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Review Article

Nanomaterials Developed by Processing Iron Coordination Compounds for Biomedical Application

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The iron oxides, widespread in nature, are used in numerous applications in practice due to their well-known properties. These properties can be modified by size lowering at nanoscale. Some applications, such as biomedical, require a rigorous selection of nanoparticles by size, shape, and surface functionality. In other applications, such as catalysis or magnetism, the composition (generally mixed oxides) and morphology of the nanoparticles are of high importance. The preparation of iron oxide nanoparticles (IONPs) is a complex process whose control raises a number of issues. The first challenge is finding the optimal experimental conditions, which would lead to the preparation of monodisperse nanoparticles. Another issue is the selection or setting a reproducible and clean manufacturing process without a need of complex purification. Even though at the moment several methods for preparing IONPs are known, there are still concerns in the scientific world to further improve existing methods or create new protocols. Therefore, the establishment of optimal methods for preparing IONPs with predetermined structural, dimensional, and morphological characteristics is an important task of scientists. Most of the methods reported in literature for the preparation of IONPs use proper metal salts as precursors. Recently, the use of the organometallic and coordination compounds of iron as precursors for IONPs has emerged as an alternative for a better control of these. Here, achievements reported in the literature in this direction are reviewed and critically analysed in relation to the conventional method based on iron salts.

1. Introduction

Physical and chemical properties of a solid material are influenced, among other aspects, by the size of the particles. Lowering their dimensions at nanoscale affects the structural and electronic characteristics responsible for the macroscopic properties, such as the electrical, optical, magnetic, surface, and chemical reactivity [1]. Therefore, one of the purposes of nanotechnology—generally defined as the manipulation of matter at nanometric scale—is to get nanostructures or nanometric level organizations with special properties, different from those of bulk materials or usual particles. These special properties come from a large surface area with a high number of corners and edges, and as a result, a high density of active sites is readily available. An increased number of atoms situated on the surface or interface generate stress/strains leading to structural deformations. The presence of discrete atom-like electronic states induces quantum size or confinement effects [1]. For example, magnetic nanoparticles exhibit a variety of unique magnetic behavior, different from the corresponding bulk materials, and have proved their usefulness and high performance in various applications from storage media for magnetic memories to probes and vectors in biomedical science [2]. Between them, a special place is occupied by iron oxide nanoparticles.

The iron oxides have a wide distribution in nature and, at the same time, can be easily synthesized in the laboratory [3]. There are more than 20 species composed of Fe, O, and/or OH groups: oxides, hydroxide, and oxohydroxides of iron [4], which differ in structure, composition, and properties (electric and magnetic) [5]. Since anions are much higher than cations (O^{2-} ion radius is 0.14 nm, and those of Fe^{2+}

and Fe^{3+} are 0.065 and 0.082 nm, respectively), the arrangement of the anions determines the crystal structure and eases topological transformations between different iron oxides [6]. The most studied iron oxides are hematite (α-Fe_2O_3), magnetite (Fe_3O_4), and maghemite (γ-Fe_2O_3) due to their unique biochemical, magnetic, catalytic, and other properties, which provide suitability for specific technical and biomedical applications. Mankind has for centuries used magnetic iron oxides [3]. Closer to contemporary period, iron oxide nanoparticles (IONPs) have attracted considerable interest, especially due to their superparamagnetic properties, biocompatibility, and nontoxicity, leading to biomedical applications [7]. IONPs have been optimized (as monodisperse single crystals coated with ordered oleic acid bilayer) for concentration or separation of uranium traces in the environment with high efficiency and low cost. Their superparamagnetic behavior allows easy subsequent separation from a dilute aqueous medium by applying a low magnetic field [8]. In particular, bioapplications based on magnetic nanoparticles have received considerable attention because nanoparticles (NPs) offer unique advantages over other materials. For example, magnetic IONPs are inexpensive and easily obtained, are physically and chemically stable, biocompatible, and environmentally safe [3]. Iron oxide nanoparticles are used as a contrast agent for *in vitro* diagnosis for about half a century. They have already been widely used in clinical practice for anaemia treatments and as drug carriers in cancer therapy [3, 9]. There have been remarkable advances in the control of iron oxide nanoparticle characteristics in terms of size adjustment, narrowing dispersity, and crystal structure. In addition, appropriate surface treatments can control the hydrophobicity/hydrophilicity of the surface and their stability in harsh conditions of pH and temperature. This allows the conjugation of nanoparticles with other molecules resulting in biocompatible coatings for *in vivo* studies.

A lot of reviews have already been published on the interest of iron oxide nanoparticles for biomedical applications as well as on the synthesis methods. However, a review focused on magnetic nanomaterials developed by processing iron coordination compounds and their advantages over the metal salt precursors is missing from the scientific literature. Therefore, in this review, we summarize the available literature including our own research on new advancements in the synthesis of IONPs from coordination compounds, as an alternative to "classic" methods, emphasizing their role in modern life, with an accent on biomedical applications.

2. Iron Oxide Nanoparticles (IONPs) in Biomedical Applications

Magnetic nanoparticles proved to be crucial in certain biomedical applications: targeted drug delivery [10], magnetic resonance imaging (MRI) [11], magnetic hyperthermia [12], tissue engineering [13], and biosensors [14].

Targeted drug delivery can be considered one of the most important applications for magnetic nanoparticles. Due to various functional groups [15] that can be attached to their surface, providing different options for loading of drugs [15, 16], and the inherent possibility to direct them to targeted sites by an external magnetic field [17]. Recently, a hidden intrinsic therapeutic effect of a compound based on IONPs (ferumoxytol) approved by the Food and Drug Administration (FDA) on untreated tumors was revealed, significantly delaying their growth rate [9]. Drug delivery systems based on nanocarriers can be designed to improve the pharmacological and therapeutic properties of conventional drugs. The incorporation of the drug molecules into the nanocarrier ensures the protection of the therapeutic molecules against degradation, at the same time offering possibilities of targeting and controlled release. Considering their small dimensions, nanocarriers are able to overcome various biological barriers such as the blood-brain barrier (BBB). Nanocarrier-drug conjugates are more effective and selective compared with the traditional form of drugs, reducing the toxicity and other adverse side effects in normal tissues by accumulating drugs in target sites; therefore, a smaller amount of the required drug is needed [17]. The determining factors [18] affecting the *in vivo* trafficking of the iron oxide particles are the size of the particles and their surface chemistry and charge. Larger particles with a diameter greater than 200 nm are easily isolated by the spleen [19] and eventually removed by the cells of the phagocyte system, resulting in decreased blood circulation times. In drug delivery applications, the ideal size range of the iron oxide particles is 10 to 100 nm [20], when they are capable to escape the RES of the body and to penetrate small capillaries offering an efficient distribution in the targeted tissues. Particles smaller than 10 nm are rapidly removed through extravasations and renal clearance [21]. The major advantage of magnetic drug targeting that involves nanoparticles as carriers in cancer treatment is that the side effects of conventional chemotherapy are prevented. The targeting of drug-magnetic nanoparticle conjugates to the affected organs can be achieved via passive or active mechanism. Passive targeting relies on the enhanced vascular permeability and retention specific to tumor tissues. The active targeting alternative is based on the coupling of recognition ligands (e.g., antibodies, aptamers, or small molecules) on the surface of the magnetic nanoparticles. A specific alternative of targeting the magnetic drug conjugates involves the use of an external magnetic field [22].

