

Synthesis, characterization, applications, and challenges of iron oxide nanoparticles

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Abstract: Recently, iron oxide nanoparticles (NPs) have attracted much consideration due to their unique properties, such as superparamagnetism, surface-to-volume ratio, greater surface area, and easy separation methodology. Various physical, chemical, and biological methods have been adopted to synthesize magnetic NPs with suitable surface chemistry. This review summarizes the methods for the preparation of iron oxide NPs, size and morphology control, and magnetic properties with recent bioengineering, commercial, and industrial applications. Iron oxides exhibit great potential in the fields of life sciences such as biomedicine, agriculture, and environment. Nontoxic conduct and biocompatible applications of magnetic NPs can be enriched further by special surface coating with organic or inorganic molecules, including surfactants, drugs, proteins, starches, enzymes, antibodies, nucleotides, nonionic detergents, and polyelectrolytes. Magnetic NPs can also be directed to an organ, tissue, or tumor using an external magnetic field for hyperthermic treatment of patients. Keeping in mind the current interest in iron NPs, this review is designed to report recent information from synthesis to characterization, and applications of iron NPs.

Keywords: superparamagnetism, iron oxide nanoparticles, surfactants, hyperthermia, biodistribution, bioelimination

Introduction

Nanoparticles (NPs) are at the forefront of rapid development in nanotechnology. Their exclusive size-dependent properties make these materials indispensable and superior in many areas of human activities.¹ Being the most current transition metal in the Earth's crust, iron stands as the backbone of current infrastructure.² However, in comparison to group elements such as cobalt, nickel, gold, and platinum, iron oxides are somewhat neglected.² Iron and oxygen chemically combine to form iron oxides (compounds), and there are ~16 identified iron oxides. In nature, iron(III) oxide is found in the form of rust.³ Generally, iron oxides are prevalent, widely used as they are inexpensive, and play an imperative role in many biological and geological processes. They are also extensively used by humans, eg, as iron ores in thermite, catalysts, durable pigments (coatings, paints, and colored concretes), and hemoglobin.⁴ The three most common forms of iron oxides in nature are magnetite (Fe_3O_4), maghemite ($\gamma\text{-Fe}_2\text{O}_3$), and hematite ($\alpha\text{-Fe}_2\text{O}_3$). These oxides are also very important in the field of scientific technology and are therefore the subject of this review.⁵ NPs composed of ferromagnetic materials and with size <10–20 nm exhibit an inimitable form of magnetism, ie, superparamagnetism. The ferromag-

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netic materials include elemental metals, alloys, oxides, and other chemical compounds that are magnetized by an external magnetic field. This is an important phenomena normally present only in NP systems.^{2,6} Due to their low toxicity, superparamagnetic properties, such as surface area and volume ratio, and simple separation methodology, magnetic iron oxide (Fe_3O_4 and $\gamma\text{-Fe}_2\text{O}_3$) NPs have attracted much attention and are especially interesting in biomedical applications for protein immobilization, such as diagnostic magnetic resonance imaging (MRI), thermal therapy, and drug delivery.⁷ Iron's reactivity is important in macroscopic applications (particularly rusting), but is a dominant concern at the nanoscale.⁸ Finely divided iron is considered pyrophoric. These are the reasons that iron NPs could not capture much attention. The extreme reactivity of iron makes it difficult to study and inconvenient for applications.⁹ However, potent magnetic and catalytic properties have diverted the attention toward iron's potential.² Iron oxide NPs can be easily and promptly induced into magnetic resonance by self-heating, applying the external magnetic field, and also by moving along the field of attraction. Synthetic methods, crystallization, size, shape, and quality of the iron oxide NPs greatly affect these behaviors. It is obvious that these approaches toward the synthesis of well-crystallized and size-controlled iron oxide NPs offer more prospects for these applications.¹⁰

The shapes of nanomaterials (NMs) also exert tremendous impact on their properties, including catalysis.¹¹ Shape change shows crystal facets, and the atomic arrangements in each facet have reflective effects on its properties. The development of protocols for desired morphology, size, and shape is under consideration.¹² Iron oxide NPs have been synthesized using mechanochemical (ie, laser ablation arc discharge, combustion, electrodeposition, and pyrolysis) and chemical (sol-gel synthesis, template-assisted synthesis, reverse micelle, hydrothermal, coprecipitation, etc) methods.¹³ Various shapes of iron oxides (ie, nanorod, porous spheres, nanohusk, nanocubes, distorted cubes, and self-oriented flowers) can be synthesized using nearly matching synthetic protocols, by simply changing the precursor iron salts. These novel protocols are easy to implement, economical, and control shape, in a sustainable manner.¹¹ As well as the synthesis (to produce more compatibility in biosystems, proper functionalization, and molecular conjugation), surface modification of iron oxide is very important. In order to avoid chemical corrosion induced by instability, surface modification is the key post-synthesis step to produce iron NPs that are both biocompatible and

stable. There are some other changes that may be applied as well and can result in additional physical and chemical properties onto iron oxide NPs.¹³

Currently, there is an increase in interest in ex vivo synthesis of NPs for diverse purposes, such as medical treatments, branches of industry production, and wide incorporation into diverse materials, such as cosmetics or clothing.¹⁴ NPs have a high surface-to-volume ratio that increases reactivity and possible biochemical activities.¹⁵ However, the interaction mechanism at the molecular level between NPs and biological systems is largely unknown.⁹ However, a thorough understanding of the role of nanosized engineered materials on plant physiology at the molecular level is still lacking.¹⁶ Plants, under certain conditions, are capable of producing natural mineralized NMs necessary for their growth.¹⁷ Nano- TiO_2 treatment, at proper concentration, accelerates the germination of aged seeds of spinach and wheat in comparison to bulk TiO_2 .^{18,19} Similarly, carbon nanotubes improve seed germination and root growth by penetrating thick seed coats and supporting water uptake. The effect of NPs on plants varies from plant to plant and species to species.¹⁶ In view of the acclaimed reports on the use of nanotechnology as an emerging discipline in almost all fields of technology, it is important to understand the course of germination in relation to NPs. Recent advances in nanotechnology and its use in the field of agriculture are increasing astonishingly; therefore, it is tempting to understand the role of NPs in the germination and growth of seeds.¹⁴ Dispersing of iron NPs upon mercury is considered one of the earliest convenient methods for producing well-defined iron NPs. Some methods have also been successfully used for organic-solvent-based procedures.²⁰ However, later mercury-based methods were replaced with organic-solvent-based methods. This change has been due to the toxic nature of mercury vapors, the low solubility of iron in mercury, and the comparative ease of removing organic solvents.² In the current era, ultrafine magnetic iron oxide particles are obtained using complex structures or organized assemblies.²¹ Various saturated and unsaturated fatty acids as primary and secondary surfactants, are also used to prepare stable aqueous magnetic suspensions.⁹

Methods for the preparation of iron NPs

Iron oxide magnetic NPs with appropriate surface chemistry are prepared by various methods (Figure 1), such as wet chemical, dry processes, or microbiological techniques.^{2,7} A detailed comparison of synthesis methods is given in Table 1, aiming to help researchers who are occupied in this field to

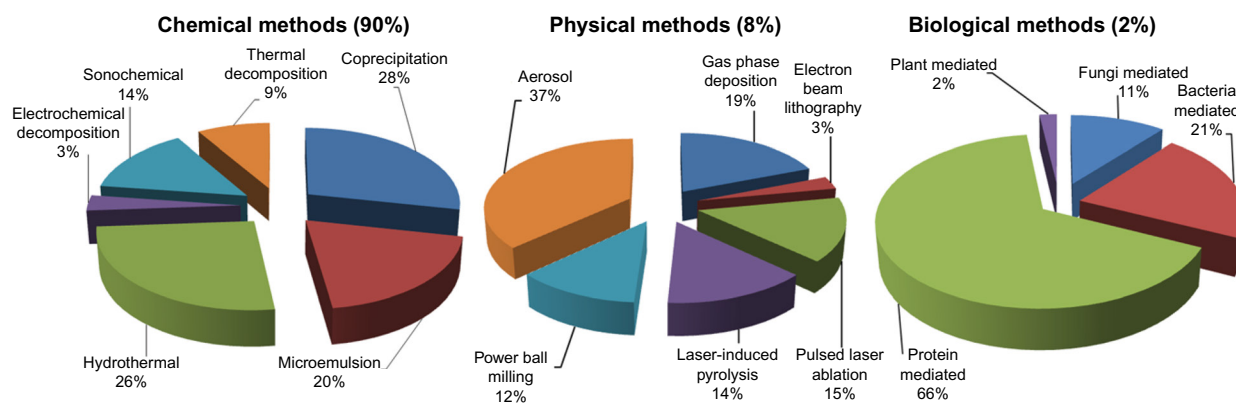


Figure 1 A comparison of the synthesis of SPIONs by three different routes.

