MINI REVIEW

Past Present And Future Trends On Iron Oxide Nanoparticles Using Biomedical Applications

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ABSTRACT:

The primary methods for producing the nanoparticles include co-precipitation, sol-gel, hydrothermal synthesis, and thermal breakdown. The most used method is co-precipitation due to its simplicity and scalability, while thermal breakdown offers superior control over particle size and crystallinity. Advanced techniques like as sol-gel and hydrothermal production enable enhanced stability and tunable particle properties. There are numerous applications for IONPs in the medical field. Because of their super paramagnetic properties, which increase imaging precision for early sickness identification, they are ideal for use as contrast agents in magnetic resonance imaging. They are also employed in targeted drug delivery systems, which use an external magnetic field to guide drug-loaded nanoparticles to particular locations in order to reduce systemic side effects. Iron oxide is the material that has been studied the most in FDAapproved nano medicines. At specific diameters, magnetic iron oxide nanoparticles (MNPs), which are composed of magnetite or maghemite, have shown promise as contrast agents, drug delivery systems, and thermal-based treatments. In biomedical applications like as imaging, photo thermal treatment, and diagnostics, this material is incredibly successful. The requirements for characteristics that organic materials cannot offer are being met by stability and biocompatibility. However, their usage in several therapeutic applications is restricted due to their poor solubility and toxicity consequences.

KEYWORDS: Iron oxide ,preparation methods, nanoparticles and applications

INTRODUCTION :

An object that has all three external dimensions in the Nano scale and whose longest and shortest axes do not differ significantly though a substantial difference is usually a factor is considered a Nano particle, according to ISO technicalspecification80004.
The term "nanotechnology" was used in 1974 by Norio taniguchi, a professor at the Tokyo University of Science, to refer to extremely thin dimensions and excellent precision. When discussing the future of nanotechnology the ability to create larger structures from their automated and molecular components Keric Drexler, some ten years later, introduced the bottom up approach.

While the development of nanotechnology is a modern multidisciplinary science involving the fields of physics chemistry, biology and engineering the production of Nano particles (nps), both in nature and by humans, dates from the pre-Christian era.

Nanotechnology was presented by Nobel laureate pilchard P.Feynman during this well famous 1959 lecture “there’s plenty of room at the bottom”(Feynman, 1960). There have been various revolutionary developments in the field of nanotechnology.

Nanoparticles (NPs) are at the vanguard of nanotechnology's explosive growth. Because of their unique size-dependent characteristics, nanoparticles are superior and indispensable in many facets of human endeavors [1].Iron oxide that is magnetic Nanoparticles are safe for the environment, biocompatible, chemically stable, and reasonably priced to create. Magnetic fields can be used to manipulate magnetic nanoparticles. These particles typically have two parts: a useful chemical component and a magnetic substance, usually iron, nickel, or cobalt. The bigger micro beads range in diameter from 0.5 to 500 micrometers, whilst nanoparticles are smaller than 1 micrometer.

Due to their intriguing electrical, magnetic, catalytic, and chemical or biological features, iron oxide nanoparticle production has drawn interest from both fundamental and practical sources. Accordingly, magnetic nanoparticles possess a wide range of special magnetic characteristics, including strong coercivity, low Curie temperature, high magnetic susceptibility, and super paramagnetic. Since many of these applications rely on the qualities, it is crucial to be able to adjust the size, morphology, and surface characteristics.

The size-related characteristics of nanoparticles can differ greatly from those of small particles or bulk materials. Nano clusters are characterized by a restricted size distribution with at least one dimension ranging from 1 to 10,000 nanometers. Agglomerates of nanoparticles, ultrafine particles, or nanoclusters are known as nano powders. Single-domain ultrafine particles, also known as nanometer-sized single crystals, are frequently referred to as nano crystals [2-4].

Nanoparticles can be classified as either organic or inorganic/metal oxide. In the fields of chemistry, physics, and materials science, metal oxides are crucial. Metal oxide nanoparticles come in a variety of forms, including gold nanoparticles. The following nanoparticles are available: iron oxide, zinc oxide, and silver.

