Biomedical Materials & Devices
https://doi.org/10.1007/s44174-023-00091-y

REVIEW

# Magnetic Iron Oxide Nanoparticles as a Tool for the Advancement of Biomedical and Environmental Application: A Review

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Received: 3 March 2023 / Accepted: 24 May 2023


**Abstract**
Recently, a number of studies have been devoted for the exploitation of magnetic nanoparticles with potential applications in medicine and environment. Among the oxide of magnetic nanoparticles, iron oxide has been emerged as essential tool in nanotechnology particularly, biotechnology. This is attributed to its exceptional properties such as size, shape, supermagnetism and biocompatibility. The iron oxide nanoparticle is less toxic and more biocompatible than other metal nanoparticles, making it an ideal substrate for biosensing, direct drug delivery, catalysis, (CT/MRI) dual-modality, photothermal therapy, and immunoassays applications. In this review, various synthetic methods of iron oxide nanoparticles have been discussed in detail. The potential applications of these iron oxide nanoparticles in the field of drug delivery, hyperthermia and MRI have also been reviewed in detail. These nanoparticles enhance the mechanical properties of a restorative material and improve the overall bonding between dentin and biomaterials, thus affecting the bond strength.

**Keywords** Nanoparticles · Supermagnetism · Biosensor · Drug delivery · Magnetite

## Introduction

The emerging field of nanotechnology finds applications in almost every field comprising physics, biology, chemistry, medicine and engineering. One of the foremost promising uses of nanotechnology is in the fields of medical and environmental technology. There is a real need to adapt nanoparticles (NPs) to fit particular applications because of their special characteristics. These materials are unique in that their physical, structural, thermal, electrical, and magnetic characteristics differ from those of bulk materials. Nanoparticles are submicron-sized particles made of inorganic or organic materials with diameters ranging from 1 to 100 nm [1–3]. The literature also refers to NPs as large, monodisperse particles with diameters > 100 nm that have novel properties compared to bulk materials [4–6]. By interacting with molecules at this nanoscale range, a particle can easily absorb, penetrate and adsorb. It is expected that nanoparticles will play an important role in all future inventions and new innovations, taking them to new heights and revolutionizing the future. These particles are known for their distinct properties in comparison to their bulk materials, making them ideal for research and development in a range of sectors including medicine, the environment, biomedicine, electrical engineering, and communication [7–11]. Nanoparticles of metal oxides are found in engines to make them more efficient [12–16]. Metal nanoparticles, particularly iron oxide nanoparticles, have a unique place among all types of nanoparticles due to their superparamagnetic properties, small size and therefore utilized for different biomedical applications which include biosensing, directed drug delivery, catalysis, (CT/MRI) dual-modality, photothermal therapy, and immunoassays [17–23]. Due to the presence of iron (II) atoms in haemoglobin, iron oxide is to some extent biocompatible with the human body. Nevertheless, a high concentration of exposure can have an adverse effect on cellular function [24]. It is possible to conjugate iron

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Published online: 13 June 2023

oxides with a variety of components in order to improve their utility.

Iron oxides are naturally occurring substances that can also be produced in the laboratory. Iron oxides are composed of iron (II) ($Fe^{2+}$) or iron (III) ($Fe^{3+}$) cations, as well as some oxygen containing anions [25]. The term iron oxide covers oxides, hydroxides, or oxide-hydroxides of iron. Despite having the same basic chemical composition, consisting of Fe, O, and hydroxide (OH), they are made up of different ferrous and ferric compounds and have different crystal structures and valencies. Thus, they can be distinguished based on the extent to which $O^{2-}$ and/or $OH^{-}$ anions are present in the crystal structure [26]. Naturally, the iron oxide exhibit three potential forms that are magnetite ($Fe_3O_4$), maghemite ($\gamma$-$Fe_2O_3$) and hematite ($\alpha$-$Fe_2O_3$). Iron oxide nanoparticles and nanocomposites are the most potential material in a variety of applications due to their distinctive properties [27]. It can be useful to describe the advantages and disadvantages of materials in different applications by using these classifications [28]. Consequently, when the material is employed in different types of applications, it is important to determine the basic type of magnetic material used. The application of hematite magnetic nanomaterials has also been widely reported in hypothermia treatment, therapy, drug delivery and cancer treatment. Maghemite ($\gamma$-$Fe_2O_3$) and magnetite ($Fe_3O_4$) are the most widely used iron oxides in vitro and in vivo diagnostics. These characteristics are due to the fact that they are superparamagnetic, biocompatible, and low toxic in the human body, as well as the fact that they are relatively simple and inexpensive to prepare [29]. Another important characteristic for sensor and biomedical purposes is the material properties such as superparamagnetic and ferromagnetic nanoparticles, which are related to thermal energy [30].

Superparamagnetic iron oxide nanoparticles (SPIONs) differ from normal iron oxide nanoparticles (NPs) in terms of their magnetic properties, size & stability, and magnetic relaxation. SPIONs exhibit superparamagnetism, which means they display no permanent magnetization in the absence of an external magnetic field, but they become strongly magnetized in the presence of a magnetic field. On the other hand, normal iron oxide NPs typically exhibit ferromagnetic or ferrimagnetic behavior, retaining some degree of magnetization even in the absence of an external magnetic field.SPIONs are usually smaller in size (typically less than 100 nm) compared to normal iron oxide NPs. Additionally, SPIONs tend to have better stability against aggregation due to their surface coating, which helps prevent particle agglomeration. In contrast, normal iron oxide NPs can be larger and may require additional stabilization methods to prevent aggregation. SPIONs exhibit faster magnetic relaxation times compared to normal iron oxide NPs. This property allows SPIONs to be rapidly magnetized and demagnetized, making them suitable for applications requiring efficient magnetic manipulation or contrast enhancement in magnetic resonance imaging (MRI) [31–33].

Nanoparticles of superparamagnetic iron oxide (SPIONs) are crystalline in form and the majority are magnetite ($Fe_3O_4$), maghemite ($\gamma$-$Fe_2O_3$) and ferrites [34]. At room temperature, these particles exhibit no magnetic coercivity or remanence, and their agglomeration effect is negligible. Magnetotactic bacteria are microorganisms that create nanosize particles within an organelle termed a magnetosome, which is connected to a membrane in nature. Magnetic nanoparticles in this chain of magnetosomes impart magnetic dipoles that act as nano-compass and help the chain to direct itself and position against earth's magnetic field [35]. In most applications, cleaning magnetite and using it requires chemical co-precipitation, so this method is better option as magnetite and therefore, is the most demanding research material due to the ease and fast production. Maghemite slowly emerged as a scientific research material as well as ferrites as hyperthermia agents [36–38]. SPIONs with sizes ranging from 3 to 15 nm have been used in a variety of medicinal applications [39]. A nanoparticle is magnetized and has a domain of magnetization in its surface. A particle exhibits its magnetic property at a temperature called Curie temperature when it consists of ferric and ferromagnetic particles [40, 41]. These nanoparticles will behave as a giant paramagnetic atom when exposed to the external magnetic field and exhibit magnetism as a result. The magnetism of each particle is null when the external magnetic field is removed [42]. A wide variety of research has focused on this peculiar behaviour of SPIONs to find an easy way to eliminate SPIONs that have been used in the working zone, or to reach targeted actions.

In this review, we have compiled various methods for the synthesis of $Fe_3O_4$ nanoparticles including sol–gel, microemulsions, co-precipitation, sonication, solvo-thermal and thermal decomposition methods. This review is further devoted to use the special properties of iron oxide nanoparticles in biomedical applications such as MRI, cancer treatment, and environmental remediation.