Abbreviations: NPs, nanoparticles; SPIONs, superparamagnetic iron oxide NPs.

Table 1 Iron NP synthesis techniques and their comparison with respect to their product morphology, advantages, and disadvantages

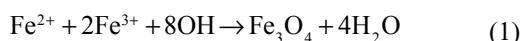
S #	Techniques	Product morphology	Advantages	Disadvantages	References	
1	Physical	Deposition of gas phase	Spheres and irregular spheres	Easy to execute	Problematic in controlling the size of particle	22
		Electron beam lithography	Spheres and rods	Well-controlled interparticle spacing	Requires expensive and highly complex machines	30
2	Chemical	Sol-gel method	Spheres, irregular spheres, porous and nonporous spheres, or spindles	Aspect ratio, precisely controlled in size, and internal structure	High permeability, weak bonding, low wear resistance	4
		Oxidation	Irregular elongated and small spheres	Narrow size distribution and uniform size	Ferrite colloids of small size	31, 32
		Chemical coprecipitation	Spheres	Simple and effective	Inappropriate for the synthesis of high untainted, precise stoichiometric phase	24, 28
		Hydrothermal	Elongated, compact irregular spheres, and numerous shapes	Particle size and shapes are easily controllable	High pressure and reaction temperature	23
		Flow injection	Small rods, irregular spheres, sheets, or rhombic shapes	Homogeneity with high mixing with a accurate control of the procedure and good reproducibility	Under a laminar flow regime in a capillary reactor, it requires continuous or segmented mixing of reagents	33
		Electrochemical	Spherical NPs, nanorods, hexagonal nanocrystals, and facets	Controllable particle size	Inability to reproduce	4
		Aerosol/vapor phase	Mesoporous single crystals and small particles, octahedral cages	Large-scale products	Requires very high temperatures	34
		Sonochemical decomposition	Bipyramids, spheres, or truncated rods	Size distribution in narrow particle	Still, mechanism is not well understood	35
3	Biological	Supercritical fluid method	Mesoporous single crystals, elongated irregular nanotubes	No organic solvents involved and efficient control of the particle size	Requires high temperatures and critical pressure	5
		Using nanoreactors	Spheres, hollow and spherical NPs	Likelihood to specifically control the size of NPs	Complicated conditions	36
3	Biological	Microbial incubation	Small platelets, spherical or rod-like spheres, irregular spheres	Good reproducibility and scalability, high yield, and low cost	Slow and laborious	25

Abbreviations: NPs, nanoparticles; S #, serial number.

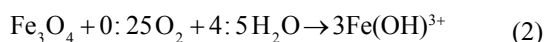
choose appropriate suitable synthesis methods. Briefly, iron NPs can be synthesized by the following three methods:

1. Physical methods: these are elaborate procedures which suffer from the inability to control the size of particles²² in the nanometer range.
2. Chemical preparation methods: these methods are simple, tractable, and efficient, in which the size, composition, and even the shape of the NPs can be managed.²³ Iron oxides can be synthesized through the coprecipitation of Fe²⁺ and Fe³⁺ by the addition of a base.²⁴ The size, shape, and composition of iron NPs synthesized through chemical methods depend on the type of salt used, Fe²⁺ and Fe³⁺ ratio, pH, and ionic strength.⁴
3. Biological methods.²⁵

Among these methodologies, chemical-based synthesis methods are mostly adopted due to low production cost and high yield. In general, magnetites are synthesized by adding a base to an aqueous mixture of Fe²⁺ and Fe³⁺ chloride at 1:2 molar ratio, resulting in black color.¹⁰ The chemical reaction of Fe₃O₄ precipitation is given in Equations 1 and 2. The overall reaction is written as follows:²⁶



Under oxygen-free environment, a complete precipitation of Fe₃O₄ is likely between pH 9 and 14, maintaining a molar ratio of Fe³⁺:Fe²⁺ (2:1). Fe₃O₄ might also be oxidized as:



The physical and chemical properties of NPs may vary depending upon the conditions. To prevent iron NPs from oxidation and agglomeration, Fe₃O₄ NPs⁴ are usually coated with organic or inorganic molecules. However, it is a prerequisite to synthesize magnetic NPs in oxygen-free environment, most preferably in the presence of N₂ gas. Bubbling nitrogen gas not only protects NP oxidation but also reduces the size.^{26,27}

Each method described earlier has its own advantages and disadvantages (Table 1). Although physical methods are easy to perform, controlling the particle size is difficult. While in wet chemical preparation, particle size can be somewhat controlled by adjusting the conditions. The chemical methods include electrochemical method, sol–gel method, supercritical fluid method, hydrothermal method, chemical coprecipitation, sonochemical decomposition method, flow injection method, and nanoreactors. However, in all these techniques, aqueous medium is a most

efficient pathway to obtain iron magnetic NPs. It has been demonstrated the particle size as well as the polydispersity of the NPs could be tailored by changing the associated factors such as Fe²⁺/Fe³⁺ ratio,^{24,28} base (NaOH, ammonium hydroxide, and CH₃NH₂), and ionic strength (N(CH₃)₄⁺, CH₃NH₃⁺, NH₄⁺, Na⁺, Li⁺, and K⁺).⁴ Some other factors also influence on the size of the NPs,²⁹ eg, an increase in mixing rate, temperature, inlet of nitrogen gas, agitation, pH, and reactants ratio. On the other hand, microbial methods ensure low cost, reproducibility, high yield, and scalability, but are time-consuming.²⁵

Brief techniques for the synthesis of magnetic NPs

Several synthesis routes to achieve shape, size, crystallinity, dispersity, and magnetic behavior have been developed.⁷ Some of them are discussed in Figure 1. The three most important published routes or procedures for the synthesis of iron oxide magnetic NPs are represented in Figure 1.

Liquid phase methods

These methods are simple and allow the preparation of magnetic NPs with rigorous control of size and shape. Homogeneous precipitation reactions are used to synthesize uniform sizes that involve the separation of the nucleation and growth of the nuclei.²⁴ One of the classic models for synthesis is proposed by LaMer and Dinegar³⁷ in which the nuclei are allowed to slowly diffuse, resulting in growth, until the final size is attained. In order to attain monodispersity, nucleation should be avoided during the period of growth.^{7,37}

Coprecipitation from aqueous solutions is one of the most frequently used methods. The reaction of Fe(II) salt, in aqueous solution, to a base in the presence of mild oxidant synthesizes spherical NP of 30–100 nm.^{24,28} The factors on which the phase and size of the particles depend are the concentration of cations, the presence of counter ions, and pH of the solution. Change in pH and ionic strength play a vital role in controlling the mean size of the particles (from 15 nm to 2 nm).³⁸ NPs usually aggregate because of large surface-area-to-volume ratio and to reduce surface energy.³⁹ The anionic surfactants as dispersing agents are added to stabilize them.⁴⁰ The stabilization can also be achieved by coating the surface with proteins,⁴¹ starches, nonionic detergents, or polyelectrolytes⁷ as the adsorption of such substances stabilizes the electrolyte concentrations of particles that would otherwise be high enough.^{6,42} The first controlled preparation using alkaline precipitation of FeCl₃ and FeCl₂ of superparamagnetic iron oxide particles was performed by Massart.⁴³ Originally, synthesized

magnetite (Fe_3O_4) particles were roughly spherical, and their diameter measured by X-ray diffraction analysis was 8 nm.⁴⁴ The parameters of this methodology demonstrate the influence of base (ammonia, CH_3NH_2 , and NaOH), pH, added cations ($\text{N}(\text{CH}_3)^4+$, K^+ , CH_3NH_3^+ , Li^+ , Na^+ , and NH_4^+), and $\text{Fe}_3^+/\text{Fe}_2^+$ ratio on the yield of this reaction and the diameter and polydispersity of the synthesized NPs. After the modulation of the studied parameters, it is possible to obtain particles with a size ranging from 16.6 nm to 4.2 nm.^{7,28}