Magnetic resonance imaging (*MRI*) is a noninvasive clinical diagnosis tool of critical importance due to the high degree of soft tissue contrast, spatial resolution, and depth of penetration [11]. Initially, a radio frequency (RF) pulse is used to transfer energy to the in vivo water protons and alter their magnetic moment. After the RF pulse is stopped, the protons return to their equilibrium state and the relaxation times (T1, spin–lattice relaxation, and T2, spin–spin relaxation) are used to generate the MRI signal [23]. In order to increase the variation of T1 and T2, the use of a contrast agent is needed to transfer energy to the surrounding protons. The contrast agents based on IONPs or ferrites provide negative contrast in T2-weighted images, thefirst being for this purpose for more than 25 years. These iron oxides can be ferromagnetic or superparamagnetic, depending on the size of the core of the nanoparticle. Two iron oxides are generally considered for biomedical applications: magnetite

(Fe_3O_4) and its oxidized and more stable form of maghemite (γ-Fe_2O_3). The critical upper size limit for the observation of superparamagnetism is approximately 25 nm for magnetite and 30 nm for maghemite. The two compounds fulfill the prerequisites of chemical stability under physiological conditions, low toxicity, and sufficiently high magnetic moments [24]. Since the transverse relaxivity r2 depends, apart from size, on the saturation magnetization (Ms), the optimization of Ms is one of the most effective ways to achieve magnetic nanoparticles with high MRI sensitivity. It has been reported that, owing to the higher magnetization, superparamagnetic iron oxide nanoparticles (SPIONs) have a higher T2 relaxivity than analogous systems containing iron oxides [25]. The most widely applied coatings for FDA-approved SPIONPs are dextran and carboxydextran. Ultrasmall IONPs are used as contrast for lymphography [26] and angiography [27], as a bone marrow contrast, or as a perfusion agent in the brain and the kidney. Only the SPION for oral administration, Gastromark® (AMAG Pharmaceuticals, Waltham, MA, USA; ferumoxsil, silicone-coated SPIONs), is currently on the market for gastrointestinal bowel marking. Colloidal suspensions of Fe/Fe_2O_3 nanoparticles are capable of providing both T1- and T2-weighted images [28]. An iron core (with its subsequent oxidation giving a ferrite shell) with added nickel ions to form a nickel ferrite shell nanoparticle has been studied; its surface is treated with dopamine-PEG to make it dispersible, and it acts as a dual-mode T1 and T2 contrast agent [29]. The IONPs without coating showed a specific cytotoxic mechanism for certain cells. Cell staining (e.g., stem cells and dendritic cells) with IONPs is an exciting new tool for monitoring these marked cells in real time by magnetic resonance tomography [30].

The method that uses heat as cancer treatment is called *hyperthermia* [31]. Hyperthermia principles are based on the fact that cancer and healthy cells show signs of apoptosis when heated in the range of 41°C to 47°C [31, 32] and necrosis when heated to above 50°C. Tumor cells are considered more susceptible to heat than normal cells due to their higher rates of metabolism [33] which makes hyperthermia a very promising cancer treatment. Hyperthermia can be generated by radio frequency, microwave, and laser wavelengths, but the use of magnetic nanoparticle-based heating is superior due to the noninvasive character of the particles, the multivalent use of the magnetic nanoparticles as diagnosis agents (MRI contrast agents) and at the same time therapeutic agents (hyperthermia), and the functional versatility of the particles which can be adequately functionalized and combined with other types of treatment strategies (chemotherapy or radiotherapy). Magnetic nanoparticle hyperthermia involves the delivery of particles into tumors and heating of the particles by using alternating magnetic fields to achieve desired temperatures [34]. Brown relaxation (heat created by friction generated by the total particle oscillations) and Néel relaxation (heat created by the rotation of the magnetic moment with each field oscillation) support the heating mechanism of magnetic nanoparticles [35]. The use of magnetic nanoparticles as hyperthermia agents in vitro and in small animal models was the topic of many publications [36, 37]. Maier-Hauff et al. studied therapeutic hyperthermia induced by the heating of implanted magnetic nanoparticles [38], where patients with recurrent glioblastoma multiforme (a type of severe brain cancer) received an intratumoral injection of aminosilane-coated IONPs. The tumor sites were located by several comprehensive MRI scans, and then the patients were exposed to an alternating magnetic field to induce particle heating. The results indicated that all patients tolerated the nanoparticles without any complications. The next CT scans and reproducible temperature measurements proved that the nanoparticle deposits were stable for a long period. Clinical studies on hyperthermic nanoparticles to treat prostate cancer were conducted by the same group of researchers [39, 40]. Further reading concerning the progress of the application of magnetic nanoparticles as hyperthermia agents can be found in reference dedicated to this aspect [41]. IONPs can be viewed as a viable alternative for hyperthermia therapy, but this application requires an improvement of the reproducibility and the size control during the synthesis of particles [42].

Alongside the well-documented uses in various therapy strategies at a cellular level, there are other incipient applications of IONPs such as *orthopedic applications*. The important role of iron in the bone processes was exploited by using magnetic nanoparticles to reverse the effects of osteoporosis [43]. To this purpose, magnetic nanoparticles coated with an adequate surfactant or biological active compounds can be directed via an external magnetic field to the affected bone structure. Upon removal of magnetic force, the particles remain attached to the bone porous structure and can promote bone growth.

The functional versatility of IONPs can be exploited to design useful *agents for in vitro bioseparation* of certain biomolecules [44]. The use of magnetic nanomaterials for separation techniques relies on the simplicity of the process without the need for traditional separation equipment (HPLC) and the possibility to make use of the magnetic properties [45].