## Methods for Preparation of Iron Oxide Nanoparticles (IONPs)

### Co-precipitation Method

Co-precipitation is one of the most common and effective chemical wet techniques for preparing $Fe_3O_4$ nanoparticles, as it allows to control over the size and shape of the aqueous solution [43]. It is also the most straightforward approach to synthesize super-paramagnetic iron oxide nanoparticles (SPIONs). To facilitate the chemical process at

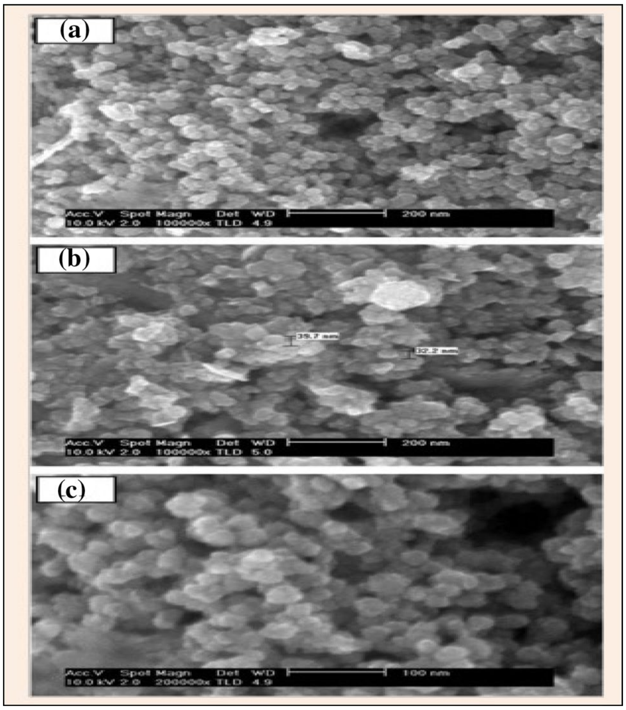


**Fig. 1** SEM images with different magnifications show the particle shape and size distribution for the synthesized magnetite powder by co-precipitation from ($FeCl_2$/$FeCl_3$) EDTA stabilized solution using sodium hydroxide as precipitating agent. Reprinted with permission from Reference [45]. Copyright 2017, Med Crave Group

room temperature, strong base solutions such as NaOH and KOH are added, while weak bases like $Na_2CO_3$ are used for slow reactions [44]. In general, the reaction is given by the equation

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

By co-precipitating iron oxide through ferric and ferrous reacting in a 2:1 or 1:1 ratio in aqueous media with vigorous stirring, $Fe_3O_4$ is synthesized. SEM images (Fig. 1) reveal nearly spherical particles in the samples, measuring approximately 30 nm. This suggests successful synthesis of homogeneous magnetite nanoparticles. The particles show less agglomeration, possibly due to the formation of a monolayer coverage facilitated by Ethylene diaminetetraacetic acid (EDTA). EDTA coordinates with FeOH sites, utilizing carboxylate functionalities and water bridges to form an outer sphere chemisorption complexation [45]. Nanoparticles of $Fe_3O_4$ are capable of exhibiting various physicochemical and magnetic properties depending on the precipitating agent [46]. Hydrolyzing agents such as KOH, NaOH and LiOH are strongly alkaline and exhibit an impurity such as Goethite αFeO(OH), whereas ammonia ($NH_3$) exhibits virtually no impurities [47]. The magnetic moment of the particles is reduced as a result of the impurities [48]. In order to prevent $Fe_3O_4$ nanoparticle aggregation through electrostatic attraction, a variety of organic materials have been used as peptizing agents, such as nitric acid ($HNO_3$), citric acid ($C_6H_8O_7$), tetra methyl ammonium hydroxide ($C_4H_{13}NO$) and per-chloric acid (HCI4) [49]. A number of factors can control the size of $Fe_3O_4$ particles, including reaction time, $Fe^{2+}$/$Fe^{3+}$, temperature, pH, ionic strength in the medium, and mixing speed [50]. In addition, many researchers have conducted studies using chemical co-precipitation to make stable, uniform and smaller-size crystals.

## Thermal Decomposition

Thermal decomposition or thermolysis is one of the method used to synthesize nanomaterials by breakdown of organic compounds at high temperatures in a sealed furnace or by using high boiling point solvents to reduce organic compounds [51–53]. Chemical decomposition occurs at a specific temperature, known as thermal decomposition temperature. The reaction is endothermic as heat is absorbed to break chemical bonds. This method allows for the production of iron oxide nanoparticles of high quality and size around 15 nm [54]. The formation of iron oxide nanoparticles is possible by heating precursor molecules such as organometallic precursors until they disintegrate into iron oxide molecules [55]. According to Hyeon et al., they synthesized (γ-$Fe_2O_3$) by thermally decomposing iron pentacarbonyl and oleic acid at 100 °C, producing a metal complex formed from iron pentacarbonyl and oleic acid [56]. For instance, iron chloride in the presence of sodium oleate surfactant at 317 °C was found to be similar to iron oxide nanocrystals as a precursor. Authors were able to successfully fabricate size controlled monodisperse magnetic iron oxide nanoparticles of size in between 6 and 15 nm (Fig. 2). The following chemical equation shows the decomposition of iron oxides in the presence of sodium oleate at 320 °C [57].

$$\underset{\text{Iron Precursor}}{FeCl_3} + \underset{\text{Sodium Oleate}}{3CH_3(CH_2)_7CH{=}CH(CH_2)COONa}$$
$$\rightarrow \underset{\text{Iron Oleate}}{Fe}\left(CH_3(CH_2)_7CH{=}CH(CH_2)COO\right)_3 + 3NaCl$$

$$\underset{\text{Iron Oleate}}{Fe\left(CH_3(CH_2)_7CH{=}H(CH_2)COO\right)_3}$$
$$\rightarrow \underset{\text{Iron Oxide}}{Fe_3O_4} + 3CH_3(CH_2)_7CH = CH(CH_2)_7COOH$$

## Sol–Gel Method

It is a method for synthesising $Fe_3O_4$ nanoparticles with unique properties that incorporates condensation, hydroxylation, and mixing precursors to produce an inorganic solid

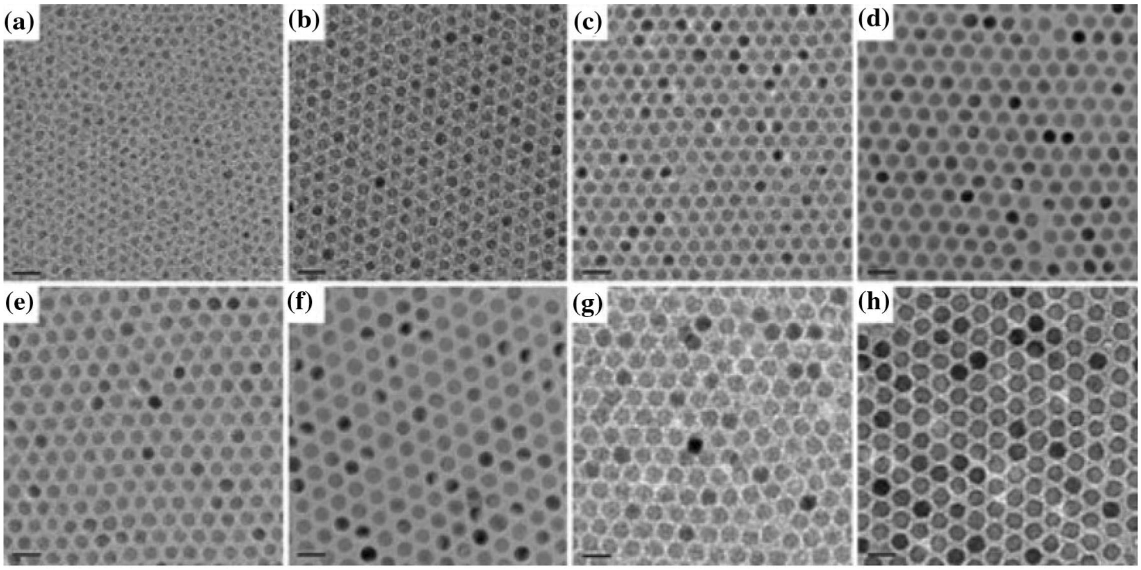


**Fig. 2** TEM images of **a**–**h** 13-nm-sized air-oxidized iron oxide nanoparticles showing the one-nanometre level increments in diameter. Reprinted with permission from Reference [57]. Copyright 2005, Wiley Online Library