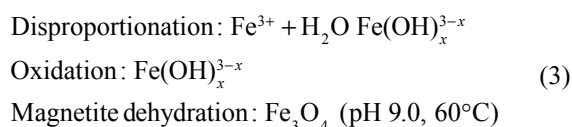
Two-phase methods (microemulsion)

Water-in-oil microemulsion consists of nanosized water droplets dispersed in oil phase which are stabilized by surfactant molecules.⁴⁵ The nanocavities lemmatize particle growth, nucleation, and agglomeration.⁴⁶ The diversity of NPs due to surfactant, nature, physiological conditions, etc, is the main advantage of this technology.⁴⁷ For the synthesis of magnetite NPs, nanoemulsion containing iron source and sodium hydroxide are mixed together, later lysed with acetone to remove the surfactant and washed with ethanol. Normally, the colloidal NPs exhibit superparamagnetic behavior with high magnetization values.^{6,7,31}

There are several dissolved components in water and oil phase; therefore, the selection of the surfactant (and cosurfactant) depends upon the physicochemical characteristics of the system. Different surfactants, such as cationic, anionic, or nonionic, can be used. The main disadvantage associated with this method is adverse effects of residual surfactants on the properties and difficulty in scale-up procedures.^{48,49}

Sol-gel method

This method revolves around hydroxylation and condensation of molecular precursors in solution. Obtained “sol” from nanometric particles is then dried or “gelled” either by solvent removal or by chemical reaction to obtain three-dimensional metal oxide network. The solvent used is water, but the precursors can be hydrolyzed using an acid or a base. Basic catalysis yields a colloidal gel, whereas acid catalysis formulates a polymeric gel.⁵⁰ The reaction is performed at room temperature; however, heat treatment is required to obtain the final crystalline state.⁵¹ Equation 3 shows the reaction mechanism of magnetite particle formation from an aqueous iron(III) solution by sol-gel system.



The parameters influencing synthesis are pH, nature, and concentration of salt precursor, kinetics, temperature, agitation, and properties of gel.⁵² Magnetic ordering in this procedure depends on the volume and phase of solvent but is sensitive to dispersion and size distribution.⁴⁵ The associated advantages include synthesis of materials with a predetermined structure, pure amorphous phase, monodispersity, good control of particle size, control of microstructure, homogeneity of the products, and chances to generate embed molecules, which maintain their stability and properties within the matrix.⁷ It is an easy method for the production of metal oxides from salts at specific conditions.

Iron oxide-silica aerogel composites are also prepared using this method⁵³ and are found more reactive than conventional iron oxide. Commercial precursors (tetraethyl orthosilicate and $\text{Fe}(\text{III})$ solutions) are dissolved in an alcoholic aqueous medium, and the gels formed are heated to generate the final materials.⁴⁵ The increased reactivity is recognized by large surface area of iron oxide NPs.⁸

Gas/aerosol phase methods

For continuous, high, and direct production of defined magnetic NPs, spray and laser pyrolysis is an efficient technique.⁵⁴ A solution of ferric salts is sprayed into the reactor in the presence of reducing agent. The solute condenses while the solvent evaporates.⁵⁵ Later, the dried residue consisting of particles is obtained, whose size is same as the original. Maghemite particles from 5 nm to 60 nm with diverse shapes have been generated using different iron precursors.⁴⁵

Laser pyrolysis of organometallic precursors⁵⁶ depends on the resonant interaction, reactant, and/or sensitizer; however, one should be in gaseous phase. A sensitizer is excited by the combination of CO_2 laser radiation that transfers energy absorbed to the reactants.⁵⁷ The energy is provided by heating the mixture of gases with CO_2 laser. The chemical reaction continues until the threshold level of nuclei is attained, finally the nucleation of particles occurs.⁴⁹ The nucleated particles produced during the reaction are entrained by the gas stream and are gathered at the exit.⁵⁸ Hasany et al⁵⁴ studied the production of iron oxide by using gas phase, laminar diffusion flame methodology for the synthesis of reduced iron oxide NPs. Gas/aerosol method usually produces high-quality products, although the yield is low. Pure product can be further obtained by decreasing gas impurities and controlling the time of heating and gas concentrations. The drawback of these methodologies is the expense associated with them.⁷

Polyols method

Polyols method is a significant technique for the preparation of well-defined NPs with controlled shape and size.⁵⁹ After controlling the kinetics of the precipitation, non-agglomerated metal particles with well-defined shape and size can be obtained. The average size of the metal particles is controlled by reactive medium, heterogeneous nucleation. The synthesis steps are independent of resulting uniform particle size. Iron NPs of 100 nm can be obtained by ferrous hydroxide in organic media.⁶⁰ The solvents used, such as polyols and polyethylene glycol, offer interesting properties due to their high dielectric constants. These solvents can dissolve inorganic compounds, and due to their relatively high boiling points they offer a wide operating temperature range (from 25°C to the boiling point).⁶¹ Polyols function as both reducing and stabilizing agents to control particle growth. These also prevent the aggregation of NPs.⁶¹ Type of polyols, salt ratio, concentration, and other physiological conditions affect growth, shape, size, and yield of the particles. The yield and size of Fe particles are found to be dependent upon the reduction potential of the polyols.

Hydrothermal reaction methods

The hydrothermal reactions are performed in a reactor or autoclave in an aqueous media, where the pressure of >2,000 psi and temperature of >200°C are maintained. The dehydration of metal salts and low solubility of oxides in aqueous phase supersaturate the medium.⁶² A thorough investigation has been performed by Hao and Teja⁶² to study the effects of temperature, precursor, and the time on morphology and particle size. The precursor concentration increases the particle size, while residence time has more effect than concentration. Monodispersed particles usually produce at short residence times.⁶³ The effect of changing the precursor (eg, ferric nitrate) concentration (with all other variables kept constant) is studied in various experiments, and the transmission electron microscopy (TEM) images of particles obtained were found to be spherical with an average particle radius of 15.6 ± 4.0 nm. A few larger rhombic particles with an average particle size of 27.4 ± 7.0 nm were also observed in some experiments (changing precursor concentration). However, the particles were mostly rhombic, and there were few smaller spherical particles.⁷

Sonolysis

Iron oxide can be synthesized by the decomposition/sonolysis of organometallic precursors. Polymers, organic capping agents, or structural hosts are used to limit the growth of the NPs.⁶⁴ Figure 2 represents the general steps of the synthesis

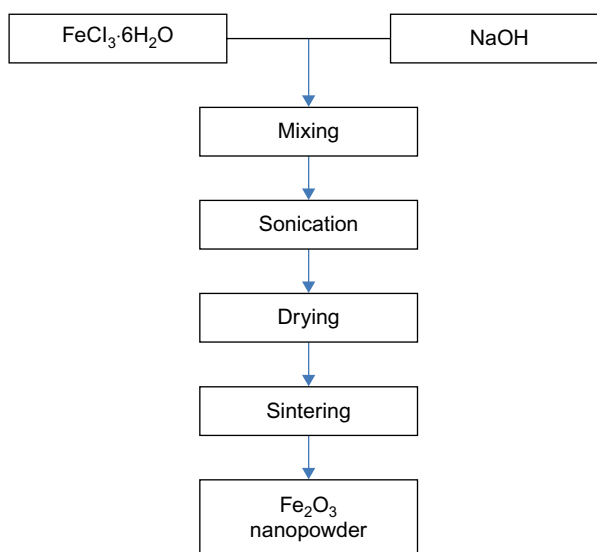


Figure 2 Flowchart of sonochemical synthesis of iron oxide.
Note: Data from a previous study.⁶⁵

of iron oxide using sonolysis technique. Ultrasonic irradiation mainly causes cavitation in an aqueous medium, where the formation, growth, and collapse of microbubbles occur.⁶⁵ Cavitation can create a temperature of around 5,000°C and a pressure of >1,800 KPa, which facilitates many unusual chemical reactions.⁶⁶ Thermal induction mainly offers crystalline NPs, while ultrasonic induction yields amorphous NPs.⁶⁷ Pinkas et al⁶⁷ studied the sonochemical synthesis of 3 nm-sized yttrium iron oxide NPs. Globular agglomerates, analyzed by scanning electron microscopy (SEM) and TEM, confirmed that they were embedded in an acetate matrix. However, stoichiometry can be achieved by Y and Fe molar ratio as starting materials.⁷