Although gold nanoparticles come in a range of sizes from 2 to 100 nm, the most effective cellular uptake was shown in the 20–50 nm particle size range. Larger particles, such as those between 80 and 100 nm, on the other hand, do not diffuse into the tumor and remain close to the blood arteries. This has various benefits, including Gold nanoparticles have special chemical and physical characteristics that improve drug loading, drug effectiveness, biocompatibility, easy blood flow to the targeted region, and non-cytotoxicity to healthy cells.[5–8]

Silver oxide nanoparticles are silver or silver oxide particles that range in size from 1 to 100 nm. Numerous medical products, such as bone cement, surgical tools, surgical masks, etc., include silver nanoparticles. Furthermore, it has been demonstrated that ionic silver can be used to cure wounds when used in the proper amounts. As an effective wound-healing agent, silver nanoparticles are actually taking the place of silver sulfadiazine. These nanomaterials have drawn a lot of interest in biomedical imaging employing SERS (Surface-enhanced Raman spectroscopy) because of their appealing physiochemical characteristics.

Because of their unique physical and chemical characteristics, zinc oxide nanoparticles—one of the most significant metal oxide nanoparticles—are widely used in many different disciplines. Superior antibacterial, antimicrobial, and UV-blocking qualities are possessed by zinc oxide nanoparticles. Today, zinc is available as a food additive after the Food and Drug Administration approved its use for treatment. They are appropriate for the glass and textile industries as coating materials for medical and other equipment because of their UV-blocking action, white color, and capacity to inhibit the formation of biofilms.

Magnetic nanoparticles: One of the three primary oxides of iron, along with ferrous oxide and magnetite, iron oxide is a reddish-brown, inorganic substance that is paramagnetic in nature. In nature, magnetite is highly paramagnetic. To target sick tissues like tumors, magnetic iron oxide nanoparticles have been functionalized with proteins, enzymes , nucleosides, and.

There are numerous uses for magnetic nanoparticles, including Super paramagnetic iron oxide nanoparticles have shown great promise for a number of biomedical uses, including targeted drug delivery, enhanced resolution contrast agents, gene therapy, stem cell tracking, molecular/cellular tracking, magnetic separation technologies for early cancer, diabetes, and atherosclerosis, and hyperthermia.

A significant class of Nano materials, magnetite nanoparticles are being researched extensively for their potential application in such applications as tailored medication delivery. The success of magnetic particles as a drug delivery method is demonstrated by Gallo and colleagues, who found that the concentration of magnetic microspheres containing the drug in the brain was 100–400 times higher than its level when taken in a solution dose form. Furthermore, it was demonstrated that encapsulating quercetin on dextran-coated Fe_3O_4 Nano-carriers is one possible method to eliminate the aforementioned issues and improve the drug's bioavailability.[9-12]

Researchers from a wide range of fields, including data storage, bio applications, magnetic fluids, and catalysis, are very interested in magnetic nanoparticles. These days, magnetic nanoparticles are also employed in significant bio applications, such as bio separation and biological label detection, bio separation and biological entity detection (cell, protein, nucleic acids, enzyme, bacterium, viral, etc.), and clinic diagnosis. However, selecting a material with modifiable physical and chemical properties is essential for the fabrication of nanostructures and devices. From geological settings to Nano scale technology applications, iron oxides can be found in a wide range of configurations and contexts.

Clusters of magnetic nanoparticles, sometimes referred to as magnetic Nano beads, are made up of individual magnetic nanoparticles with a diameter ranging from 50 to 200 Nano meters .Nano material-based catalysts, biomedicine, magnetic resonance imaging, microfluidics, tissue-specific targeting, magnetic particle imaging, data storage, environmental remediation, Nano fluids, optical filters, defect sensor, magnetic cooling, and caution sensors are just a few of the intriguing properties that have recently drawn attention in research due to their potential applications in catalysis.

Following the use of iron oxide nanoparticles, iron ions may be released and build up in bodily tissue. This is dependent on the iron oxide nanoparticle's size, concentration, surface charge, coating type, and side groups. Damage to macromolecules may result from iron ions under oxidative stress .As a result, using iron oxide nanoparticles in the central nervous system requires extreme caution.