on a chemical wet plate [58, 59]. $Fe_3O_4$ prepared through sol–gel has a high level of purity and homogeneity [60]. Several parameters can be adjusted to control morphology and structure, including the concentration of the salt precursors, agitation, pH, and temperature. The magnetic characteristics of the resultant materials are also affected by the change in pH [58]. This method requires four steps to produce $Fe_3O_4$ nanoparticles; (a) hydrolysis of iron precursors and polycondensation of the resulting particles to form a colloidal suspension, (b) an emulsion formed by the gelation of the sol, (c) the ageing process and (d) particles drying. Although the sol–gel process is similar to co-precipitation, it is very challenging to produce monodisperse particles and preventing agglomeration. Sol–gel processes have been reported as a method of synthesizing monodisperse and non-agglomerated materials to overcome all these limitations. The researchers have found that polyethylene glycol (PEG) can be utilised as a capping agent for nanoparticles of $Fe_3O_4$ to agglomerate and give them a uniform size. Authors also reported that molar ratio of ethylene oxide (EO) and $FeCl_3$ should be more than 1.5 to obtain desired morphology and crystallinity of iron oxide nanoparticle (Fig. 3) [61]. Nanocomposite materials can be synthesized using the sol–gel method with an aqueous method of synthesis [62]. A number of merits are associated with the method used in this study. Its capacity to monitor the fine structure identification of reaction outputs is a significant advantage. Its ability to produce a pure amorphous phase, solo-dispersity, and precise particle diameter monitoring are also impressive. Furthermore, it is possible to receive items with prearranged shells that correspond to empirical circumstances.

## Solvo-Thermal Method

One of the most eminent techniques for fabricating magnetite materials is the solvo-thermal method. The synthesis process is almost identical to the hydrothermal method except that organic solvents are used in place of water as a solvent [63]. When acids such as alcohol or glycerol are used as solvents, solvo-thermal reactions are frequently referred to as alcohothermal or glycothermal processes [64]. An organic solvent like ethanol, methanol, or polyol is heated to an extremely high pressure and temperature in a solvo-thermal method. In a solvo-thermal process, an organic solvent such as ethanol, methanol, or polyol is heated to a very high pressure and temperature [65]. In recent years, many authors demonstrated that synthesizing SPIONs via hydrazine ($N_2H_4$) and ethylenediamine ($C_2H_8N_2$) had been accomplished [66, 67]. In this method, the iron precursor and surfactant combine to form a unique morphology and good uniformity [68]. The size of $Fe_3O_4$ nanoparticles can be regulated by altering the ratio of surfactant and NaOH concentrations, as well as the precipitation agent used [69]. As a result of solvo-thermal techniques, the dispersion of iron salts, the reaction temperature, and the aging time play

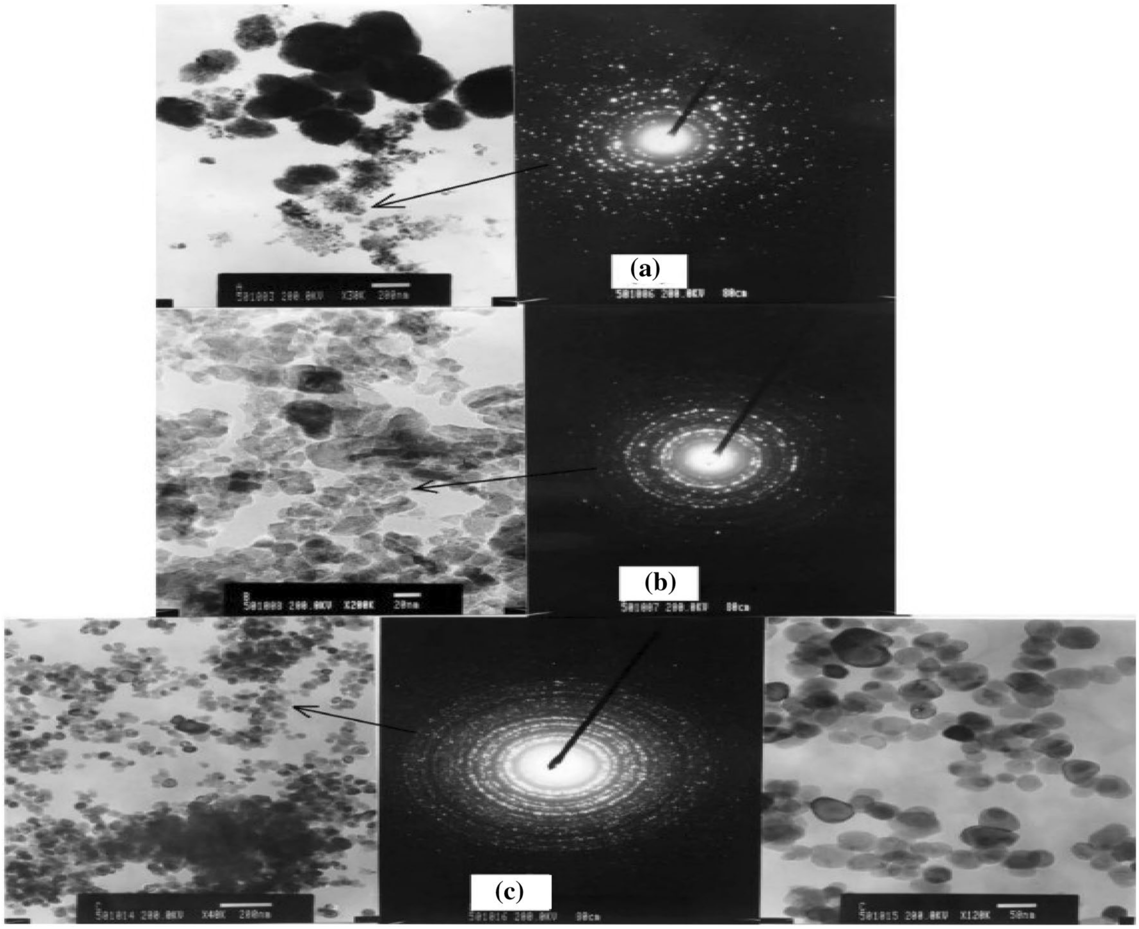


**Fig. 3** TEM view of **a**–**c** α-$Fe_2O_3$ nanoparticles prepared with different molar ratios of EO and Cl. Reprinted with permission from Reference [61]. Copyright 2002, Royal Society of Chemistry

vital roles in controlling the size distribution and growth processes [70, 71]. The composition of $Fe_3O_4$ nanoparticles with high monodispersity is prepared by using a variety of surfactants, including oleic acid, sodium dodecylbenzene sulfonic, and polyacrylic acid [69, 72]. This method produces hydrophilic $Fe_3O_4$ nanoparticles that may be distributed in aqueous or polar solvents [73]. The advantage of this method is that it does not require any surfactant or reducing agent except liquid polyols and just requires controlled experimental conditions [74].