Microwave irradiation

Microwave chemistry has gained much attention in recent years, as it has been used in preparative chemistry and material synthesis since 1986.⁶⁸ The shorter crystallization time and homogeneous nucleation due to uniform heat of microwave oven are major disadvantages of this system. Kijima et al⁶⁸ reported that the synthesis of ultrafine α -Fe₂O₃ NPs with an extremely narrow distribution by microwave heating resulted in significantly high electrochemical performance due to uniformity and size.⁶⁹ Most primary particles had ellipsoid shapes and were connected to each other. The average diameter of these primary particles was <10 nm with single crystals confined by electron diffraction pattern. Parsons et al⁶⁹ also reported the synthesis of iron oxide/oxyhydroxide NPs by microwave ovens. The controlled growth and structure of NPs are usually due to slow reaction of the reactants (iron salt and sodium hydroxide).

Chemical properties of iron NPs

Iron NPs are extremely reactive with oxidizing agents, particularly with air.² For the complete and permanent protection from oxidizing, each NP is covered with a thin covering that has little or no impact on the magnetic property of NPs, different coating materials are used for this purpose, ie, gold and silica, but these coatings weaken the magnetic properties.²³ Magnesium coating is also used, which has little effect on magnetic properties of iron particles. However, the produced material is not simple; iron nanoparticles are submerged within submicrometer magnesium particles.⁷⁰ The most convenient method for the production of almost fully magnetic iron particles protected from oxidation is the coating of iron carbide; however, the resulting particles are greater in size (20–100 nm), polydisperse, and ferromagnetic, so are not ideal. Even so, this represents real progress.⁷¹ Air-stable cobalt NPs are synthesized by the decomposition of cobalt carbonyl in the presence of aluminum alkyls. Iron carbonyl synthesized in same manner produced meaningful results.² Iron oxide NMs have great importance because of their magnetic properties and wide applications. The correlation among numerous characteristic features of magnetic NPs prepared through different approaches is shown in Table 2.

The investigation of iron and iron oxide NPs in biological and material sciences is booming in recent times because of their various chemical and physical properties. They exhibit multiple potential applications, including magnetic fluid, magnetic micro-device, MRI, magnetic hyperthermia, water purification, and drug delivery.^{27,72–74} Significant size-dependent structural and optical properties of colloidal iron and iron oxide NPs correspond to electrical structure and

quantum size effects of NPs. The respective synthesis method can affect their size and crystal structure as well.⁷⁵

Iron NPs display dual characteristics of zerovalent iron (reduction) and iron hydroxides (complex formation). A number of studies in the field of magnetic NPs have been carried out on various types of iron and iron oxides (typically Fe₃O₄ magnetite, Fe⁺² Fe⁺³ O₄, ferrimagnetic, superparamagnetic <15 nm): a-Fe₂O₃ (hematite, weakly ferromagnetic, or antiferromagnetic), c-Fe₂O₃ (maghemite, ferrimagnetic), FeO (antiferromagnetic), e-Fe₂O₃, and b-Fe₂O₃.^{6,42} Among those, magnetite and maghemite are well known and promising candidates since their biocompatibility has been proven.²³ During the synthesis, the simultaneity of Fe₃O₄ and γ-Fe₂O₃ can be attributed to the oxidation of magnetite to maghemite. Both NPs are single crystalline in structure, and each is made of a magnetic domain. Consequently, they show the superparamagnetic behavior and only retain magnetic moment in the presence of an external magnetic field. On detaching magnetic field, these NPs will immediately return to their nonmagnetic states.⁷⁶ After the synthesis, iron NPs rapidly form layers of iron oxide at their surface. These layers do not necessarily penetrate the whole particle; therefore, the NP itself may disparately be a core-shell structure to a pure iron NP.⁷⁷ Under ambient conditions, Fe₃O₄ NPs are not very stable and can easily be oxidized to Fe₂O₃ or dissolve in an acidic medium. Therefore, to avoid possible oxidation in the air, preparation must be performed in an anaerobic condition. Based on oxidation, Fe₃O₄ NPs can be used to synthesize Fe₂O₃ NPs (under oxygen atmosphere or annealing treatment). Because of the chemical stability in acidic

Table 2 Fabrication of iron oxide NPs: comparison of different methods

Characteristics of the iron oxide	Synthesis methods of iron oxide NPs				
	Aerosol/vapor (pyrolysis) method	Gas deposition method	Bulk solution method	Sol-gel method	Microemulsion method
Size and size distribution	Approximately 5–60 nm with broad distribution	Approximately 5–50 nm with narrow size distribution	10–50 nm	20–200 nm	4–15 nm
Morphology	Spherical	Spherical	Spherical	Spherical	Cubic or spherical
Magnetization values	10–50 emu/g with desired magnetic property	>20 emu/g	20–50 emu/g with superparamagnetic behavior	10–40 emu/g with paramagnetic behavior	>30 emu/g with superparamagnetic behavior
Advantages	High production rate	Useful for protective coatings and thin film deposition	Synthesis in bulk	Desired shape and length and hybrid NPs	Uniform properties
Disadvantages	Large aggregates are formed	Requires very high temperatures	Uncontrolled oxidation of magnetite to maghemite, diamagnetic contribution	Product contains sol-gel matrix components	Surfactants are difficult to remove; small amount can be synthesized

Abbreviation: NPs, nanoparticles.

or alkaline environment, oxidation does not influence Fe₂O₃ NPs. Chemically, the bare iron or iron oxide NPs are very active and can easily be oxidized in air (especially magnetite), generally resulting in the loss of dispersibility and magnetism. Thus, it is important to keep the stability of magnetic iron oxide NPs by developing some effective protection strategies and providing proper surface coating (or grafting) with organic molecules, polymers, surfactants, biomolecules, or inorganic layer such as silica, metal, metal sulfide, metal oxide, or nonmetal elementary substances.²³

Surface coatings of NPs

Iron oxides with bare surface tend to agglomerate due to strong magnetic attraction among particles, van der Waals forces, and high energy surface.⁷⁸ Consequently, the reticuloendothelial system eliminates the agglomerated iron oxide NPs.⁷⁹ High concentration of local Fe ions is also toxic to organisms from Fe dissolution.⁸⁰ These can be avoided by coating a shell on the iron oxide NP surface which makes them hydrophilic, compatible to bioenvironments, and functionalized.¹³ The appropriate surface coating allows a targetable delivery with particle localization in a specific area and is also considered nontoxic and biocompatible. So far, most work has been carried out to improve the biocompatibility of this material, but regarding the improvement in the quality of magnetic particles, their size distribution, shape, and surface, very few scientific investigations and developments have been carried out. The nature of surface coating of NPs and geometric arrangement not only determines the overall size of the colloid but also plays a significant role in biokinetics and biodistribution of NPs in the body.^{31,81} For NPs the types of coating or derivatization depends on the application, and is aimed at either inflammation response or anticancer agents. Drugs, proteins, enzymes, antibodies, or nucleotides can bind to magnetic NPs and can be adsorbed at a specific site using magnetic field, or can be heated in alternating magnetic fields for use in hyperthermia.⁹ The synthesis of iron oxide NPs coated with biological molecules, eg,

gluconic acid, lactobionic acid, or polyacrylic acid, through the most effective method of coprecipitation as compared to organic solvent heating method and/or polyol method are reported in the literature.^{28,82} NPs of such types have narrow size distribution and are highly water soluble. They have great potential in numerous biomedical applications such as tissue engineering because of the biological coatings such as liposome coating.^{27,31,48} Due to hydrogen bond formation, these NPs also show hydrodynamic size in solution.⁸³