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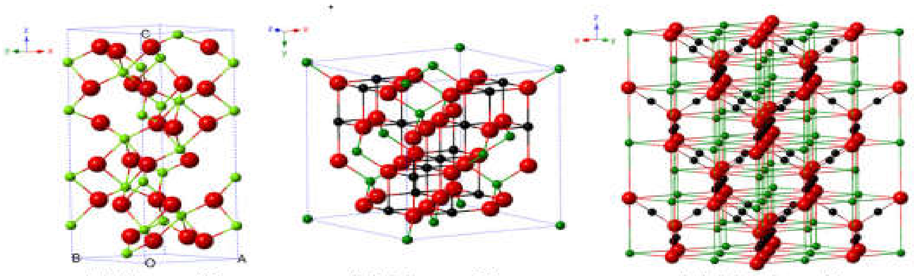
1.1. **IRON OXIDES:** Eight iron oxides are known, among these iron oxides, hematite (α-Fe_2O_3), magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) are very promising and popular candidates due to their polymorphism involving temperature-induced phase transition. These three iron oxides have unique biochemical, magnetic, catalytic, and other properties which provide suitability for specific technical and biomedical applications.

1.1.1.Hematite (α-Fe_2O_3): Hematite (α-Fe_2O_3) is the most stable iron oxide and n-type semiconductor in ambient settings. Because of its great corrosion resistance and inexpensive cost, it is utilized extensively in gas sensors, catalysts, and pigments. Additionally, it can serve as a starting material for the production of maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4), two compounds that have been actively sought for both basic scientific and technological purposes. At normal temperature, hematite exhibits modest ferromagnetism, and its saturation magnetization is frequently less than 1 emu g^{-1}.The valence band of hematite, an n-type semiconductor with a band gap of 2.3 eV, is made up of occupied 3d crystal field orbitals of ferric ions with some admixture from the conduction band, which is made up of unoccupied d-orbitals of ferric ions. the O 2p non-bonding orbitals. Two-thirds of the octahedral positions limited by the nearly perfect hexagonal close-packed O lattices depicted in figure 1(a) are occupied by ferricions.

1.1.2. Magnetite (Fe_3O_4): As illustrated in figure 1(b), magnetite is composed of 32 super oxide (O2−) ions and has a face cantered cubic spinel structure. Both divalent and trivalent iron are present in magnetite, which sets it apart from the majority of other iron oxides. All ferrous ions occupy half of the octahedral sites in magnetite's cubic inverse spinel structure, which is made up of a cubic close-packed array of oxide ions. The ferric ions are uniformly distributed among the remaining tetrahedral sites and octahedral sites. Magnetite can therefore be classified as an n-type or p-type semiconductor. However, because of its narrow band gap, magnetite has the lowest resistivity of all the iron oxides.

1.1.3. γ-Fe_2O_3 (maghemite): According to figure 1(c), each unit of maghemite has 32 superoxide ions, 21 ferric ions, and 2 vacancies. Maghemite has a cubic structure. While ferric ions are dispersed over tetrahedral sites (eight ferric ions per unit cell) and octahedral sites (the remaining ferric ions and vacancies), oxygen anions form a cubic close-packed array. As a result, maghemite is regarded as totally oxidized magnetite, an n-type semiconductor with a 2.0 eV band gap. At ambient temperature, ferrimagnetism is present in magnetite and maghemite, with saturation magnetization up to 92 emu g−1.



(a) Hematite
Rhombohedral, $R\bar{3}c$

(b) Magnetite
cubic, Fd3m

(c) Maghemite
Cubic, $P4_332$/Tetragonal, $P4_12_12$

Figure 1 Crystal structure and crystallographic data of the hematite, magnetite and maghemite (the black ball is Ferrous ions, the green ball is Ferric ions and the red ball is superoxide ions).

1.2.1 The Core-Shell Framework: The inorganic or organic covering that encases the iron oxide core in this structure makes the entire particle stable and biocompatible and could potentially sustain biomolecules. The yolk structure is another name for iron oxide nanoparticles, which are typically not found in the center of the functional coating material. In fact, the magnetic composite Nano materials not only give the material better stability of the nanoparticle building blocks, but they also add new biological and physical characteristics as well as multifunctional behaviors. Therefore, in the inverse core–shell configuration, the surface of non-magnetic functional materials will be coated by magnetic iron oxide nanoparticles. Additionally, on the functionalized surface with an additional functional substance. magnetic iron oxide nanoparticles have the ability to mix one or more functional components and coat.