## Sonication Method

This method uses ultrasonic irradiation to generate very high temperature and pressure to result in the producing of SPIONs and other nanostructures, up to 5000 K and 2000 atmosphere, respectively, by decomposition of iron precursors [43]. In a transient ultrasonic environment, high temperatures lead to the formation of magnetic nanoparticles by the decomposition of iron salts [31]. The sonication method has enhanced the hydrophilic and monodisperse characteristics of SPIONs [75, 76]. Ultrasonic irradiation promoted the accelerated formation of magnetite in an ethanol–water solution, while mechanical stirring limited its formation in the same solution. Figure 4 demonstrates that the particle sizes of the samples synthesized with ultrasonic irradiation were larger compared to those synthesized with mechanical stirring [75]. The presence of a suitable stabilizer is widely reported in recent literature to contribute to synthesis of SPIONs with high dispersion through ultrasonic irradiation [43]. Because of the high temperatures and pressures involved, this process results in an amorphous morphology [77]. Furthermore, the acoustic cavitation mechanism prevents crystallisation during the production of SPIONs. The crystalline characteristics of SPIONs can also be modified by heat treatment [78]. It has also been reported that SPIONs with crystalline properties have been synthesized at low ultrasonic temperature [79–81]. This method requires several parameters to

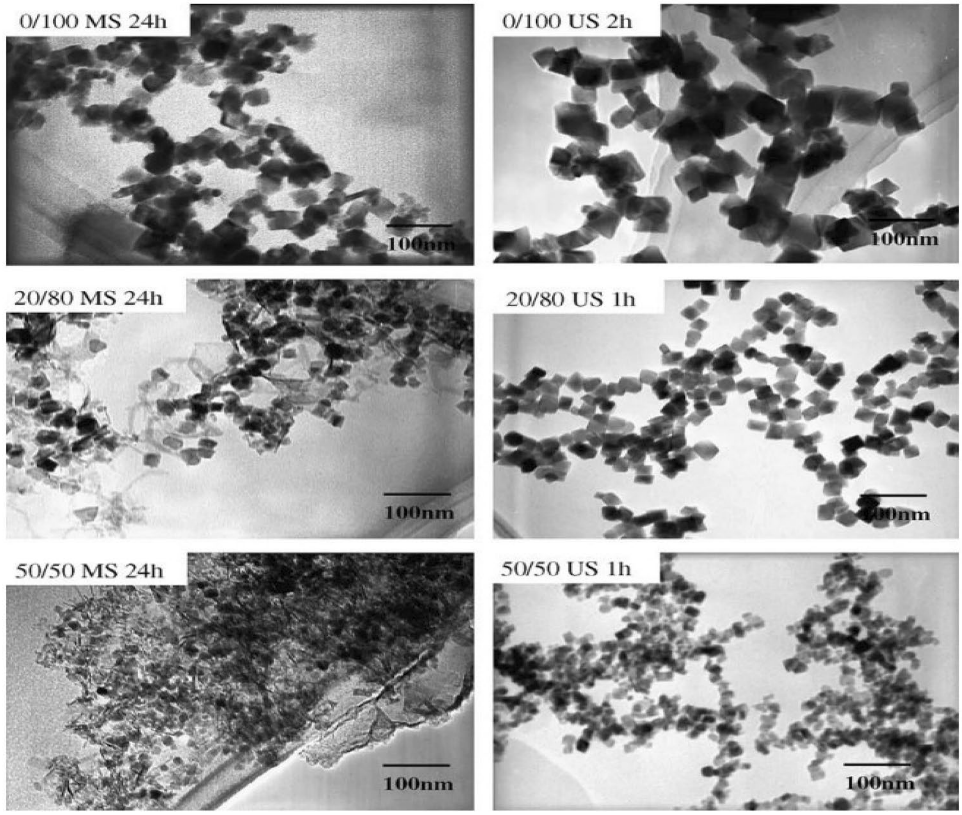


**Fig. 4** TEM photographs of the magnetite nanoparticles under ultrasonic irradiation and mechanical stirring in ethanol–water solutions. Reprinted with permission from Reference [75]. Copyright 2009, Elsevier

synthesize $Fe_3O_4$ nanoparticles, such as time, temperature, and sonication frequency, to control the size distributions and morphology [78].

## Microemulsions

In a microemulsion, oil, water, and surfactants are combined into a thermodynamically stable isotropic mixture. It is not necessary to apply high shear forces in order to form microemulsions. In general, microemulsions fall into three main types: direct emulsions (oil in water), reversed emulsions (water in oil), and bicontinuous emulsions. This classification of microemulsion is determined by the ratio of oil to water (w/o), as well as the balance of hydrophilic and lipophilic values [82]. The microemulsion process involves four stages in the production of nanoparticles; (a) components of microemulsion are mixed combined, (b) substances are exchanged using nano-droplets, (c) nucleation of the reaction and (d) outgrowth as a reaction [83]. The amount and kind of surfactant in the dispersion medium, as well as the pH of the medium, all play a role in particle stability using this procedure [84]. Micelle formation in the microemulsion occurs because of a nanoreactor consisting of water droplets with magnetic nanoparticles surrounded by surfactant molecules. Micelle layers are involved in restricting the nucleation, growth, and aggregation of nanoparticles. The solution is then treated with a second emulsion in order to precipitate nanoparticles [85]. Nanosized water droplets are disseminated in an oil phase and stabilised by surfactant molecules at the water/oil interface as water in oil (water/oil) microemulsion. A pool of water with a surfactant coating provides a perfect environment for the formulation of nanoparticles of certain size and shape. In recent studies, metal nanoparticles with both uniform and small sizes have been synthesized using reverse microemulsion methods in conjunction with surfactants. The production of iron oxide nanoparticle microemulsions has been studied and experimented on extensively. A non-ionic surfactant was used to synthesize silica-coated iron oxide nanoparticles [86]. The reverse microemulsion approach was utilised by Lopez et al. to synthesize iron oxide nanoparticles, where water droplets were produced in an organic solvent to adjust particle size [87]. Microemulsions may be synthesised using another traditional method, which requires reactants to be treated with a reducing agent such as ammonia [88]. Using a microemulsion process with surfactant, water, and oil, the size distribution and shape of $Fe_3O_4$ nanoparticles with a diameter as small as 3 nm could be controlled while varying the temperature during the reaction [89–91]. The major advantage of this model is its environmentally friendly and cost effectiveness. Moreover, the production of SPIONs utilizing this method is highly dependent on surfactant, droplet size, and reactant concentration [92].