Magnetic iron oxide particles have hydrophobic surfaces with a large surface-area-to-volume ratio in the absence of any surface coating material. These particles agglomerate and form large clusters due to hydrophobic interactions between the particles, resulting in increased particle size. These clusters then exhibit strong magnetic dipole–dipole attractions between them and show ferromagnetic behavior.⁸⁴ Each of them comes into the magnetic field of the neighbor when two large-particle clusters approach one another. In addition to arousal of attractive forces between the particles, each particle is in the magnetic field of the neighbor and receives further magnetization.⁸⁵ Mutual magnetization takes place due to adherence of remnant magnetic particles which results in the increased aggregation properties.⁹ Since particles are attracted magnetically, in addition to the usual flocculation due to van der Waals forces, surface modification is often indispensable. A high density coating is often desirable in order to stabilize the iron oxide NPs. To prevent the aggregation of the nanoscale particulate stabilizer, a surfactant or a polymer is usually added at the time of preparation. Most of these polymers adhere to surfaces in a substrate-specific manner.⁸⁶ Table 3 shows different surface modifications and strategies for the fabrication of magnetic iron oxide NPs.^{9,87}

Materials with polymeric coating can be classified as synthetic or natural. Examples of distinctive synthetic polymeric systems are: polyethylene glycol, poly(vinyl alcohol), poly(lactic-*co*-glycolic acid), poly(vinyl-pyrrolidone), poly(ethylene-*co*-vinyl acetate), etc.⁴ Natural polymer systems

Table 3 Different approaches for the preparation and surface modification of magnetic iron oxide NPs

Diameter (nm)	Approaches for the preparation and surface modification of magnetic iron oxide NPs
1–20	Precipitation of magnetic iron oxide NPs in either solution or aqueous core of water in oil microemulsions. Oxygen-free and lower temperature environment provide the SPIONs with high magnetization values
20–30 (up to 50)	Precipitation of magnetic iron oxide NPs in the presence of polymers or surfactants. NPs obtained are monodispersed and fairly stable in solution
50–100	Surface coating of magnetic iron oxide NPs with surfactants or polymers (core–shell structure). Ferrofluids obtained are stable under in vivo and in vitro conditions, and also the particles could be derivatized with bioactive molecules

Note: Inside the aqueous droplets of reverse micelles, uniform and ultrasmall NPs can be fabricated

Abbreviations: NPs, nanoparticles; SPIONs, superparamagnetic iron oxide NPs.

include the use of gelatin, pollutant, dextran chitosan, etc.^{88,89} In order to enhance dispersibility in an aqueous medium, various surfactants, such as sodium oleate, dodecylamine, and sodium carboxymethyl cellulose, are usually used.⁹⁰ But, one should be careful about choosing the coating materials for the NPs. Table 4 shows the various summarized coating methods and materials. Some coating techniques are designed for protecting iron oxide cores from corrosion, and some are designed with additional chemical and physical functions for specific applications.^{13,31}

According to the properties of magnetic NP cores, the experimental conditions vary from each other, eg, size, solubility, and surface chemistry. Several coating methods are considered for protecting iron oxide cores from corrosion, and some are premeditated with additional physical and chemical functions for their precise applications. Various typical coating techniques and materials to protect iron oxide cores from corrosion are summarized in Table 5. Table 5 also portrays some chemical and physical functions for the specific applications.³¹

Characterization of magnetic NPs

For a better understanding of surface properties, comprehensive surface characterization techniques are used such as surface morphology, chemical composition, and spatial distribution of the functional groups.¹⁰² Fundamental techniques employed to investigate magnetic NPs include: X-ray diffraction analysis, Fourier transform infrared spectroscopy, TEM, SEM, atomic force microscopy, X-ray photoelectron spectroscopy, vibrating sample magnetometry, and thermal gravimetric analysis.¹⁰ Other characterization techniques include ion-particle

probe, thermodynamic, NP tracking analysis, tilted laser microscopy, zeta-potential measurements, isopycnic centrifugation, hydrophobic interaction chromatography, field-flow fractionation, electrophoresis, and turbidimetry.^{103,104} Detailed properties, successfulness, and restrictions of each technique are summarized in Table 6.

Factors enhancing the efficiency of iron oxide NPs

- The most effective, cheap, and simplest pathway (technique) to obtain magnetic particles, eg, the simplest one is the precipitation technique to obtain iron oxide particles.¹⁰⁵
- Cost-effectiveness of iron NP preparation technique (depends on the final product and its application), relatively higher cost of production is tolerable, eg, for high end use such as in drug delivery systems; however, it is necessary to use low-cost chemicals during the synthesis of a product that may be utilized in a less-sensitive exertion, eg, waste water mitigation from toxic ions.¹⁰⁵
- Size of NPs, ie, small size gives a high surface-area-to-volume ratio that enables interaction with various types of chemical species, both aqueous and gaseous.¹⁰⁶ The materials at nanoscale are potentially highly efficient for binding metal ions.
- Controlled shape, nucleation, growth, durability, reproducibility, scalability, dispersibility (particularly for building complex magnetic nanostructures).^{7,37,105,107} For example, the activation of iron oxide by changing its particle shape to expose its most active catalytic site could produce efficient and cheap catalysts for several reactions.

Table 4 Different coating molecules/polymers for magnetic NPs to stabilize ferrofluids

Molecules/polymers	Benefits	References
PEG	Improves biocompatibility by noncovalent immobilization of PEG on the surface, internalization efficiency of the NPs, and blood circulation time	91
Dextran	Stabilizes the colloidal solution and increases the blood circulation time	92
PVP	Stabilizes the colloidal solution and enhances the blood circulation time	93
Fatty acids	Terminal functional carboxyl groups and colloidal stability	94
PVA	Gives rise to monodisperse particles and prevents coagulation of particles	95
Polyacrylic acid	Improves biocompatibility of the particles, also helps in bioadhesion, and increases the stability	96
Polypeptides	Worthy for cytology, such as targeting to cell	97
Phosphorylcholine	Coagulation activating and colloidal solution stabilizer	98
Poly(d, l-lactide)	Low cytotoxicity and biocompatible	48, 99
PolyNIPAAm	Cell separation and drug delivery	72
Chitosan	A widely used natural cationic linear polymer as nonviral gene delivery system, is biocompatible, used in medicine and food, applied in water treatment, polymers, textiles, biotechnology, hydrophilic, and used in agriculture	88, 100
Gelatin	Biocompatible, natural polymer, emulsifier hydrophilic, and used as a gelling agent	101

Abbreviation: NPs, nanoparticles; PEG, polyethylene glycol; polyNIPAAm, poly(N-isopropylacrylamide); PVA, polyvinyl alcohol; PVP, polyvinyl pyrrolidone.