1.2.2 Matrix dispersed structure: To stop the super paramagnetic nanoparticles from clumping together to form massive ferromagnetic species, magnetic iron oxide nanoparticles are scattered across a matrix. matrix-dispersed Nanoparticles can be produced in a variety of ways, such as grafted onto bigger, mesoscale particles, distributed throughout an amorphous matrix, or as distinct, three-dimensional superstructures of nanoparticles.

1.2.3 Janus structure: Functional materials make up one side of the Janus structure, while magnetic iron oxide nanoparticles make up the other. Even if self-assembly is not a concern, applications involving anisotropic surface chemical compositions are intriguing. Target-specific platin delivery is possible with this Janus particle.

1.2.4 Structure of shell, core, and shell: The magnetic iron oxide nanoparticles in this structure are situated in the space between the two functional materials. In the majority of applications, magnetic iron oxide nanoparticles must be embedded in nonmagnetic layers to prevent aggregation and sedimentation and to provide them suitable surface characteristics for a given use.

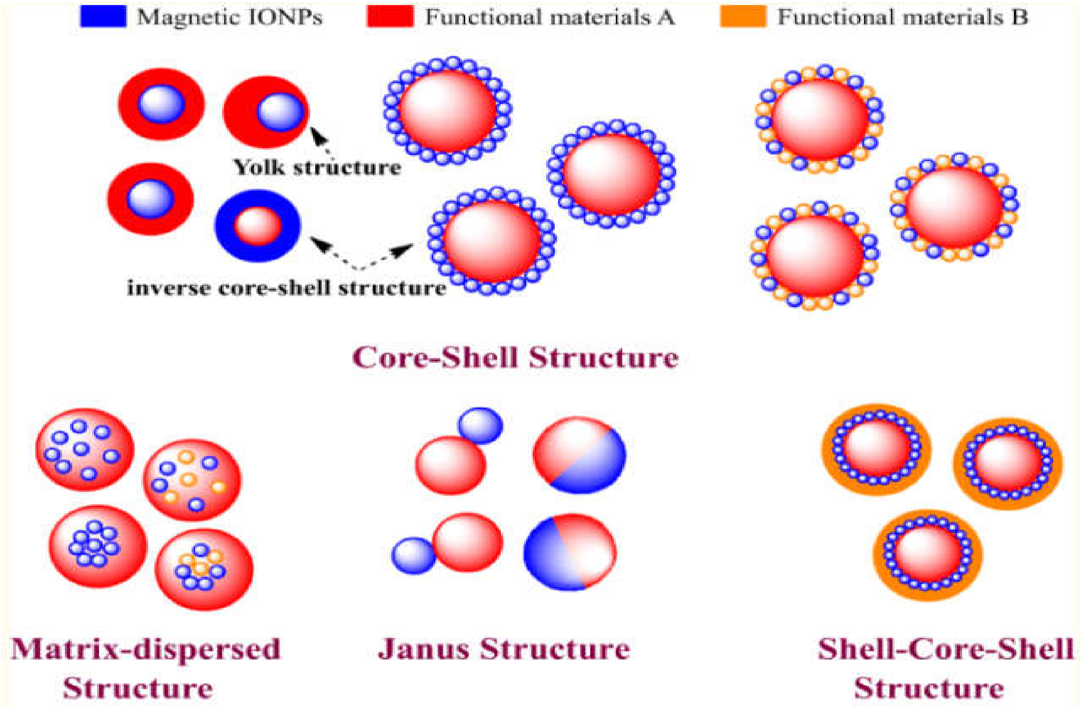


Figure 2.DIFFERENT STRUCTURES OF IRON OXIDE NANOPARTICLES

1.31.31.3SYNTHESIS OF MAGNETIC IRON OXIDE NANOPARTICLES:

Magnetic iron oxide nanoparticles with the right surface chemistry can be generated using a variety of synthetic techniques. The following three techniques are used to create iron oxide nanoparticles.

1.3.1 Chemical methods: The size, content, and even shape of the nanoparticles can be controlled using these straightforward, manageable, and effective techniques. The type of salt employed, the ratio of ferrous to ferric ions, pH, and ionic strength all affect the size, shape, and makeup of iron nanoparticles produced chemically. Various chemical techniques exist.