In the context of exploring various options to solve the issue created by increasing microbial resistance to antibiotics, inorganic nanomaterials, such as metal oxide nanoparticles—among them iron oxides and their derivatives with other metals occupying an important place—have become serious candidates due to advantages such as low toxicity, inhibition of a wide range of bacteria, and low cost. However, research is still needed to evaluate and understand the cytotoxicity mechanism of these nanoparticles [46]. Nanoparticles of gold and iron oxides show high performance in the release of drugs, imaging, and therapy and are thus promising theranostic anticancer agents. For this, they were formulated as PEG-PCL-coated micelles [47]. Nanoparticles with magnetic core, such as Fe and Co encapsulated in silica shell, are used as biolabeling agents [48].

3. Challenges in the Preparation of IONPs

Obtaining IONPs of high quality, dispersible either in aqueous or organic medium, opens up broad opportunities

for their application both in the medical field (as contrast agents for MRI, drug carriers for target specific drug delivery, gene carriers for gene therapy, therapeutic agents for hyperthermia-based cancer treatments, magnetic sensing probes for *in vitro* diagnostics, and nanoadjuvant for vaccine and antibody production) but also in lithium ion batteries [49], supercapacitors [50], catalysis [3, 51], magnetic storage devices [52], composites [53, 54], and ferrofluids [55].

Most applications, including biomedical ones, require a rigorous selection of nanoparticles by size, shape, and surface functionality. In more details, the main benefit that makes iron oxides useful in a wide range of applications is their magnetic properties, which is very sensitive to type (hematite has weak ferromagnetism, magnetite and maghemite is ferrimagnetic while goethite is antiferromagnetic at room temperature), size (i.e., magnetite is superparamagnetic below or about 15 nm), and shape (i.e., cubic nanoparticles produces more heat for hyperthermia application than spherical nanoparticles of the same size) of the nanoparticles [3]. Thus, finding the optimal experimental conditions, which would lead to the preparation of monodisperse nanoparticles, is essential.

The heteronuclear oxides are of interest because the presence of at least two types of nuclei can enhance the activity of the oxide (e.g., magnetism) or broaden the temperature range or time within which they are active (e.g., catalytically) [56]. Multimetal oxide nanoparticles are of great interest as antimicrobial agents due to the beneficial synergistic effects of their components, being promising alternatives to pure metal oxide nanoparticles that present agglomeration and cytotoxicity issues [46]. Methods known in the art for the preparation of mixed, heteronuclear iron oxide nanoparticles are limited to the use of metal salts in various ratios, which does not allow for good control of the resulting mixed oxide composition.

Due to the magnetic attraction, van der Waals force, and high surface energy, IONPs as such tend to agglomerate, this being a large disadvantage in practical use. Therefore, in each case, the working protocols must be adapted to ensure their good dispersion.

4. Synthetic Pathways to IONPs

Different procedures have been developed for the preparation of IONPs, either by physical, chemical, or biological pathways, each with their advantages and disadvantages [57]. *Physical procedures* consist of gas phase deposition, electron-beam lithography, pulse laser ablation, laser-induced pyrolysis, powder ball milling, and aerosol [58, 59]. *Biological pathways* are fungi-, bacteria-, or protein-mediated synthesis of oxide nanoparticles [59]. The microbial enzymes or the plant phytochemicals with redox properties could reduce salts into their respective highly biocompatible NPs through a green chemical and ecofriendly route. For IONPs, specific bacteria—-magnetotactic bacteria and iron reducing bacteria—are used [3]. The main *chemical methods* are coprecipitation, solvothermal, hydrothermal, microwave irradiation, thermal decomposition, sonochemical, inverse microemulsion, sol-gel synthesis, flow injection, and electrospray synthesis [57, 59–61]. One of the most common methods to prepare IONPs is the *coprecipitation* of Fe^{+2} and Fe^{3+} precursors in strong alkaline medium. The nanoparticle morphology can be controlled by choosing suitable precursor, ion ratio, stirring time, pH, and reaction temperature. The main advantage of this method is its high scalability. *Thermal decomposition* method consists in the injection of the precursors into a hot reaction mixture or simply heating (100-350°C) the reaction mixture in a closed or open reaction vessel. Nanoparticles with very narrow size distribution and very good shape control can be prepared by this procedure [3]. *Solvothermal synthesis* taking place in sealed reactors in nonaqueous solution at high temperatures (150-250°C) and pressure (0.3-4 MPa) is generally known as a technique of crystallization [3]. In the synthesis of iron oxide, this method leads to high quality crystals and allows good control of the composition [3]. Solvothermal techniques proved to allow obtaining IONPs with various morphologies, such as nanorods, rings, cubes, spindles, and hollow particles.[58]. In the last time, the *microwaves* (MW) are often used as irradiation source for preparing IONPs. As a result of microwave exposure, the molecules are aligning through their dipoles. The molecule reorientation process induces an instantaneous strong internal heating in a homogeneous and selective manner, different from the classical procedures [3]. The reaction time is much shorter compared with other methods. The main drawbacks of these procedures are low dispersion in solvents and wide distribution by size and shape of the resulted nanoparticles. The particles obtained by these methods easily aggregate [60]. A competitive alternative to other methods for obtaining iron oxide nanoparticles is *sonochemical method*. High-intensity ultrasounds are an unconventional route often used to prepare known compounds or materials, without bulk high temperatures, high pressures, or long reaction times. This uses the chemical effects of the oscillating cavities created within a material as a result of the alternating expansive and compressive acoustic waves. Acoustic cavitation consists in the formation, growth, and implosion of bubbles in the liquid. Collapse by implosion generates a local hot spot adiabatic compression by forming shock waves in the gas phase inside the bubble that implodes. The conditions encountered in these hot spots have been determined experimentally as being transitional temperature of 5000 K, a pressure of 1000 atm, and cooling rates of more than 1010 K/sec [62]. These extreme conditions are beneficial to the formation of new phases and have a strong effect of breaking the agglomerate, which leads to nanoparticles with narrow size distribution [63]. This procedure is also applicable in the preparation of size- and shape-controlled IONPs.