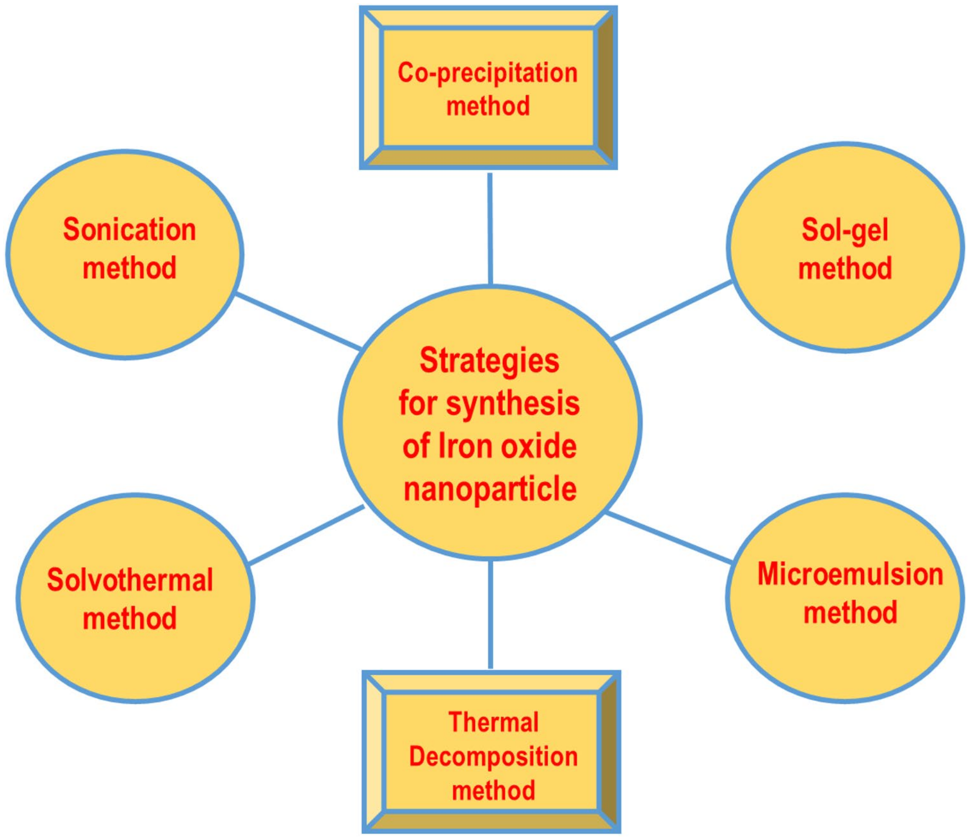


**Fig. 5** Different strategies for synthesis of iron oxide nanoparticles

All of the methods discussed above have their own advantages and limitations. Different strategies for synthesis of iron oxide nanoparticles have been shown in Fig. 5. In order to determine the best method to produce magnetic iron oxide nanocomposites, it is important to consider several aspects in the fabrication of nanoparticles such as uniform shape, size, magnetic properties, easy separation, cost effectiveness, easy synthesis etc. The comparison of different methods of the synthesis of iron oxide nanoparticles is presented in Table 1.

## Properties of Iron Oxide Nanoparticles (IONPs)

### Physical Properties

Maghemite (γ-$Fe_2O_3$), hematite (α- $Fe_2O_3$), and magnetite ($Fe_3O_4$) are three commonly found iron oxides present in polluted sources. The crystal structure of these oxides involves oxygen anions and iron cations occupying octahedral or tetrahedral interstitial sites. In hematite, oxygen ions adopt a hexagonal close-packed arrangement, while Fe (III) ions occupy octahedral sites. Magnetite and maghemite exhibit a cubic close-packed structure with oxygen ions. Distinguishing magnetite from maghemite using conventional spectroscopy like XRD is challenging, but Mössbauer spectroscopy proves useful. Hematite (α-$Fe_2O_3$) exhibits significant diffraction peaks at (012), (104), (110), (024), and (116). Magnetite has an inverse spinel structure, with randomly distributed Fe (III) ions between octahedral and tetrahedral sites, while Fe (II) ions occupy octahedral sites. Cubic magnetite displays reflections at (220), (311), (400), (511), and (440). Maghemite commonly exhibits additional peaks at (210) and (211), forming a spinel structure with variations in cation sublattice vacancies. Two-thirds of the sites are filled with arranged Fe (III) ions, followed by one vacant site [42, 98]. Iron oxide nanoparticles should have an increased effective surface area with decreasing size. Magnetite nanoparticles have approximately a diameter of 50 nm, and hematite nanoparticles are approximately 70 nm in size. It is presumed that magnetite and hematite nanoparticles are nonporous. In comparison with other types of iron oxide nanoparticles, hematite (α-$Fe_2O_3$) nanoparticles are the most stable (under ambient conditions).

### Chemical Properties

Nanoparticles of iron oxide have a surface-to-volume ratio that is considerably larger than that of other nanoparticles. It allows nanoparticles in solutions to be significantly more dispersed and have a higher binding capacity. In addition,

**Table 1** A comparison of different synthetic methods used to prepare iron oxide nanoparticles

| Method | Product properties | Condition | Advantage | Yield | References |
|---|---|---|---|---|---|
| Co-precipitation | Magnetization value: 20–80 emu/g<br>Size distribution: Broad<br>Shape control: Not good | Temp: 20–90 °C<br>Duration: Minutes | Facile, simple, cost-effective, easy and controllable size | High | [93] |
| Thermal decomposition | Magnetization value: up to 91 emu/g<br>Size distribution: Very narrow<br>Shape control: Very good | Temp: 100–320 °C<br>Duration: Hours-days | Monodisperse, low-cost and high quality of nanoparticles | High | [94] |
| Sonication | Magnetization value: 63 emu/g<br>Size distribution: Narrow<br>Shape control: Bad | Temp: 20–50 °C<br>Duration: Minutes | Facile, rapid and Eco friendly | Medium | [95] |
| Sol–gel | Magnetization value: 10–40 emu/g<br>Size distribution: Narrow<br>Shape control: Good | Temp: 25- 200 °C<br>Duration: Hours | Desired shape and hybrid nano-particles | Medium | [96] |
| Solvothermal | Magnetization value: up to 108 emu/g<br>Size distribution: Narrow-broad<br>Shape control: Good | Temp: 150–220 °C<br>Duration: Hours-days | High purity, good crystallinity | High | [68] |
| Microemulsion | Magnetization value: up to 113 emu/g<br>Size distribution: Narrow<br>Shape control: Good | Temp: 20–50 °C<br>Duration: Hours | Uniform and thermodynamically stable nanoparticles | Low | [97] |

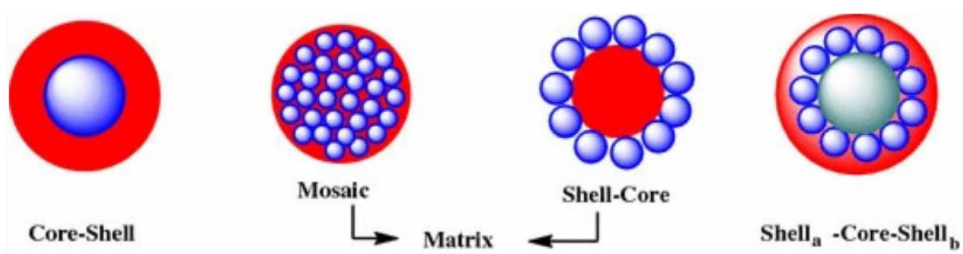


**Fig. 6** The representative structure of organic materials functionalized magnetic iron oxide NPs (if iron oxide NPs were always assumed as the core). Reprinted with permission from Reference [4]. Copyright 2008, Springer Nature

the materials are biocompatible and nontoxic. Comparatively to traditional iron oxides, these nanoparticles demonstrate improved size tunability, monodispersion and crystalline structure. Coating iron oxide nanoparticles with organic compounds has great potential for various applications. The structure of these functionalized magnetic nanoparticles can be divided into two main parts: the magnetic properties of the iron oxide core and the other properties of the organic molecules. Typically, when considering iron oxides as the core, the structure can be categorized into three types: core–shell, matrix, and shell-core–shell [4]. Figure 6 illustrates that coating a group of iron oxide nanoparticles with organic material creates a core–shell nanostructure.

## Thermal Properties

Melting and boiling points of magnetite ($Fe_3O_4$) are reported to be 1590 and 2623 °C, respectively. Fusion, decomposition, and vaporization heats are 138.16, 605.0, and 298.0 kJ/mol (at 2623 °C), while the melting and boiling points for hematite are measured at 1566 and 2600 °C and the heats of fusion and vaporization are 41.1 and 67.0 kJ/mol (at 2623 °C), respectively.

## Surface Charge

The surface charge may impact particle stability and functionality in a direct way. If the nanoparticle has a high magnitude positive or negative zeta potential, it means it is extremely stable and can be dispersed throughout the system [99]. The zeta potential value and the stability of surfaces are also affected by electrostatic interactions. In turn, particle stability determines the length of time a nanoparticle can remain within the system before degradation. To be used as therapeutics, nanoparticles must be extremely stable and dispersive [100].