1.3.1.1 Co-precipitation: added to the Fe_2+/Fe_3+ solution either at room temperature or at a higher temperature. Different salts, including nitrates, sulfates, and chlorides, can be used to control size and shape.
change in the ratio of Fe_2+ to Fe_3+.Changes in temperature and pH (e.g.Fe_2O_3 nanoparticles are produced by precipitation at 60°C, while Fe3O4 nanoparticles are produced by precipitation at 80°C. Media's ionic strength One way to simplify the reaction mechanism is as follows:

$$Fe^{2+} + 2Fe^{3+} + 8OH^{-} \leftrightarrows Fe\,(OH)_2 + 2Fe\,(OH)_3 \rightarrow Fe_3O_4\downarrow + 4H_2O.$$

Gas protection is typically applied to the reaction. When the pH of the solution is less than 11, the magnetite nucleus is simpler to nucleate, and when the pH of the solution is greater than 11, the magnetite nucleus is easier to grow. Cations such as tetra methyl ammonium ions, potassium ions, methyl ammonium ions, lithium ions, sodium ions, and ammonium ions are added to regulate the pH. Aggregation and biocompatibility issues with iron oxide nanoparticles have been addressed by the direct introduction of many surfactants, proteins, starches, and biomolecules into the co-precipitation process.

For maximum saturation magnetization, the resulting nanoparticles are vacuum-dried at 70°C. The diameter of the synthesized magnetite particles, as determined by X-ray diffraction examination, was 8 nm, and they were approximately spherical.

The experimental conditions, including the types of iron salts (chlorides, perchlorates, sulphates, nitrates, etc.), the ferrous/ferric ratio, the pH value, the added cations to maintain pH, and the influence of bases, all affect the size, shape, and composition of the iron oxide nanoparticles. One of the effective and traditional methods for creating iron oxide nanoparticles with high saturation magnetization is the co-precipitation method. The iron oxide nanoparticles produced using this technique have a high degree of poly dispersity and a low degree of Crystallinity.

1.3.1.2 Micro emulsion method: The micro emulsion method is used to get over issues such the co-precipitation method's high polydispersity and low degree of crystallinity. Clear, isotropic, and thermodynamically stable liquid mixes of oil, water, and surfactant—often in conjunction with a co-surfactant—are known as microemulsions. The hydrophilic head groups of the surfactant molecules dissolve in the aqueous phase, while the hydrophobic tails dissolve in the oil phase, forming a monolayer at the water-oil boundary. The "oil" in this system may actually be a complex combination of various hydrocarbons and olefins, while the aqueous phase may contain metal salts and/or other substances.

Iron oxide nanoparticles with certain size and shape have all been created using the two fundamental forms of micro emulsions: direct (oil dispersed in water, o/w) and reversed (water dispersed in oil, w/o). Coalescence and decalescence are dynamic processes that the micro emulsion droplets go through with other droplets. As a result, the water pool content is exchanged, and a reaction takes place. Any solubilized reactant in the water pool will be distributed uniformly thanks to this dynamic action.

Magnetic iron oxide nanoparticles have been made using common surfactants such as bis (2-ethylhexyl) sulfosuccinate (AOT), sodium dodecyl sulphate (SDS), cetyltrimethylammonium bromide (CTAB), and polyvinyl pyrrolidine. By altering the ratio of water, oil, and surfactant, the size of the microemulsion—whether direct (oil dispersed in water) or indirect (water dispersed in oil)—can be regulated, which in turn affects the size of the IONPs. The size distribution of the nanoparticles and, hence, their magnetism are significantly influenced by the surfactant type, ferrous/ferric ion concentration, temperature, and pH level, as shown by microemulsion tests. This technique works well for creating metal oxides with a large surface area. Saturation magnetization, homogeneity of the microemulsion process, and other benefits of particle size and functionalization is simple.

1.3.1.3 Solvothermal and hydrothermal techniques: The hydrothermal approach produces homogenous iron oxide nanoparticles by exposing iron precursors to vapor in a sealed container at high temperatures and pressures in an aqueous solution. In these circumstances, the regulated oxidation of Ferric ion mineralization and magnetite formation take place. Mono disperse iron oxide nanoparticles with high crystallinity and a regulated shape can be formed by using the solvo thermal approach, which involves substituting other organic solvents for water when aqueous synthesis methods produce particles with low crystallization. Highly crystalline iron oxide nanoparticles, such as hematite, maghemite, and magnetite nanoparticles, are frequently produced by hydrothermal and solvo thermal synthesis.