5. Coordination and Organometallic Compounds as Precursors for IONPs

The classical procedures for preparing IONPs are based on mixing ferric and ferrous salts as precursors. This synthetic approach however limits the working temperature to the boiling temperature of water in which they are soluble, while this in turn limits the crystallization degree and widens the

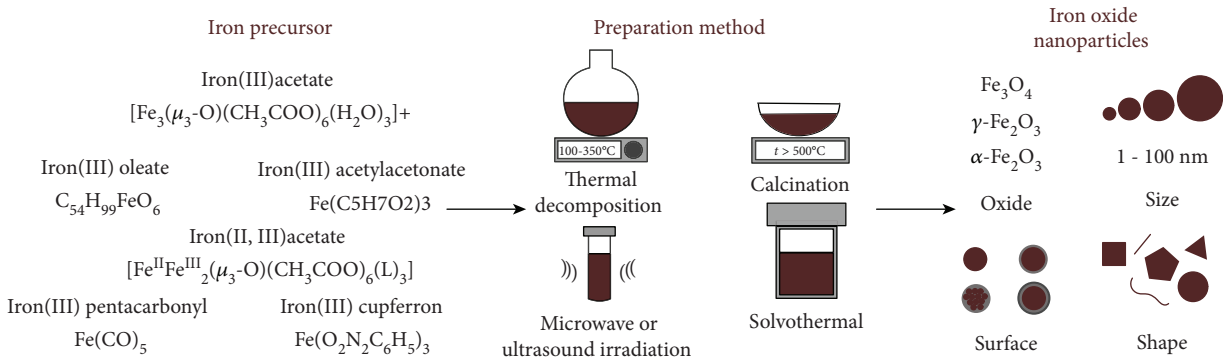

Figure 1: Schematic representation of main chemical procedures for the preparation of metal oxide nanoparticles from iron coordination compounds.

	Thermal decomposition	Solvothermal method	Microwave irradiation	Ultrasonication	Calcination
Complexity	Complex	Medium	Simple	Simple	Very simple
Temperature (°C)	100 - 350	150 - 250	100 - 200	20 - 50	> 500
Time	Hours - days	Hours - days	Minutes	Minutes	Minutes - hours
Size distribution	Very narrow	Very narrow	Medium	Narrow	Broad
Shape control	Very good	Very good	Good	Medium	Bad
% Yield	High scalable	High scalable	Medium	Medium	High scalable

Figure 2: Comparison of preparation methods of IONPs based on proper coordination compounds.

nanoparticles polydispersity. The procedures commonly applied for the synthesis of mixed, heteronuclear iron oxide nanoparticles consist, in principle, in mixing the metal salts in various ratios. The use of a single precursor that contains two or more metals in predetermined ratio is less known. Recently, the use of coordination compounds as precursors was found as a solution to increase the quality of IONPs. Thus, resulted nanoparticles are better controlled in structure, shape, and size and are highly crystalline [51]. Schematic representation of the main chemical procedures for the preparation of metal oxide nanoparticles from iron coordination compounds is presented in Figure 1.

IONPs originated from iron coordination compounds are mostly prepared using thermal decomposition, solvothermal method, microwave or ultrasound irradiation, and calcination. The estimated complexity degree, reaction temperature and time, size distribution, shape control, and yield are presented in Figure 2 for each method. In the following, examples of iron complexes and experimental details of their conversion into iron oxide NPs are presented.

Iron oleate complex ($C_{54}H_{99}FeO_6$) can be synthesized following various approaches described in the scientific literature. Park et al. [64] synthesized iron oleate complex by heating iron chloride and sodium oleate at 70°C for four hours, in a mixture of ethanol, distilled water, and hexane. Iron pentacarbonyl [65] or iron nitrate nonahydrate [66] can also be used as precursors for iron oleate complex. Iron oleate is one of the most common precursors for the preparation of IONPs using thermal decomposition method. IONPs were prepared by heating the iron oleate in 1-octadecene at 275, 290, or 320°C [67]. It was found that increasing the temperature leads to increasing in nanoparticle size up to 10 nm. When an excess of oleic acid is used, nucleation is delayed and growth is slowed, thereby the presence of the surfactant offers a sufficient time to afford single crystalline and monodisperse nanoparticle tuned up to 25 nm [67]. Fe/Fe_3O_4 core/shell nanocubes were prepared by thermal decomposition (310–320°C) of iron oleate complex in the presence of squalene used as a solvent and sodium oleate and oleic acid as surfactant. The use of squalene and sodium oleate was found to induce the cubic shape of nanoparticles. Basedon iron oleate as precursor, Park et al. [65] have synthesized monodisperse IONPs with sizes between 6 and 15 nm by controlling the growth of previously synthesized nanoparticles. Thermal decomposition of the $M(II)Fe(III)_2$ oleate complex in the presence of 1-octadecene at 300°C (under N_2) for 30 min results in cubic 9 nm $CoFe_2O_4$, near-spherical 11 nm $NiFe_2O_4$, or perfectly spherical 7 nm $MnFe_2O_4$ and 24 nm $FeFe_2O_4$ nanoparticles [68]. The mixture of iron oleate, oleic acid, and alkanols (ethanol, methanol, 1-propanol, 1-butanol, and 1-hexanol) was heated in the autoclave at 180°C for 5 h in order to prepare IONPs [69]. Compared to decomposition in air, the solvothermal approach results in the formation of magnetite because, with increasing the pressure, the oxygen flux, which is crucial in formation of magnetite, also increases. Due to the lower boiling point of alkanols compared with 1-octadecene, higher pressure is produced, which facilitates the crystallization of resulted nanoparticles. The reaction made in methanol leads to the formation of hematite and magnetite. In less polar solvents (ethanol, 1-propanol, 1-butanol, and 1-hexanol), only magnetite nanoparticles were obtained. The nanoparticle size

varies between 7 and 10 nm, depending on the solvent and can be increased by increasing the iron oleate concentration, or the reaction temperature.