### Magnetic Properties

All magnetic substances have a dipole and a magnetization that indicates its capacity to keep its magnetic properties. In the presence of a magnetic field, the substance retained a dipole or magnetization, due to the alignment of individual domains within the magnetic substance. SPIONs act as magnets when exposed to any magnetic field and return to their non-magnetized state when no magnetic field exists. Nanoparticles may exhibit superparamagnetism by those which are magnetic but without an external magnetic field. Biological systems can be benefitted greatly from it since it can react to magnetic fields anywhere, and can be detected by thermometers even with systems, as it produces heat when exposed to magnetic fields. It is necessary to use an external magnetic source when increasing magnetization. Due to this property, magnetic nanoparticles in solutions are more stable. Nanoparticles of iron oxide have attracted considerable interest due to their superparamagnetic properties and their possible applications in medicine.

### Electrical Properties

The electrical properties of IONPs can be characterized by their surface charge, conductivity, and dielectric properties. The surface charge of IONPs can affect their stability and interaction with cells and tissues. Generally, IONPs with a neutral or negative surface charge show less toxicity and higher stability in biological systems [101]. In contrast, positively charged IONPs have shown higher cellular uptake but also have higher toxicity and instability [102]. The conductivity of IONPs can also affect their behavior in biological systems. IONPs with higher conductivity have been shown to have better heating properties under an alternating magnetic field, making them suitable for hyperthermia therapy [103]. Additionally, the conductivity of IONPs can also affect their interaction with cells, as it can influence the rate of electron transfer and oxidative stress [104]. The dielectric properties of IONPs, including permittivity and conductivity, also play a significant role in their interactions with biological systems. The dielectric properties of IONPs can affect their heating efficiency under an alternating magnetic field, which can be used for hyperthermia therapy [105]. The electrical properties of IONPs are essential for their behavior in biological systems and their suitability for biomedical applications. The surface charge, conductivity, and dielectric properties of IONPs can affect their stability, toxicity, and interaction with cells and tissues. Therefore, a better understanding of the electrical properties of IONPs is critical for the development of safe and effective biomedical applications.

## Application of Iron Oxide Nanoparticles (IONPs)

In this part, selected applications of iron oxide nanoparticles have been discussed including MRI, drug delivery, hyperthermia, and environmental remediation.

### Magnetic Resonance Imaging (MRI)

In vivo imaging with MRI is a non-invasive technique utilized to diagnose medical conditions. The enhanced monitor is capable of recognizing high contrast cells and cells that contain a large number of SPIONs [106]. The MRI technique has several advantages over other methods such as single-photon emission computed tomography (SPECT), positron emission tomography (PET) and computed X-ray tomography (CT) such as deep penetration of magnetic field, high accuracy for anatomic images, and non-ionizing contrast agents [107, 108]. This activity is based on the behaviour of proton particles in the body which exhibit nuclear magnetization. Magnetic fields can induce longitudinal magnetism by rotating the protons in the body through a parallel motion and aligning them with the magnetic field direction. As a result of radio frequency (RF) pulse, which induces transverse magnetization through the spin of the protons, the magnetic field aligns antiparallel with each other. Excited protons emitted energy when their state is returned to its initial state when the RF pulses are stopped. The relaxation procedure involves two distinct processes, first longitudinal relaxation ($T_1$-recovery) and then transverse relaxation ($T_2$-decay).

In terms of contrast agent (CA), images over $T_1$ were brighter and darker over $T_2$. According to a previous study, SPIONs are now widely used as MRI contrast agents for $T_2$-based MRIs due to its susceptibility, superior contrast impact, high relaxiblity, high saturation magnetization, low cost, biocompatibility, and non-toxicity. The inherent theranostic properties of iron oxide nanocomposites make these materials appealing for medical purposes using MRI and CT scans etc. Accordingly, these nanocomposites can have dumbbell-shaped, core/shell and flower-shaped structures, and their structures affect their transverse relaxation values

[109–115]. In the MRI contrast, $Fe_3O_4$ nanocomposites show relatively higher transverse reflexivity ($r_2$) value [112].

## Drug Delivery

It is still one of the most prominent methods of treating cancer since it is the only one that relies on the circulatory system to deliver drugs to cancer cells since it lacks specificity for the tumour. Due to this method, the toxicity of the drugs can be increased in non-affected tissues by introducing so many drugs into the body. As a consequence of these serious complications on the patient, targeted drug delivery that provides treatment for the tumour area has attracted significant attention as a potential alternative to chemotherapy [116]. Research has demonstrated that $Fe_3O_4$ nanoparticles are preferred over other targeting approaches due to their capabilities to combine with electric fields or ultrasound. In this case, the $Fe_3O_4$ nanoparticles are biocoated so that a drug can be attached to the surface, thus enabling surface functionalization. By using the magnetic field for guidance, the particles are delivered directly to the site of the tumour. Magnetically targeted drug delivery (MTD) is an effective method for treating malignant cells by accumulating chemotherapeutic agents at the site of infection. It is important to note that a number of factors play a role in MTD, such as shape, biocompatibility, stability, and magnetization [117–120]. The application of SPIONs/Au core shells packed with doxorubicin (DOx) as an anticancer drug has been studied by combining both drug delivery and hyperthermia to find a possible cancer therapy [120]. Drug release efficacy has been studied in a variety of conditions, such as temperature, oscillatory magnetic fields and different pH levels. The effective release of drugs was improved by an acidic pH and oscillating conditions, while high temperatures had no effect. In the drug release study, pH level 5.5 was found to release more drugs than the other pH levels. In recent years, the use of SPIONs for the delivery of drugs has been proved to be safe and effective. Consequently, a higher concentration of drug consumption is required to observe the effects and pharmacodynamics of the drug.

## Hyperthermia

Hyperthermia is a condition in which SPIONs react with alternative magnetic fields in the form of release of heat energy when their temperature rises above 45 °C [121]. In SPIONs, alternative magnetic fields (AMF) produce magnetization reversal dynamics, which are governed by Brownian alignment and Néels rotation [122]. A particle in solution whose magnetic moment is constantly present is said to be in Brownian alignment, whereas in Néels rotation, the magnetic moment causes the electron spins of the particle to reorient towards the applied field [123]. This struggle produces heat energy as SPIONs in AMF make their way through the duality. However, heat energy (hyperthermia) emitted primarily as a result of rotation of Néel is more noticeable [124]. It is generally recommended to use hyperthermia rather than radiation therapy or chemotherapy for the treatment of cancer. In order to increase their biocompatibility, stable SPIONs are coated in a biopolymer. The SPIONs can be injected intravenously at the target site, for example, a tumour exposed to an external alternating magnetic field (AMF). Consequently, the dipole of that SPION shifts according to the direction of the applied alternating magnetic field, causing heat to be generated. By rapidly raising the temperature, cancer cells are killed on the spot [125]. Moreover, anticancer drugs can be incorporated into SPIONs to boost their efficacy and apoptosis death in tumour cells [126].

## Dentistry

Dental professionals have also attracted to use nanoparticles in oral cavity because of it's unique properties. Magnetite and Maghemite are the two common forms of iron oxide nanoparticles which are popular in biomedical science due to its properties like ultrafine size, magnetic properties, biocompatibility and non-toxic to human [31]. Iron-oxide nanoparticles are widely utilized to eradicate biofilms on dental implants as shown in Fig. 7 [127]. The incorporation of nanoparticles also prevents biofilm build up over the composite, which avoids micro-leakage and secondary caries [128, 129]. These nanoparticles enhance the mechanical properties of a restorative material and improve the overall bonding between dentin and biomaterials, thus affecting the bond strength. Nanoparticles used for diagnosing, preventing and treating the prominent dental diseases like dental caries, periodontal diseases, oral cancer and replacement of missing teeth etc. hence it cover a wide range of application in dentistry like restorative dentistry, prosthetic dentistry, endodontics, implantology, periodontology and oral surgery as shown in Fig. 8 [130]. Although it is clear that nanoparticles can be effective due to their incorporation with dental biomaterials, to use them for clinical applications, in vivo results with long-term data are necessary. Besides the benefits of nanoparticles, the research on long-term in vivo results, methods of nanoparticle incorporation and characterization, and data on their long-term antibacterial action is needed for clinical applications [131].