Table 5 Summarization of various typical coating techniques and materials to protect iron oxide cores from corrosion

S #	Coating material	Synthesizing procedure	Experimental conditions	Application/ purpose	Core-shell form of FeO NPs	Advantages
1.	Gold and/or silver	By reducing Au or Ag precursor in the presence of iron oxide NPs	Differ according to the properties of iron oxide NP cores, such as the solubility, surface chemistry, and size	Protect iron oxide NPs from low pH corrosion	Fe ₃ O ₄ /Au and/or Fe ₃ O ₄ /Au/Ag	Provide additional optical properties. Facilitate organic conjugation by Gold–silver chemistry
2.	SiO ₂	By alkaline hydrolysis of TEOS in the presence of core NPs	Changing reaction conditions to either porous or dense	Colloid surface modification	Fe ₃ O ₄ /SiO ₂	Compatible with many chemicals and molecules for bioconjugations. Small molecules such as dye and drug, and even quantum dots can be incorporated. Covalently attaches to various ligands and biomolecules to target organs via antibody–antigen recognition. Stable and can be easily dispersed in an aqueous or organic solution, even without surfactants
3.	TaO _x	By thermal decomposition of iron oleate precursor and fast hydrolysis of TaO _x	In a mixture of Igepal CO-520, NaOH, and other organic solvents	Clinical applications. CT for imaging newly formed blood vessels in the tumors, while MRI detects tumor microenvironment	Fe ₃ O ₄ /TaO _x	Low-cost CT contrast agent. Bifunctional agent for CT and MRI. Potential for accurate diagnosis of cancer
4.	Polymer (both natural and synthetic)	By polymerization of precursors in the presence of iron oxide NPs	Similar to the hydrolysis synthesis of silica-coated Fe ₃ O ₄ NPs	To enhance dispersibility in an aqueous medium	Fe ₃ O ₄ and CdSe/ZnS NPs incorporated into the PLGA matrix	Gives a protective and biocompatible organic surface for functionalization
5.	Small molecules	By thermal decomposition of Fe(CO) ₅ . 4-MC employed as surfactants, which could be directly conjugated with a peptide, c(RGDyK), through the Mannich reaction	Oxidation under air	To avoid a large hydrodynamic size	c(RGDyK)–MC–Fe ₃ O ₄	Stable. Target specifically to integrin avb3-rich tumor cells. Enhanced the MRI contrast for tumor cell detection. RGD-coated Fe ₃ O ₄ NPs were found stable in aqueous solution for months
6.	Carbon	Carbonization of hydrocarbon precursors. By a CVD method at 800°C under nitrogen gas protection	High temperature annealing that needs to be lowered to optimize the process	Gives cytotoxicity results	Carbon-coated FeCo and/or Fe ₃ O ₄	Cells can uptake both single NPs and small NP clusters, which affect the evaluation of the cytotoxicity

Note: Also shows some chemical and physical functions for their specific applications.

Abbreviations: CVD, chemical vapor deposition; CT, computed tomography; 4-MC, 4-methylcatechol; MRI, magnetic resonance imaging; NPs, nanoparticles; PLGA, poly(lactic-co-glycolic acid); RGD, arginylglycylaspartic acid; TEOS, tetraethyl orthosilicate; S #, serial number.

- Tailoring the composition of iron oxides, selective adsorption of different metal ions can also be induced. Iron oxide NPs are now considered very attractive for the adsorption or recovery of metal ions from natural water streams or industrial wastes.¹⁰⁸
- High magnetic susceptibility for an effective magnetic enhancement.²³ Further, the diameter of coated (with metallic or nonmetallic) iron oxide NPs is prone to tailoring, and the indispensable diameter can be attained by adjusting reduction and the repeat times.¹⁰⁵
- Characteristics associated with the use of magnetically responsive and magnetically guided NPs in magnetofection and drug delivery.⁷²
- Particles should be nanosized (6–15 nm; particles below 15 nm would consist of a single magnetic field, ie, a particle that is in a state of uniform magnetization and has

Table 6 The analytical techniques for the assessment of the physicochemical properties of NMs

Modalities	Analyzed physical and chemical properties	Successfulness	Restrictions
DLS	Size distribution based on hydrodynamic.	Constructive way for rapid and more consistent measurement. Measures in some liquid media, solvent of interest for monodisperse, hydrodynamic sizes are exactly determined. Moderate expenses on equipment.	With a particular composition, unresponsive correlation of size fractions. Effect of small numbers of large particles in polydisperse sample. Size restrictions. Restricted size determination. Possibility of samples, spherical in shape.
FCS	Dimension, binding kinetics of hydrodynamic.	High temporal and spatial magnification. Uptake sample is low. For studying concentration effect, molecular diffusion, chemical kinetics, and conformation dynamics are specifically performed via fluorescent probes methods.	Due to deficiency of proper methods, it causes limitation in fluorophore species and restriction in usage and inaccuracy.
SERS RS TERS	Size distribution and hydrodynamic size. Conformational variations in structural, chemical, conjugate and electronic characteristics.	No need of sample preparation. Complementary data obtained from IR Capability of detecting tissue abnormality. Improved Raman scattering signal. SERS. Enhanced spatial resolution of the NMs. Topological information.	Compared to Rayleigh scattering, there is comparatively a weak single restricted spatial resolution, enormously minute cross-section. Disturbance of fluorescence irreproducible measurement.
Zeta-potential NSOM	Stability concerning to charge on surface NMs, shapes and size.	Concurrent measurement of numerous particles. Sudden measurement of fluorescence and spectroscopy. Close situation analysis. Nanoscaled surface categorization of chemical information and interactions at nanoscaled declaration.	Electro-osmotic effect deficiency of accurate and repetition measurement. Lengthy scanning time. Analysis of minute sample area. Intensity of incident light is deficient to stimulate delicate fluorescent molecules. Problems in visualization of soft materials. Analysis restriction toward the NM surface.
CD	In biomolecules. Structural and conformational variations (such as DNA and protein). Thermal constancy.	Constructive and motivated methods.	Conformational fluctuations are due to the involvement of nonspecific residue absorption. Methods are more sensitive than this. For nonchiral. Chromophores, CD signals, are weak. For analysis of molecules consisting of multiple chiral chromophores facing challenges.
MS	Molecular weight. Composition. Structure. Surface properties (secondary ion MS).	High accuracy and precision in measurement. High sensitivity to detection (a very small amount of sample required).	Expensive equipment. Lack of complete databases for the identification of molecular species. Limited application to date in studying NM bioconjugates.
IR ATR-FTIR	Bioconjugate. Surface properties such as structure and conformation.	Rapid and cheap measurement. No or minimal sample preparation demands. Irrespective of sample thickness enhanced reproducibility.	Sample preparation (IR) is complex intervention and efficient absorbance of water. In nanoscale analysis sensitivity is comparatively low.
SEM ESEM	Size and size distribution. Shape. Aggregation. Dispersion.	Simultaneous measurement of the size navigation and shape of NMs. High deliration (below to subnanometer) in natural state visualization of biomolecules supplied by the usage of ESEM technique.	Requirement of conducting sample or coating conductive materials. Need of dry samples. In nonphysiological states, the sample analysis occurs. Size distribution is based on biased statistics. Heterogeneous samples are required. Costly apparatus. For numerous NP bioconjugates, cryogenic method is needed. ESEM resolution is reduced.

(Continued)

Table 6 (Continued)

Modalities	Analyzed physical and chemical properties	Successfulness	Restrictions
TEM	Shape heterogeneity. Size and size navigation. Dispersion. Accumulation.	With higher spatial resolution than SEM, direct measurement of the size transportation and shape of NMs occurs. For investigation of chemical composition and electronic structure of NMs. A lot of analytical techniques are paired off with TEM.	Ultrathin samples are needed. Requirement of samples in nonphysiological states. Damage or variations in sample. Sampling is insufficient. Equipment is expensive.
STM	Shape heterogeneity. Size and size navigation. Dispersion. Accumulation.	Sudden measurement at atomic level, high, spatial resolution takes place.	Demand of conductive surfaces. Electronic structure and surface topography inevitably having an easy linkage with surface.
AFM	Shape heterogeneity. Size and size navigation. Dispersion. Accumulation and sorption.	Mapping of 3D sample surface resolution of sub-nanoscaled topographic samples. Direct measurement in dry state, ambient, or aqueous environment.	Lateral dimensions over description. Sampling is poor and time consuming The exterior of NM analysis is generally restricted.
NMR	Indirect analysis of size. Structure purity. Concentration. Conformational variations.	Noninvasive and constructive procedure. Minute or less sample preparation required.	Sensitivity is low. Time wasting. Comparatively large amount of sample needed.
XRD	For crystalline materials, shape, size, and structure determination.	Well-organized modalities. At atomic level, high spatial resolution.	Usage in crystalline materials is reduced. Only one binding or conformation site for sample; accessibility compared to electron diffraction is low.
SAXS	Shape, structure, size, and size transportation.	Constructive procedure sample preparation is very simple. Accessibility of amorphous materials and sample in solution.	Resolution is comparatively low.