Iron(III) acetylacetonate ($Fe(C_5H_7O_2)_3$) can be prepared by heating on a steam bath for 15-20 min of a mixture of anhydrous iron (III) chloride and ammonia in water [70]. Iron(III) hydroxide is also widely used for iron acetylacetonate synthesis [71]. Water soluble magnetite nanoparticles were obtained by thermal decomposition of iron(III) acetylacetonate in the presence of phenol and benzyl ether. Using a phenol to iron acetylacetonate ratio of 15 : 2, nanoparticles of 9.7 ± 1.5 nm were obtained. When the ratio was 10 : 2, the size was slightly increased to 10.4 ± 1.3 and by using a ratio of 4 : 2 the size was tuned to 19.3 ± 4.4 nm [72]. Thermal decomposition of iron acetylacetonate in 2-pyrrolidone leads to the preparation of water soluble 5 nm magnetite nanoparticles [73]. 2-Pyrrolidone was used as a medium for high-temperature reaction and also as stabilizer, due to its polarity, high boiling point, and capacity to coordinate with transitional metal ions. Mixed oxide nanoparticles can be obtained using as precursors two iron coordination compounds in the desired ratio or a heterometallic compound with preestablished ratio between metals. For the synthesis of $CoFe_2O_4$ nanocrystals, iron(III) and cobalt(II) acetylacetonate in 2 : 1 molar ratio were used as precursors in the presence of oleic acid, oleylamine, phenyl ether, and 1,2-hexadecanediol [74]. Short-term (30 min) heating of the mixture at 260°C led to the formation of 5 nm spherical nanocrystals. Using these as seeds in a particle growth solution consisting of iron and cobalt acetylacetonate, 1-octadecanol, oleic acid, and oleylamine, 8 nm spherical or 9 nm cubic $CoFe_2O_4$ nanoparticles were obtained depending on the concentration of precursors in similar time and temperature conditions to the preparation of 5 nm nanoparticles [74]. Starting from iron acetylacetonate, n-octylamine, and n-octanol IONPs were prepared through a solvothermal approach [75]. Using a volume ratio of octylamine to octanol of 8 : 8, 6 : 10, and 4 : 12 resulted in magnetite nanoparticles of~4, 5, and 6 nm, respectively. So, the size can be decreased by increasing the ratio of octylamine to octanol, because the higher amount of surfactant will limit the further growth. Larger but polydisperse nanoparticles resulted if the volume ratio was less than 4 : 12. Acicular hematite nanoparticles of 8–12 nm wide and over 150 nm in length were obtained through solvothermal synthesis (at 160°C for 8 h) from iron acetylacetonate dissolved in toluene and in the presence of hydrogen peroxide [76]. Solvothermal synthesis (at 280°C for 150 min) of mixed oxide nanoparticles was also carried out by using a mixture of iron acetylacetonate and Fe, Co, Mn, Ni, or Zn acetylacetonate in a molar ratio of 2 : 1 and in the presence of triethylene glycol, when nanoparticles of about 7.6 nm Fe_3O_4, 5.0 nm $CoFe_2O_4$, 10.0 nm $MnFe_2O_4$, 9.9 nm $NiFe_2O_4$, and 4.8 nm $ZnFe_2O_4$ resulted [77]. In another strategy, IONPs were formed by reduction-hydrolysis of iron(III) acetylacetonate, in the presence of $NaBH_4$. It was found that under these conditions, iron(III) acetylacetonate underwent hydrolysis and reduction to form Fe(III) ($Fe(OH)_3$ FeO(OH)) and Fe(II) ($Fe(OH)_2$) intermediates, which by further condensation in a proper ratio led to the nucleation of Fe_3O_4. By adding 3-aminopropyltriethoxysilane, in basic conditions, results a shell consisting in aminopropyl-functionalized silica results [78]. Microwave-assisted synthesis of mixed oxide nanoparticles was performed using a mixture of iron and metal acetylacetonate (Fe, Co, Mn, Ni, and Zn) in 2 : 1 molar ratio and in the presence of triethylene glycol [77]. The reaction time was limited to 10 min at 220°C in order to prepare nanoparticles of Fe_3O_4, $CoFe_2O_4$, or $ZnFe_2O_4$ with average sizes around 5.7, 5.1, and 6.2 nm, respectively, while nanoparticles of $MnFe_2O_4$ and $NiFe_2O_4$ with sizes of about 6.6 and 1.8, respectively, were obtained by heating at 280°C.

Iron pentacarbonyl ($Fe(CO)_5$) is generally prepared by the reaction of carbon monoxide with fine iron particles. This reaction is used in industry and requires 150°C and 175 atm. For preparation in the laboratory, in order to avoid such reaction conditions, an iodine intermediate ($Fe(CO)_4I_2$) is used [79]. Using iron pentacarbonyl as iron precursor, oleic acid as surfactant, and octyl ether as solvent, maghemite nanoparticles were obtained by thermal decomposition method. Varying the ratio of iron pentacarbonyl to oleic acid as 1 : 1, 1 : 2, and 1 : 3, the nanoparticles size was 5 nm, 11 nm, and 19 nm, respectively [80]. Teng and Yang [81] studied the minimum required oleic acid to $Fe(CO)_5$ molar ratio for preparing monodisperse IONPs at 275 ± 5°C (just below the refluxing temperature). When the ratio was <2, only polydisperse nanoparticles were obtained, while using the ratio ≥ 3 resulted in monodispersed nanoparticles. The authors also studied the influence of the reaction time on nanoparticles, under the same temperature (275°C) and reaction composition (oleic acid: $Fe(CO)_5$ ratio of 3). Increasing time from 60, 90, to 150 min resulted in nanoparticles of 10, 16, and 25 nm, respectively. Magnetite nanorods with a length of 63 nm and a diameter of 6.5 nm were prepared through solvothermal method from iron pentacarbonyl in the presence of oleic acid, hexadecylamine, and n-octanol at 200°C for 6 h [82]. The size of nanorods can be tuned up to 140 nm by adjusting the reaction parameters (time or concentration of the added hexadecylamine). In the first step, iron oleate was formed from the reaction of oleic acid and iron pentacarbonyl. In the next step, iron oleate, in the presence of water, generated by condensation between hexadecylamine and oleic acid, hydrolyzes resulting in iron oxide. The reaction is promoted by the products of the remaining iron precursor decomposition and by controlling the release of water. The prepared nanorods show improved electrochemical and magnetic properties compared to nanoparticles and nanoplates. Shafi et al. [83] studied sonochemical decomposition of iron pentacarbonyl in the presence of different surfactants. Amorphous IONPs were prepared by ultrasonication (Ti-horn, 20 kHz, 100 W/cm^2) at 0°C for 3 h of a mixture composed of iron pentacarbonyl as iron precursor, decane as solvent, and octyl phosphonic acid ($C_8H_{17}PO_3H_2$), undecenoic acid (CH_2=$CH(CH_2)_8COOH$), or dodecyl sulfonic acid ($C_{12}H_{23}SO_3H$) as surfactant. The resulted surfactant-coated nanoparticles are near spherical with a size of 5-16 nm. According to FTIR spectra, surfactants

are bound to the iron oxide via ionic bond. It was observed that phosphonate-coated nanoparticles show a very low value in magnetization with a constant magnetization increment as compared with nanoparticles coated with other surfactants, which exhibit a superparamagnetic behavior [83].