One easy and common way to produce hollow iron oxide nanoparticles is by the hydrothermal and solvo thermal approach. Acetate, urea, and sodium citrate are combined with ethylene glycol while stirring in a standard process that uses ferric as the iron resource. The resulting homogenous mixture is then transferred to a Teflon-lined stainless-steel autoclave and sealed to heat at roughly 200°C for 8 to 24 hours. It then crystallizes and cools, forming nanoparticles. Additionally, shape-controlled iron oxide nanoparticles can be obtained by using the hydrothermal and solvothermal synthesis technique, which has been designed to produce iron oxide nanoparticles with variable size and form.

The hydrothermal process has a number of benefits, including the ability to produce crystalline phases that are unstable near the melting point. Additionally, the hydrothermal process can be used to create materials with high vapour pressures close to their melting temperatures.

Additionally, the technique works well for growing high-quality iron oxide nanocrystals while retaining strong compositional control.

1.3.1.4 Sol-gel technique: A good wet method for creating nanostructured metal oxides is the sol-gel procedure. This procedure creates a "sol" of nanometric particles by hydroxylating and condensing chemical precursors in solution. A three-dimensional metal oxide wet gel is produced by further condensation and inorganic polymerization. The final crystalline state requires additional heat treatments after these reactions are carried out at ambient temperature. An acid or a base hydroxylates molecular precursors. In contrast to acid catalysis, which creates a polymeric gel, base catalysis creates a colloidal gel. Solvent, temperature, nature, and concentration are the primary factors that affect the kinetics, growth reactions, hydrolysis, and condensation processes, and hence the gel's structure and characteristics.

1.3.1.5 The polyol method: is a flexible chemical technique for creating nanoparticles and microparticles with precise sizes and shapes. Polyol solvents, like polyethylene glycol, have two intriguing characteristics: they dissolve inorganic compounds because of their high dielectric constants, and they have a broad operating temperature range because of their comparatively high boiling points.temperature range for making inorganic compounds (between 25°C and the boiling point). In order to regulate particle development and stop interparticle aggregation, polyols act A precursor is suspended in liquid polyol during this procedure. After stirring, the suspension is heated to a temperature that can raise the polyol's boiling point. In the course of this reaction, the metal precursor dissolves in the diol, creates an intermediate, and is then reduced to create metal nuclei, which in turn generate metal particles. By raising the reaction temperature or causing heterogeneous nucleation by adding foreign nuclei or creating foreign nuclei in situ, submicrometric-sized particles can be produced.This strategy has a number of advantages over the aqueous method.

Hydrophilic polyol ligands are present on the surface of the generated magnetite nanoparticles, allowing forParticles having a higher crystallinity and, thus, a higher magnetism are favored by this system's comparatively higher reaction temperature. Lastly, compared to particles made using conventional techniques, the nanoparticles' size distribution is substantially more constrained.

1.**3.1.6 Sonolysis**: Organometallic precursors can be broken down (either by thermal or sonolysis)

1to produce iron oxide.To restrict the growth of nanoparticles, structural hosts, polymers, and organic capping agents are employed. Ferrous salts can be transformed into magnetic nanoparticles thanks to the extremely high A stable hydrosol of amorphous magnetite nanoparticles is produced when sodium dodecylsulphate is added to an aqueous solution of iron pentacarbonyl through sonolysis. The primary determinants of particle size are the ultrasonic wave strength and reaction temperature. Among the benefits of the sono-chemical approach are its homogeneous mixing and decreased crystal formation, which can help accelerate chemical dynamics and reaction rates.

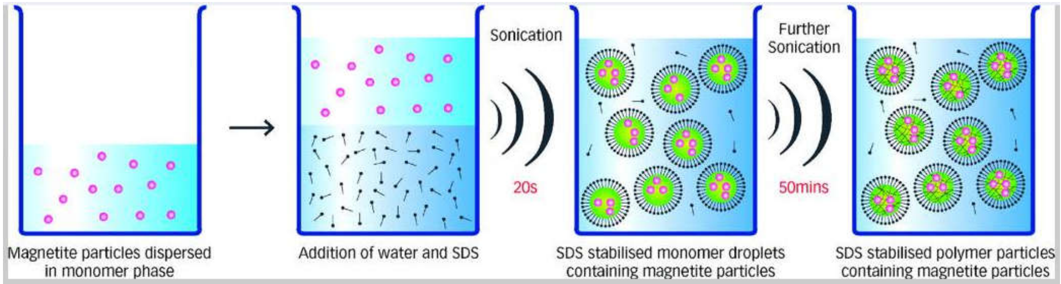


Figure 3.Schematic diagram of the procedure for the encapsulation of magnetite Nanoparticles and monomer droplet to latex particle conversion by the sonochemically driven miniemulsion polymerization pathway.

