen P, Liu H, Yin H, Li H. Magnetotactic bacteria, magnetosomes and their application. Microbiol Res. 2012;167:507–19.

Yang C, Bian X, Qin J, Guo T, Zhao S. Fabrication and hyperthermia effect of magnetic functional fluids based on amorphous particles. Appl Surf Sci. 2015;330:216–20.

Yin B, Wang Y, Dong M, Wu J, Ran B, Xie M, Joo SW, Chen Y. One-step multiplexed detection of foodborne pathogens: combining a quantum dot-mediated reverse assaying strategy and magnetic separation. Biosens Bioelectron. 2016;86:996–1002.

Yoffe S, Leshuk T, Everett P, Gu F. Superparamagnetic iron oxide nanoparticles (SPIONs): synthesis and surface modification techniques for use with MRI and other biomedical applications. Curr Pharm Des. 2013;19:493–509.

Zhou H, Hou X, Liu Y, Zhao T, Shang Q, Tang J, Liu J, Wang Y, Wu Q, Luo Z, Wang H, Chen C. Superstable magnetic nanoparticles in conjugation with near-infrared dye as a multimodal Theranostic platform. ACS Appl Mater Interfaces. 2016;8:4424–33.

Zhu Y-J, Chen F. Microwave-assisted preparation of inorganic nanostructures in liquid phase. Chem Rev. 2014;114:6462–555.