μ_3-Oxo trinuclear iron(III) furoate ($[Fe_3O(C_4H_3O\text{-}COO)_6(CH_3OH)_3]NO_3$) can be prepared from a mixture containing copper furoate, iron nitrate nonahydrate, and methanol [84]. Turta et al. [84] prepared 1.3 and 5.5 nm maghemite and amorphous IONPs by thermal decomposition at 320°C in the presence of sunflower oil (for the first time used as surfactant in such approach), trichloroacetic acid, and 1,2-hexadecylamine.

μ_3-Oxo trinuclear iron(III) acetate ($[Fe_3O(CH_3\text{-}COO)_6(H_2O)_3]NO_3{\bullet}4H_2O$) can be prepared from a mixture of iron nitrate nonahydrate, sodium acetate, glacial acetic acid, and distilled water [85]. Iacob et al. [86] optimized the thermal decomposition of μ_3-oxo trinuclear iron(III) acetate in order to prepare iron oxide nanowires. The concentration of the surfactant (oleic acid) was selected as the controlling parameter and optimized using the so-called artillery approach for targeting the reaction parameters. By varying the concentration, nanoparticles with various morphologies were obtained. Using wide angle X-ray diffraction (WAXD), small angle X-ray scattering (SAXS), polarized optical microscopy, and differential scanning calorimetry (DSC), it was found that surfactant-coated iron oxide nanowires were self-assembled into smectic crystals. In addition, transmission electron microscopy (TEM) images of nanowires heated in nitrogen atmosphere at 700°C show formation of nanoparticles with various sizes including nanotubes. This approach was also applied for preparing iron oxide with various shapes: cubic, spherical, and hair-like structures, protruding from the surface at various angles, but generally in a radial direction from the sphere center [87]. Iron-chromium oxide nanoparticles of 11 nm were obtained using μ_3-oxo heterotrinuclear ($FeCr_2O$) acetate as metals precursor, oleic acid and dodecylamine as surfactants, and trichloroacetic acid as solvent heated at 320°C for 1 h. The molar ratio of iron and chromium in the obtained nanoparticles was similar to the precursor. In this case, the authors also found that the obtained material is self-assembling into smectic crystals [88]. Amorphous iron-chromium oxide nanoparticles of 3.5 nm were prepared by the thermal decomposition of μ_3-oxo heterotrinuclear ($FeCr_2O$) acetate in the presence of dodecylamine, sunflower oil, and trichloroacetic acid at 320°C for 1 h. According to XRD results, the formed nanoparticles remained amorphous even after 2 years. Solvothermal method was used to study the influence of surfactant concentration (dodecylamine and sodium oleate) and the type of solvent on decomposition at 200-250°C of μ_3-oxo trinuclear iron acetate ($[Fe_3O(CH_3COO)_6(H_2O)_3]\ NO_3{\cdot}4H_2O$) into IONPs [87]. It was found that both dodecylamine and sodium oleate concentrations influence the size and the shape of the resulted nanoparticles, while the chosen solvent did not greatly affect their morphology. Ultrasonication of μ_3-oxo trinuclear iron acetate in a strong alkaline medium for 5 and 30 min resulted in amorphous iron oxide. By thermal treatment of the as-prepared amorphous oxidic material at 400°C, 20 nm spheroidal hematite nanoparticles can be easily obtained [87]. It was shown that microwave irradiation of μ_3-oxo trinuclear iron acetate in an alkaline medium leads to the formation of amorphous irregularly shaped IONPs when the pH of the reaction mixture was adjusted to 11, while at pH 12 agglomerates of hematite nanorods of approximately 15 nm in width and 10 nm irregularly shaped nanoparticles were obtained [87].

Iron(II) acetate ($Fe(CH_3COO)_2$) results from the reaction between iron powder and hot acetic acid [89]. This compound has a polymeric structure with octahedral Fe(II) centers bridged by acetate ligands. Sonication with a high-intensity ultrasonic horn (Ti-horn, 20 kHz) under argon atmosphere of iron(II) acetate in water for 3 h resulted in superparamagnetic magnetite nanoparticles of 10 nm [90].

Mixed valence μ_3-oxo trinuclear iron(II, III) acetate ($[Fe_2^{III}Fe^{II}O(CH_3COO)_6(H_2O)_3]{\cdot}2H_2O$) can be synthesized following the procedure reported in the literature [91] by using iron(II) chloride and iron(III) chloride at a molar ratio of 1 : 2, calcium acetate, and glacial acetic acid. The thermal decomposition of mixed valence μ_3-oxo trinuclear iron(II, III) acetate at 320°C in the presence of sunflower oil, dodecylamine, and tricloroacetic acid resulted in monodisperse 3.5 nm magnetite nanoparticles.

Iron(III) glucuronate ($Fe(C_6H_{11}O_7)_3$) was synthesized by refluxing a mixture consisting of sodium salt of D-glucuronic acid, iron(III) chloride, ethanol, methanol, and water [92]. Patsula et al. [92] used iron(III) glucuronate, as a nontoxic alternative precursor instead of organometallic compounds, such as iron(III) pentacarbonyl. Magnetite nanoparticles were prepared by thermal decomposition using iron glucuronate as iron source and oleic acid as surfactant. The shape, size, and particle size distribution were controlled by varying the reaction parameters, such as the reaction temperature, concentration of the stabilizer, and type of high-boiling-point solvents. A series of experiments with constant concentration of reagents in 1-octadecene was made in order to study the influence of reaction temperature on the resulted product. Experiments made at 255 and 270°C failed because no nucleation was initiated. At 285 and 300°C polydisperse nanoparticles of 32 and 13 nm, respectively, were obtained. Monodisperse nanoparticles of 12 and 18 nm with cubical shapes were obtained when the reaction was conducted at 320 and 343°C, respectively. By replacing the hydrocarbon solvent with a polar mPEG/Brij O10 (polyoxyethylene (10) oleyl ether) mixture, at 285-320°C, polydisperse nanoparticles were obtained, because the separation of the nucleation and growth steps did not occur. Authors also demonstrated that, with increasing the concentration of oleic acid, the nanoparticle size decreased.

Iron(III) oxalate ($Fe(C_2O_4)_3$) was synthesized by the reaction between iron powder dissolved in acetic acid and oxalic acid solutions [93]. Thermal decomposition of α- and β-ferrous oxalates at 500°C in CO/CO_2 results in magnetite with crystallite sizes of 35 and 40 nm, respectively. Increasing the temperature to 700°C leads to magnetite with crystallite sizes of 50 and 55 nm, respectively [93]. Thermal decomposition of ferrous oxalate in air ($T \geq 250$°C) results

in hematite, whereas at low oxygen partial pressures the final product is magnetite.