Abbreviations: AFM, atomic force microscopy; ATR, attenuated total reflection; CD, circular dichroism; 3D, three dimension; DLS, dynamic light scattering; ESEM, environmental SEM; FCS, fluorescence correlation spectroscopy; FTIR, Fourier transform infrared; IR, infrared; MS, mass spectroscopy; NM, nanomaterial; NMR, nuclear magnetic resonance; NPs, nanoparticles; NSOM, near-field scanning optical microscopy; RS, Raman scattering; SAXS, small-angle X-ray scattering; SEM, scanning electron microscopy; SERS, surface-enhanced Raman scattering; STM, scanning tunneling microscopy; TEM, transmission electron microscopy; TERS, tip-enhanced Raman spectroscopy; XRD, X-ray diffraction analysis.

high saturation magnetization values.¹⁰⁹ These nanosized range particles are rapidly removed through excretion and renal clearance.¹¹⁰

- The property of superparamagnetic crystal suspension to absorb energy of an oscillating magnetic field. This energy can be converted into heat for destroying the pathological tissue or cells (in vivo) by hyperthermia, since the tumor cells are more sensitive to high temperature as compared to healthy ones.¹¹¹
- Tailored surface chemistry for specific biomedical applications.¹¹²
- Development of iron oxide NPs that should be characteristically suitable for optimal cell labeling and efficient MRI. There is a need to formulate standard procedures to control and compare different NPs in terms of cytotoxic effects and uptake efficiency. The effects of iron oxide NPs should be carefully evaluated on cultured cells prior to assessing their clinical potential in cell transplantation research.^{27,48,99,113}

- Yielding efficient and cheap catalysts for various reactions by activating and changing the shapes of magnetic NPs that could expose their most active catalytic site.¹¹⁴
- High coactivity and low Curie temperature.²

Applications of iron oxide NPs

Iron oxide NPs due to their strong magnetic properties were used first in biology and then in medicine for the magnetic separation of biological products and cells as well as magnetic guidance of particle systems for site-specific drug delivery.^{72,115} The surface chemistry, size, and charge of magnetic particles influence biodistribution of the NPs.¹¹ Activities in the clinical applications, in the past decades, of magnetic carriers and particles are increasing due to their role in diagnostics and treatment modalities.⁸³ Magnetic NPs have attracted much interest as a labeling material in life sciences and various other major fields of the scientific world.¹¹⁶ Some well-known fields with the possible applications of magnetic NMs are summarized in Table 7.

Table 7 The main fields where magnetic NMs have been employed

Fields	Applications of magnetic NPs	References
Biomedical	Magnetic NPs (particularly coated with liposomes) for drug delivery, magnetic hyperthermia, MRI contrast agent, magnetic separation, controlled drug release, cellular therapy, eg, cell labeling, tissue repair, cell separation and handling of cells, purifying cell populations, magnetofection, diseases of the musculoskeletal system, severe inflammation, disability, and pain	9, 31, 99, 113
Health care	Therapeutic targets in chemotherapy (cancer and tumor); nanoscale biosensors and imaging; nanocoatings on surfaces; implants; nanocarrier for vaccination; antimicrobial activities; SLN in drug delivery and research; nanophotothermolysis with pulsed lasers for the treatment of cancer, hepatitis B virus, respiratory syncytial virus, influenza virus, antiviral agents against HIV-1, monkeypox virus, herpes simplex virus type 1, and Tacaribe virus; delivering antigens for a particular disease into the blood stream; preventing aging of the skin	9, 15, 27, 105, 117
Agriculture and food	Nano-based products (nanofertilizers, nanofungicides, nanopesticides), engineered NPs, and CNTs boost crop yields; pyrite NPs are used as a seed treatment for various plants prior to sowing the seeds. Broader leaf morphology, larger leaf numbers, increased biomass. Enhanced breakdown of stored starch. This raises the possibility of developing iron pyrite NPs as a commercial seed treatment agent (pro-fertilizer). The strategy is safe, as the process does not put NPs into the soil. Reduced dose requirement as compared to chemical fertilizers. No adverse effects on plant growth. Nanosensors, nanofood, encapsulation, food packing, nanocoatings, precision farming (remote-sensing devices), nanocomposites, gene transfer (crop improvement), and nanoporous membranes	14, 116, 118, 119
Environmental remediation	Pollution prevention (detection, monitoring, and remediation). Waste water treatment (permeable reactive barriers, membrane filtration, adsorption). Catalyst coatings such as palladium (Pd), climate change (carbon capture), artificial leaf for CO ₂ sequestration, mineral carbonation, biomimetic carbonation, N ₂ O decomposition, methane combustion. Improves manufacturing processes (efficiency, waste reduction), dematerialization (reduction in material quantity), sensing (pollutant sensors, nanoporous membranes, chemical and bio-nanosensors, nanowire sensor for explosives), and energy (heat distribution, eg, ceramic-like materials that provide sufficient reliability and durability of the entire structure)	15, 73, 111, 120, 121
Energy	Photovoltaic film coatings, improved efficiency of fuel production and consumption, fuel cells and batteries, nanobioengineering of enzymes, thermoelectric materials, and prototype solar panels, batteries, aerogels, conversion of waste heat in computers, automobiles, homes, power plants, etc, to usable electrical power	4, 122, 123
Defense and aerospace	Nanocomposites, nanocoatings, sensors and electronics, fuel additives and energy devices, and smart materials	124–126
Construction	Nanocoatings, nanocomposites, nanoscale sensors, smart materials, and additives to concrete. Iron oxide pigments are used in coloring concrete, brick, tile, and other construction materials	127, 128
Automotive	Additives in catalysts and lubricants, nanocoatings, fuel cells, composite fillers, and smart materials	129, 130
Textiles	Sensors, nanofibers, coatings, and smart materials	131, 132
Electronics	Printed electronics, carbon nanotubes, nanoscale memory, nanowires, NEMS, spintronics, and quantum dots	124, 133, 134

Abbreviations: CNTs, carbon nanotubes; MRI, magnetic resonance imaging; NEMS, nanoelectromechanical systems; NPs, nanoparticles; SLN, solid lipid NPs.

Biodistribution and bioelimination of iron NPs

Currently, iron oxide NPs have wide applications in various fields such as in medical sciences, whereas a lower number of studies report uptake and biodistribution of iron NPs (Figure 3). Size, shape, and surface characterization of iron NPs determine their biological distribution¹³⁵ and can involve opsonization (serum protein interaction) and particle cell interaction.¹³⁶ Various biodistribution studies report blood, spleen, liver, and kidney as probable localization for the NPs, and preferentially accumulation occurs in liver and spleen.¹³⁷ Recent studies report that ultrasmall iron oxide NPs can be used as potent MRI contrast agents.^{27,138} This MRI system is very important in the visualization of bio-events, such as gene expression, and metastasis at cellular and subcellular levels.¹³⁹

NP levels along with biodistribution data show that both kidney and liver are involved in NP elimination (Figure 3). Recently, it has been reported that after 6 hours of injection >50% of iron is found in liver.⁷⁹ These studies suggest the involvement of reticular endothelial system in the clearance of NPs and major problem in biomedical application of these particles.¹³⁷ Higher vascularization and permeability of iron NPs are responsible for their uptake by reticular endothelial system¹⁴⁰ and macrophage. Opsonization is one of the important processes for the elimination of magnetic NPs from circulation through liver macrophages.^{141,142} In different studies, magnetic NP accumulation has also been reported in lungs due to vascularized and monocyte-rich nature.¹³⁷ Chaves et al¹⁴³ reported the accumulation of magnetic NPs in the lungs of mice for up to 3 months and found no associated toxicity. Normally the human body contains: hemoglobin protein, myoglobin,