## Environmental Remediation

A thorough investigation of SPIONs has revealed its striking role in environmental remediation. In recent years, a widespread topical problem has arisen from the contamination of potable water resources with toxic pollutants, such

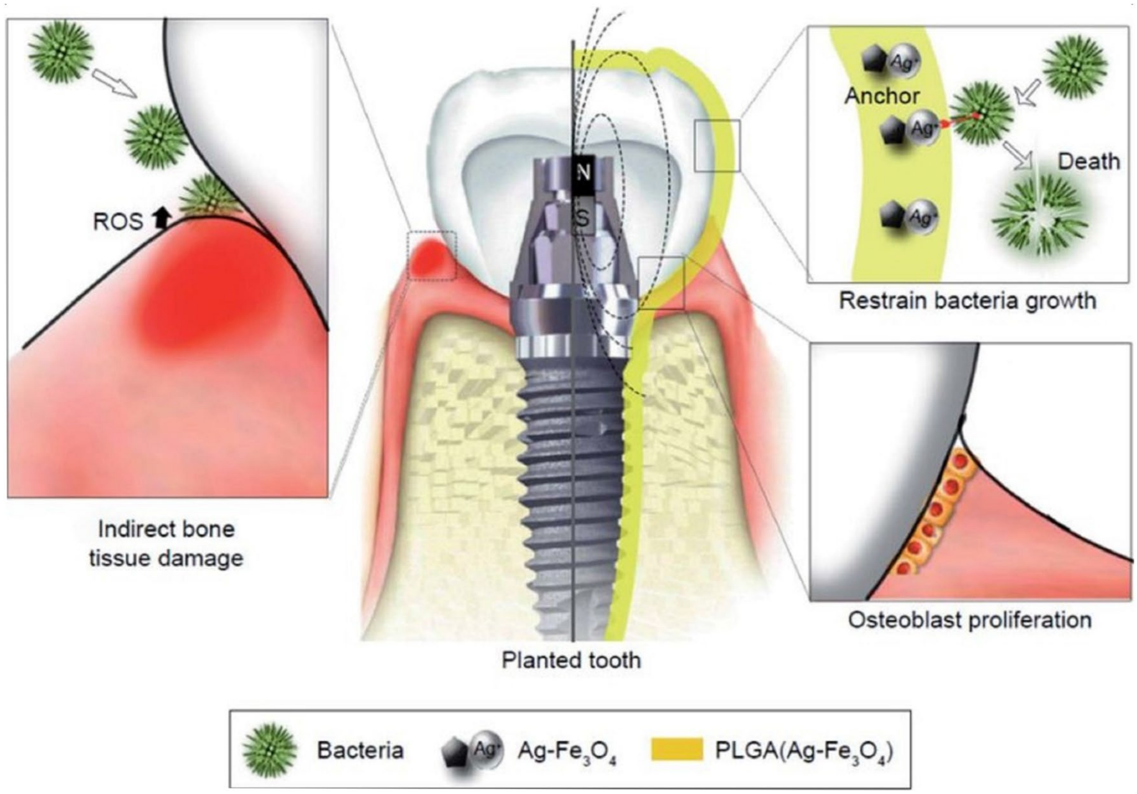


**Fig. 7** Schematic diagram of PLGA (Ag–$Fe_3O_4$)-coated on dental implants

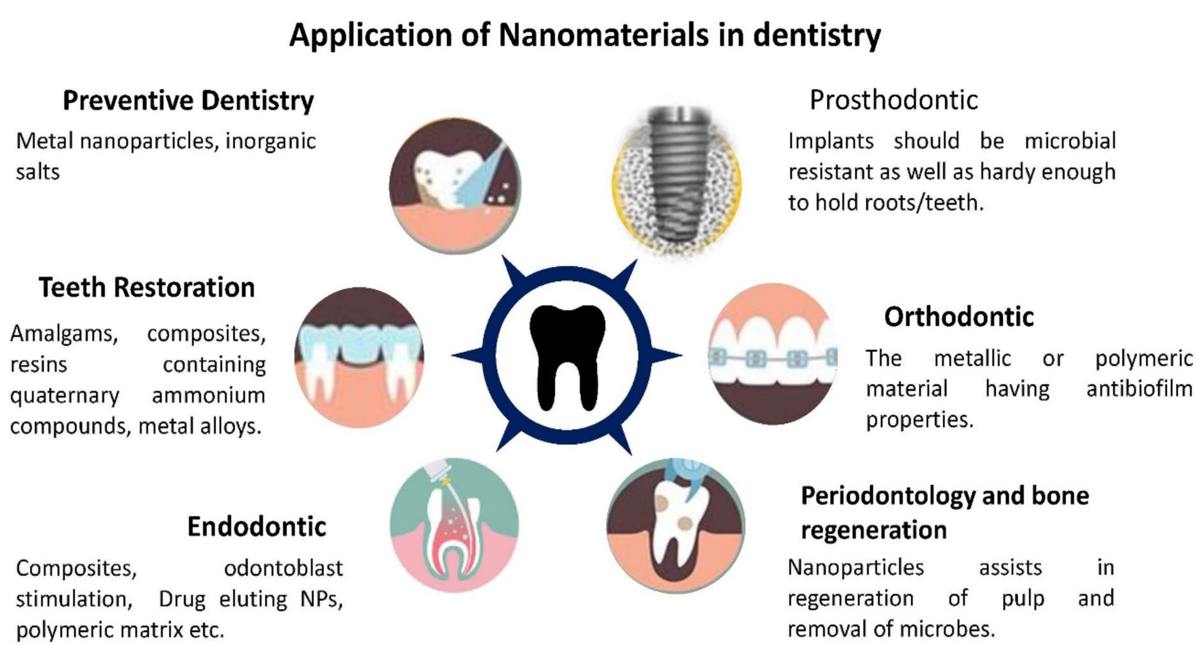


**Fig. 8** Pictorial representation of applications of nanomaterial in dentistry

as heavy metals, dyes and other chemicals [132–136]. This poses a great risk to mankind and the ecosystem in terms of dyes, heavy metal toxicity and bio-magnification [137–139]. Metal pollutants such as cadmium, cobalt, lead, and chromium are most common, and dyes include congo red, methylene blue, crystal violet and brilliant green [140–142]. A number of studies have proposed that crystal violet dye and chromium metal accumulation can cause adverse health effects on humans, including kidney, respiratory system and cancer [141, 143]. Considering that nanoparticles are able to form more molecular interactions because of their smaller size, SPIONs were tested for their ability to remove toxic pollutants from water. The SPIONs were found capable of adsorbing dyes and heavy metals onto the surface through electrostatic interactions, and ultimately eliminated these pollutants from the liquid phase. Adsorption efficiency differed according to the extent of surface coating and amalgamation of SPIONs. Samrot et al. reported that SPIONs coated with chitosan biopolymer had the ability to remove hexavalent chromium (100 mg/L) at pH 2 when the solution contained acid [144]. A biopolymer coating on SPIONs greatly enhances their adsorption efficiency over naked SPIONs, so they can be used to remove heavy metals. An SPION hybrid nanoparticle prepared by polymerization of poly (methylmethacrylate) (PMMA) showed adsorption against Pb (II), Hg (II), Cu (II), and Co (II) where adsorption is correlated with ion radii [145]. The SPIONs adsorbent combined with amberlite resin worked well for removing cadmium from industrial effluents with a neutral pH (Fig. 9) [146]. It has also been reported that SPIONs can remove synthetic dyes based on the pH and electric charge of the adsorbent and adsorbate. In the presence of an alkaline pH, cationic dyes like crystal violet dye showed better adsorption on SPIONs, whereas anionic dyes like congo red or methyl orange were preferable [147].