Hematite nanoparticles were prepared by thermal decomposition of a solution consisting in 0.1 M iron(III) precursor (iron(III) oxalate, *iron(III) citrate* ($Fe(C_6H_5O_7)$), and iron(III) acetate or iron(III) acetylacetonate) for 4 h with heating rate of 10°C·min^{-1} [94]. It was demonstrated that the type of precursor implies the temperatures of nanoparticle formation and affects the size of the resulted material. Using the iron oxalate as precursor leads to nanoparticles of 24 nm, the decomposition of iron(III) citrate results in 29 nm hematite nanoparticles, while using iron(III) acetylacetonate the particles size was 37 nm.

A poly(siloxane–azomethine) iron(III) coordination compound can be prepared following the procedure described in reference [95]. Calcination at 600°C for 5 h in air of this iron complex based on a siloxane containing macromolecular ligand results in 29 nm core-shell nanoparticles, where the core consists of hematite and the shell of silica [87]. Nanoparticles with completely different morphology were prepared by calcination in the same condition of μ_3-oxo trinuclear iron acetate and μ_3-oxo trinuclear iron furoate, when polydisperse (50–350 nm) hematite and iron chromium oxide nanoparticles resulted.

Iron-urea complex ($[Fe(CON_2H_4)_6](NO_3)_3$) can be synthesized using a mixture of iron(III) nitrate, urea, and ethanol. Thermal decomposition of this compound in diphenyl ether at 200°C results in iron oxide self-assembled in prismatic particles [96].

Iron(III) and manganese(II) benzoylacetonate was prepared as the reaction between 1-benzoylacetone and metal acetate in ethanol. The preparation of $MnFe_2O_4$ using iron(III) and manganese(II) acetylacetonate as precursors is problematic in terms of controllable chemical composition of resulted nanoparticles, because the decomposition temperatures between iron and manganese acetylacetonate differ with more than 60°C. In order to reduce the gap in the decomposition temperatures of the precursors, Song et al. [97] substitute the methyl group from acetylacetonate ligand with a phenyl group. The difference in the decomposition temperature of iron and manganese benzoylacetonate is much smaller (13°C). Furthermore, iron and manganese benzoylacetonate in molar ratio 2 : 1 were used as precursors for the nanoparticles in the presence of oleic acid, oleylamine, phenyl ether, and 1,2-hexadecanediol. The reaction mixture was kept for 30 min at 260°C, resulting in 3-4 nm $MnFe_2O_4$ nanocrystals. Similar with the procedure described for $CoFe_2O_4$ [74], the prepared nanoparticles were used as seeds to tune the size of nanoparticles up to 12 nm [97].

Iron(III) and cobalt(II) cupferron can be prepared following the procedure described by Thimmaiah et al. [98]. Cobalt ferrite nanoparticles ($CoFe_2O_4$) were prepared on the basis of iron cupferron and cobalt cupferron as precursors in a molar ratio of 2 : 1, in the presence of n-octylamine used as a surfactant and toluene as a solvent [98] heated at 220°C. Nanoparticles with an approximately spherical shape having an average diameter of 7.3 nm and a standard deviation of 1.5 nm were formed. Authors also pointed that decomposition in the same conditions of cobalt cupferron resulted in $Co(OH)_2$ instead of oxidic nanoparticles, while iron cupferron decomposition resulted in maghemite nanoparticles with the average size of 10.4 nm, larger than cobalt ferrite nanoparticles. The reason for this could be that the decomposition temperature of cobalt cupferron (165°C) is significantly lower than that of iron cupferron (180°C), therefore the number of nuclei at 220°C increases and results in smaller nanoparticles. In the formation process of maghemite, fewer nuclei are formed, so the particles can grow larger.

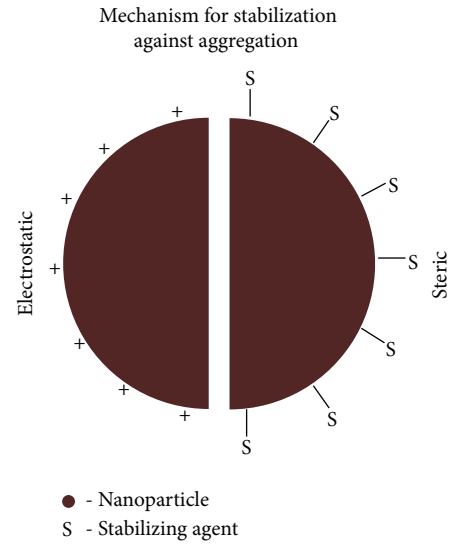

Figure 3: Schematic representation of nanoparticle stabilization possibilities.

6. Surface Coating of IONPs

The agglomeration of the IONPs can be avoided or limited by two main mechanisms for stabilization against aggregation: steric or electrostatic [99], as presented in Figure 3. Covering the nanoparticles surface with a shell, besides protecting against oxidation and agglomeration, may influence their solubility, interfacial interactions, and reactivity, conferring other properties (hydrophilic or hydrophobic) or functions needed for specific applications [51].

Nontoxicity and biocompatibility of magnetic nanoparticles can be enhanced further by special coating with organic or inorganic molecules, including surfactants, polymers, biomolecules, metals, metal oxides, metal sulfides, silica, and carbon (Figure 4) [3, 42, 100].

In order to be used in biomedical applications, IONPs can be functionalized by various *organic materials* through functional groups such as –OH, –NH_2, –COOH, and –SH on which various bioactive molecules can be subsequently attached. For example, –NH_2 and –SH can be anchored using silanes such as p-aminophenyltrimethoxysilane, (3-aminopropyl)-triethoxysilane, and mercaptopropyltriethoxysilane [3].