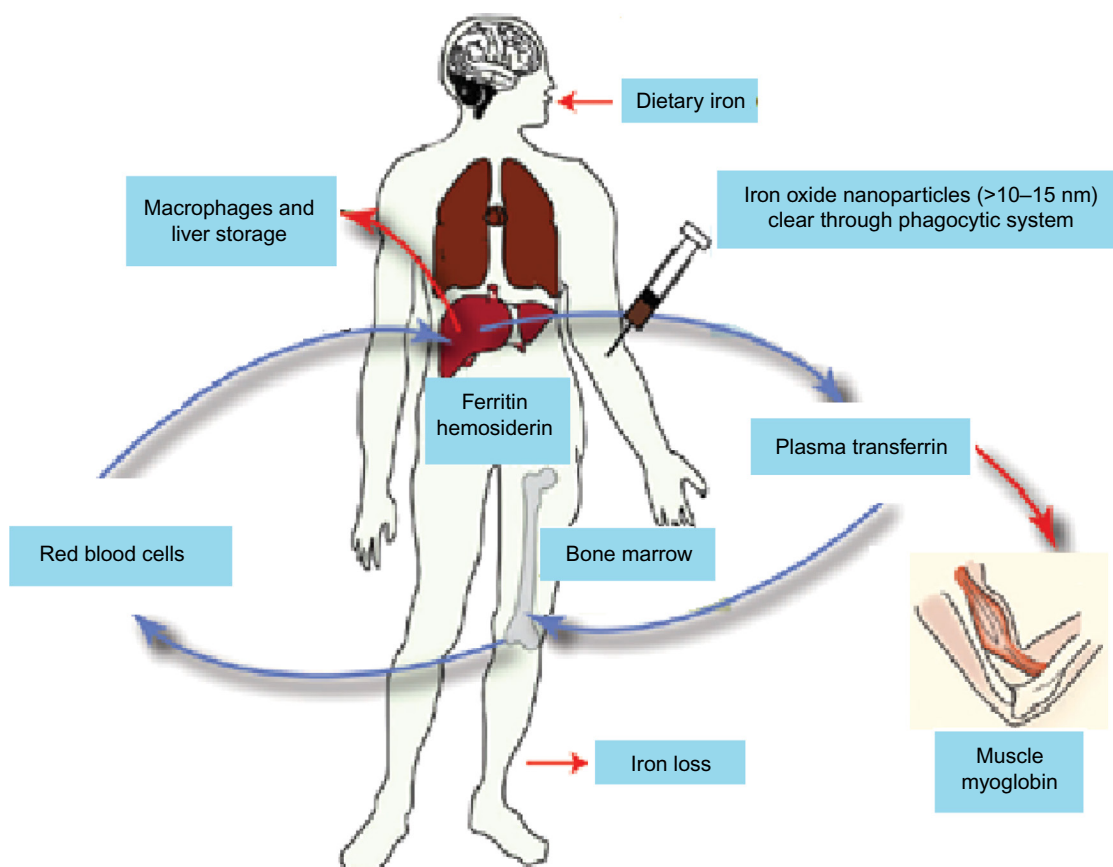


Figure 3 General pathway showing metabolism, transport, and biodegradation of iron oxide NPs.
Abbreviation: NPs, nanoparticles.

transferrin, and ferritin at 65%, 4%, 0.1%, and 15%–30% of magnetic NPs, respectively. It is believed that the degradation of iron oxide NPs occurs similarly like ferritins at molecular level.¹³⁷ The degradation of iron NPs leads to increase in the iron level in the organs. Iron level is regulated by two main iron–protein complexes, ferritin and transferrin, which are involved in storing and shuttling of iron ions.¹⁴⁴ Nissim and Robson¹⁴⁵ and Richter¹⁴⁶ are the founding researchers who reported the *in vivo* biodegradation of iron oxide particles along with the role of ferritin and transferrin in the biodistribution of degradation products.

Mononuclear phagocytic system degrades the intravenously administered NP (>15 nm). Hemosiderin and ferritin generate iron–protein complexes. Transferrin can also be generated from ferritin and transported to bone marrow as a precursor of hemoglobin. Myoglobin is also an important iron–protein complex involved in oxygen transport in the muscle. Insubstantial and aged red blood cells burst in the spleen and release hemoglobin that results in enrichment of iron content. Macrophages metabolize hemoglobin into ferritin that is stored in hepatocytes or converted to transferrin used in the synthesis of red blood cells.

Concerns for the application of NPs

Nanotechnology is the science that involves the control of atoms and molecules to create new materials with a variety of useful functions, including many that could be exceptionally beneficial in many fields.¹⁴⁷ The basic challenges fronting in the fabrication of convenient NPs for biologics include the means to achieve monodispersity, controlled shape and size, reproducibility, scalability, and building complex nanostructures.¹⁰⁷ NMs are very costly to produce as compared to more traditional materials, but greater quantities are produced, and according to normal economic principles their unit cost of production can be decreased, hence their price decreases.¹⁴⁸ Since the properties of NPs are not easily understood and predicted, there are some concerns associated with human beings and agriculture which are given in Table 8.

Conclusion and perspectives

Substantial progress has been made in the synthesis of monodisperse iron oxide NPs for application in nanobiotechnology. Various facile methods are in the progress of rapid development, offering different kinds of monodis-

Table 8 Concerns and prospects of iron oxide nanoparticles associated with human beings and agriculture

Implications for the health of humans		References	Agriculture		References
Source	Effects		Source	Effects	
Orally inhaled or ingested	Proposed harmful side effects, lung cancer	15, 149, 150	Agrichemicals	Seed germination and growth, affect soil nutrients, harms bacteria important for plant growth	118, 151, 152
Skin absorption	Irritation, skin cancer		NPs, eg, CeO	Complete inhibition of the plants' ability to fix nitrogen in the roots	
Catalysis	Speeds up reactions, illness, or death		Environmental	Airborne particles affect plants, loss of soil fertility	
Absorption in microbes	Toxic effects upon ingestion or inhalation, kills useful microbes and nonbacterial cells		Cosmetics industry (ZnO NPs)	Contaminant in solid waste from sewage treatment, and are used as organic fertilizers	

Abbreviations: CeO, cerium oxide; MRI, magnetic resonance imaging; NM, nanomaterial; NPs, nanoparticles.

persed spherical nanocrystals with controllable particle sizes, compositions, shape, and magnetic properties. Owing to the biological environment, iron oxide soluble in an aqueous solution and in colloidal form is the main consideration when selecting synthesis methods. So the wet-chemical methods, such as coprecipitation and thermal decomposition of organometallic precursors, satisfy this requirement. Although coprecipitation can make water-soluble iron oxide NPs directly, the slow crystallization and the lack of size control restrict its use. A shortcoming of iron oxide NPs is their hydrophobic surface chemistry, which makes them merely soluble in nonpolar solvents such as toluene and hexane. Much effort in the past few years has been made in altering iron oxide NP surface chemistry to hydrophilic and biocompatible. A major challenge for all the methods is the design of magnetic NPs with effective surface coatings that provide optimum performance in in vitro and in vivo biological applications. Typical surface modification techniques of various kinds are summarized, including noble polymer coating, small molecular coating, silica coating, metal coating, and liposome coating. Further challenges include toxicity, scale-up, and safety of large-scale particle production processes.

Monolayer polymer coating and organic ligand coating have successfully been converted hydrophobic nature into water soluble and biocompatible. Other than this, iron NPs coated with other biomolecules have enhanced their biocompatibility gaining them approval by authorities such as the US Food and Drug Administration. Therefore, the iron NPs are routinely used in the fields of MRI, target-specific drug delivery, gene therapy, cancer treatments, in vitro diagnostics, and many more. Although magnetic NPs exhibit many distinctive properties, more toxicological research is needed and the criteria to evaluate toxicity

should be clearly defined. The use of better and faster methods to develop our understanding of NP toxicity will advance the field. Moreover, the biocompatibility of iron NPs is linked with toxicity and biodegradation capability and this situation varies when surface is modified with other molecules which off course will effect biodistribution and bioaccumulation. The successful engineering of multifunctional NPs would be of particular interest for the development of theranostic nanomedicine. However, the challenge remains in the clinical translation of NP probes and in issues such as biocompatibility, toxicity, and in vivo and in vitro targeting efficiency.

Disclosure

The authors report no conflicts of interest in this work.

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