## Environmental Effects Caused by SPIONs

It has long been known that iron oxide nanoparticles are efficient for environmental clean-up because of their small particle size, high surface-area-to-volume ratios, and strong redox capabilities [148]. In environmental remediation,

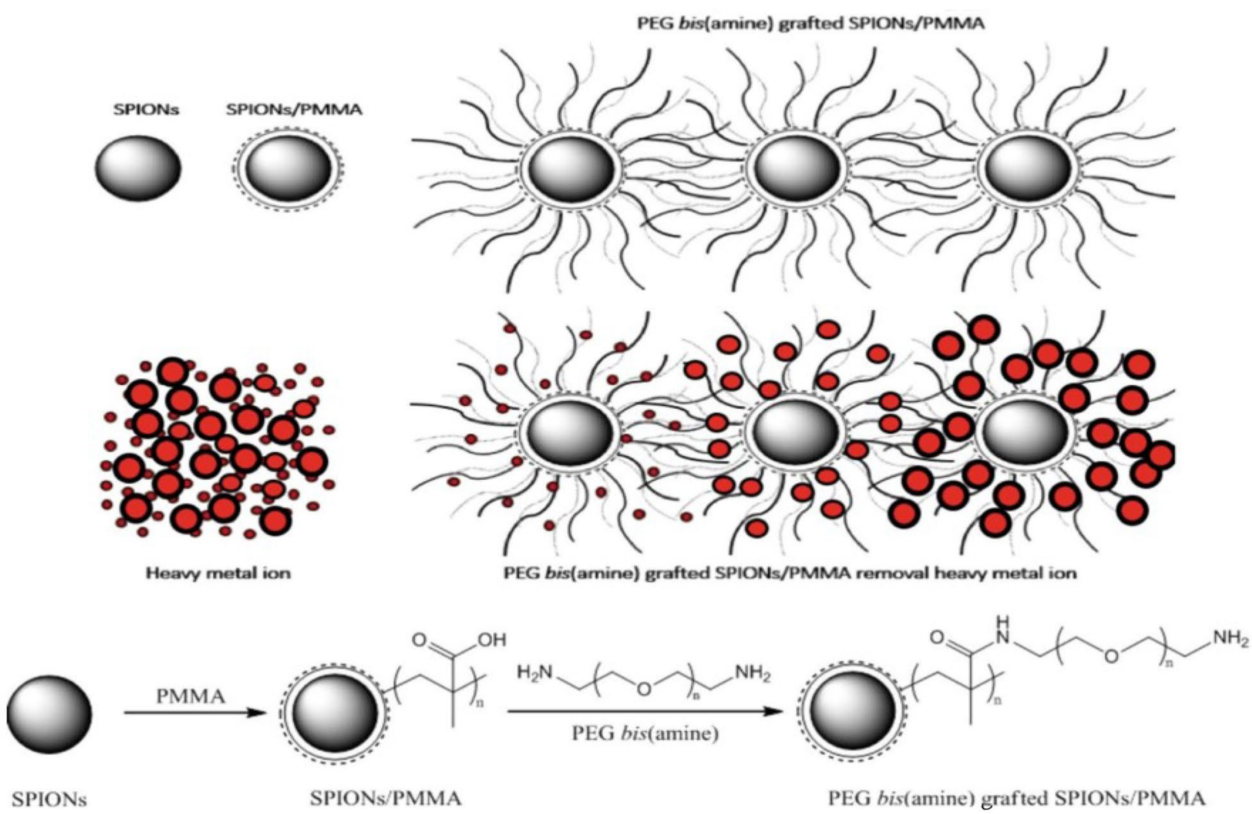


**Fig. 9** Chemical route for preparation of PEG bis(amine) graft onto surface SPIONs/ PMMA nanohybrid particles and a schematic model for the heavy metal ion binding. Reprinted with permission from Reference [146]. Copyright 2016, Elsevier

SPIONs are affected by pH, ionic strength, and coexisting ions, which researchers have investigated [149]. Although SPIONs corrosion affects surface and chemical properties, it also affects the pH of the environment and the speciation of heavy metals with adverse effects for organisms. In general, SPIONs change the pH and species of contaminants during the reaction mechanism. The SPIONs are also affected by the pH of the environment and their interactions with contaminants [150]. Moreover, SPIONs are directly toxic to organisms and can change the pH and the speciation of pollutants within organisms [151].

## Limitations of SPIONs

The superparamagnetic iron oxide nanoparticles (SPIONs) are used in more varied fields, but have few limitations in their applications as follows: There are several problems associated with SPIONs, including their instability and lack of stability of nanostructure, and also their agglomeration, even though functionalization can make it stable, but not for longer storage [144, 152–154]. SPIONS of size less than 2 nm can cross a cell membrane and may accumulate inside the cell, damaging cell organelles, for use in biological systems, specific precautions must be taken during its preparation and use. It has been shown that macrophages absorb SPIONs into the system [155]. It is possible for nanoparticles to accumulate inside the cell by at least one of these methods: (a) simple diffusion, or (b) receptor facilitated endocytosis [156, 157]. When SPIONs enter the cell, lysosomal enzyme converts them into $Fe^{2+}$, resulting in the production of reactive oxygen species and inflammation [158]. In a research study, SPIONs coated with citrate were shown to participate in oxidative stress and protein degradation, resulting in reactive oxygen species (ROS). It is found that ferritin plays a role in the generation of ROS and consequently, in vivo neurodegeneration [17]. In vivo, magnetite nanoparticles coated with poly aspartic acid have caused an increase in micronuclei [159]. The toxicity of this compound has been reported in earthworms in several reports involving the degradation of epidermis and guts [100, 160]. There are more researchers reporting efforts to reduce toxicity, but there is much more work that needs to occur to reduce the toxicity and also provide proper disposal for SPIONs.

## Conclusion

This review provides detailed survey about superparamagnetic iron oxide nanoparticles, (SPIONs). SPIONs have been synthesized using various techniques, from high-tech devices to easy one-pot synthesis, as well as the production of SPIONs by biological agents. Among all the methods, chemical co-precipitation method is more convenient and can be applied to many different uses. Although various synthetic routes have been utilized, a significant challenge persisting in the synthesis field is achieving reproducible size- and phase-controlled synthesis. To address the current obstacles in achieving controlled and reproducible synthesis, it is essential to meet the following criteria: (a) ensuring direct, thorough mixing of reactants; (b) implementing automation; and (c) precisely controlling reaction parameters. A discussion is given about the properties and characteristics of SPIONs, with a special emphasis on its magnetic properties. This review also emphasizes the importance of functionalizing (SPIONs) with appropriate agents in order to ensure stability. The SPION nanoparticle is less toxic and more biocompatible than other metal nanoparticles making it an ideal nanomaterial for biomedical as well as environmental applications. Consequently, we have addressed the current and future use of SPIONs in targeted drug delivery, hyperthermia, MRI, and environmental applications including heavy metal ion and toxic dye removal. The SPIONs utilized drug delivery system may be more effective than conventional cancer treatment.

**Acknowledgements** One of the authors (Khalid Ansari) is highly thankful to UGC-New Delhi for providing financial assistance.

**Funding** Funding was provided by UGC-DAE Consortium for Scientific Research, University Grants Commission Khalid Ansari.

## Declarations

**Conflict of interest** The authors declare that they don't have any conflict of interest.

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