The most common organic coatings for IONPs are oleic acid and oleylamine. Such surfactants allow preparing iron oxide at a high temperature resulting in high quality nanoparticles with various shapes and sizes. However, such

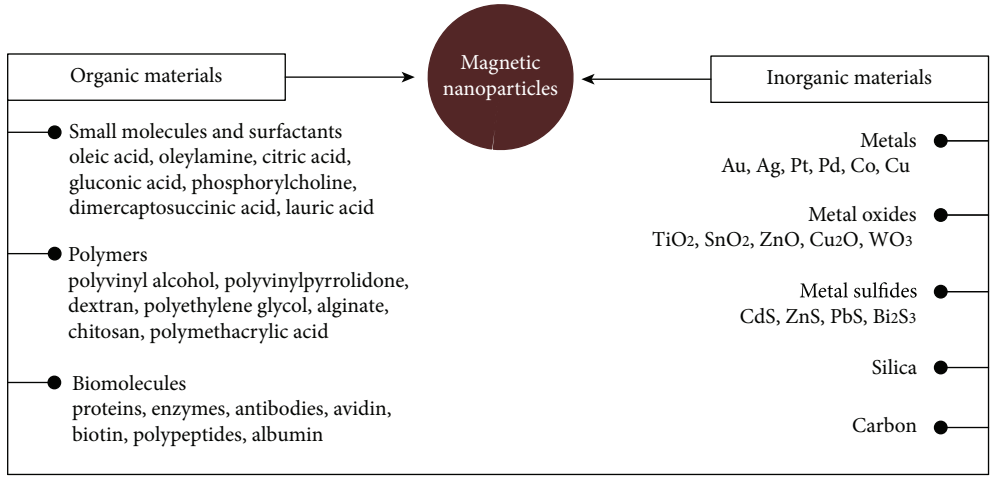

Figure 4: General presentation of organic and inorganic materials suitable and usually used for coating nanoparticles.

nanomaterials are oil soluble and are not suitable for biomedical applications where water soluble particles are required. To transfer nanoparticles from organic to aqueous phase, the hydrophobic surface of the nanoparticles can be modified using polyethylene glycol, folic acid, modified poly(amidoamine) dendrimers, cyclodextrine, Pluronic-type surfactants, etc. [101–103]. Encapsulation of hydrophobic IONPs or a combination of these with a hydrophobic drug (nystatin) in biocompatible siloxane surfactants made magnetic nanoparticles safe for biomedical applications [104, 105].

Citric acid is another widely used surfactant for IONPs. Li et al. [106] synthesized citric acid-coated IONPs by different approaches: preaddition or postaddition of citric acid in the reaction mixture. The core size of citric acid coated nanoparticles is dependent on the chosen approach and ranges from 6 nm to 13 nm. Coating IONPs of 9 nm with citric acid did not affect their superparamagnetic behavior, while the coating of 25 nm nanoparticles led to the decreasing of coercivity compared to uncoated nanoparticles. Padwal et al. [107] demonstrated that magnetic nanoparticles coated with citric acid doubles the uptake of existing antituberculosis drugs. The water-dispersed IONPs can also be obtained using molecules such as gluconic acid [108], glucose [109], poly(vinyl alcohol phosphate) [110], and hexadecylphosphonic acid [111].

Polymer stabilizers are some of the most efficient coatings for magnetic nanoparticles in order to use them in biomedical applications due to higher colloidal stability and biological fate [3, 112]. Coating of magnetic nanoparticles with polymers can be done *in situ* (during the synthesis process) or postsynthesis (grafting the polymeric surfactants) [113]. There are many polymers that were found to be efficient in the stabilization of magnetic nanoparticles such as dextran [114], polyethylene glycol [115], polyvinyl alcohol [116], poly(acrylic acid) [117], chitosan [118], poly(lactic acid) [119], polysaccharides [120], and poly(ε-caprolactone) [42].

Inorganic materials such as silica, carbon, metals (Au, Ag, Co, Cu, Pd, Pt, etc.), metal oxides (TiO_2, ZnO, SnO_2, WO_3, and Cu_2O), and metal sulfides (CdS, ZnS, PbS, and Bi_2S_3) are widely used in the stabilization of IONPs, providing a good stability in the solution and helping to bind biological ligands for medical applications [42].

Silica is one of the most promising coating layers for magnetic nanoparticles due to its biocompatibility, chemical stability, and versatility for surface modification [121]. In addition, silica layer could protect nanoparticles in acidic environment and screen the magnetic dipolar attraction between magnetic nanoparticles. Silica-coated magnetic nanoparticles are in general explored for applications, such as targeted drug delivery in the treatment of various diseases and transfection [122]. Silica-covered IONPs can be obtained through three different approaches: Stöber process [123, 124], microemulsion synthesis [125, 126], and aerosol pyrolysis [127]. Stöber process is the most used method consisting in formation of silica *in situ* as a result of hydrolysis and condensation of alkoxysilanes. In most of the experiments reported in literature, the silica coating is formed by adding silane (the most common is tetraethoxysilane [128]) to IONPs dispersed in alcohol, followed by adding ammonia or water to the mixture. The silica shell width can be adjusted by varying the silane concentration [129]. Li et al. [124] synthesized core/multishell type silica-coated IONPs highly uniform in size. These nanoparticles are superparamagnetic and were found to be useful in biomolecule separation. Silica-covered IONPs with the size less than 50 nm and tunable shell (from 5 to 13 nm) were prepared via optimized inverse microemulsion method. The silica layer width was adjusted by varying the precursor concentration and reaction time. In this way, Abbas et al. [126] prepared high quality superparamagnetic core-shell nanoparticles with great potential for medical application.

Gold layer for magnetic nanoparticles functionalization was also explored in biomedicine for applications such as protein separation [127], targeted drug delivery, or magnetic resonance imaging contrast agents [128]. The gold layer can be formed on IONPs by direct or indirect coating [129]. Direct coating of gold onto iron oxide cores (in aqueous or organic phase) can be realized by reducing Au^{3+} with reducing agents (sodium citrate and sodium borohydride).

Indirect gold coating is achieved by using a "glue layer" between the iron oxide core and the gold shell. As for the "glue layer," various materials are used such as poly-L-histidine, poly(cyclotriphosphazene-co-4,4′-sulfonyldiphenol), and polyethyleneimine [129].

7. Conclusion

The preparation of iron oxide nanoparticles (IONPs) with well-controlled structure, size, and shape is very actual and of high importance, especially for biomedical applications. The use of coordination compounds as precursors for IONPs proved to be a reliable approach, ensuring improved control of the structure and composition. Several synthetic methods can be applied to transform iron complexes into nanoparticles, such as thermal decomposition, solvothermal, microwave irradiation, ultrasonication, or calcination. Biocompatible and hydrophilic coatings ensure dispersion of the IONPs in water, for biomedical use. This can be achieved by direct methods or by postsynthetic procedures. Depending on their size, coating, magnetic properties, etc., IONPs have found numerous applications in health care, such as antimicrobial agents, magnetic hyperthermia, targeted drug delivery, magnetic resonance imaging (MRI), tissue engineering, and biosensors.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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