1.3.1.7 Microwave-assisted synthesis: When molecules are excited by microwave radiation, their dipoles align in the external field. An high internal heating results from strong agitation brought on by molecules oriented in phase with the electrical field stimulation. Due to its nearly immediate "in core" heating of materials in a homogeneous and selective way, microwave-assisted synthesis can thereby drastically cut down on processing time and energy costs. Recently, magnetic iron oxide nanoparticles with tunable sizes and shapes have been produced in large quantities using the microwave-assisted synthesis technique.

The biggest benefit is that, in comparison to traditional heating, it may heat a material consistently through a glass or plastic reaction container, resulting in more homogenous nucleation and quicker crystallization. The stabilization of the iron oxide nanoparticles made using the microwave-assisted synthesis pathway in organic solvents can be readily dissolved in water without the need for time-consuming ligand exchange or purification procedures, in contrast to the thermal decomposition method. These features may be appealing for producing iron oxide nanoparticles on a big scale.

1.3.1.8 Methods for the Aerosol/Vapour Phase: Because they are continuous chemical processes that enable high- A mixture of ferric salts and a reducing agent in an organic solvent is sprayed into a sequence of reactors in spray pyrolysis, where the aerosol solute condenses and the solvent evaporates, producing dry residue. The size of the particles that make up this residue is determined by the size of the original droplets. Various iron precursor salts in alcoholic solution have been used to create maghemite particles with sizes ranging from 5 to 60 nm and various morphologies. Using flame spray pyrolysis is an advancement in spray pyrolysis.The foundation of FlameSpray Pyrolysis is the exothermic burning of a metallo organic liquid spray.

A appropriate nozzle-equipped burner is used to disseminate a metal-organic compound and a solvent into a flame. The resulting mixture droplets are then combusted, creating tiny clusters that are then grown up by collisions and sintering processes occurring in the high temperature environment of

the fire. In the presence of oxygen, solvents and metalloorganic compounds totally burn in carbon dioxide and water. The nanoparticles produced by flame spray pyrolysis are crystalline and completely oxidized because of the high flame temperatures and the presence of oxygen. The following figure displays the spray pyrolysis schematic diagrams:3. A appropriate filtering device is positioned above the flame to collect the powders. Flame conditions can control properties like surface area, porosity, degree of agglomeration and aggregation, crystalline phase, and crystallite size.

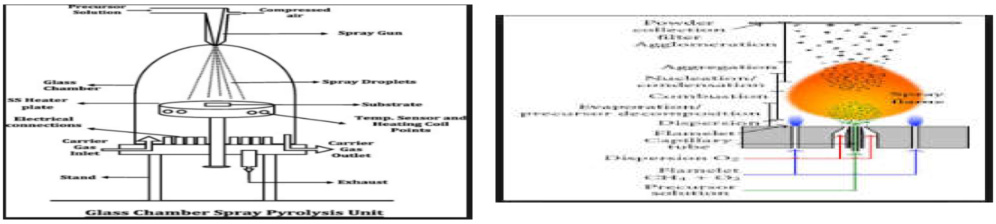


Figure 4. Schematic diagrams of spray pyrolysis and flame spray pyrolysis

a) **Laser pyrolysis:** This technique can be applied to lower the volume of the reaction. A gaseous mixture of iron precursor and a flowing gas combination are heated by a laser to create tiny, non-aggregated nanoparticles. The crystal size of maghemite nanoparticles varies between 2 and 7 nm with a relatively narrow size distribution when the pyrolysis experimental conditions are changed. Recent results reported in the fabrication of iron-based nanostructures, where sensitized iron-pentacarbonyl-based combinations and ethylene are energy-transfer agents with air as an oxidant, demonstrate the use of laser pyrolysis as a gas-phase synthesis method for nanoparticles.

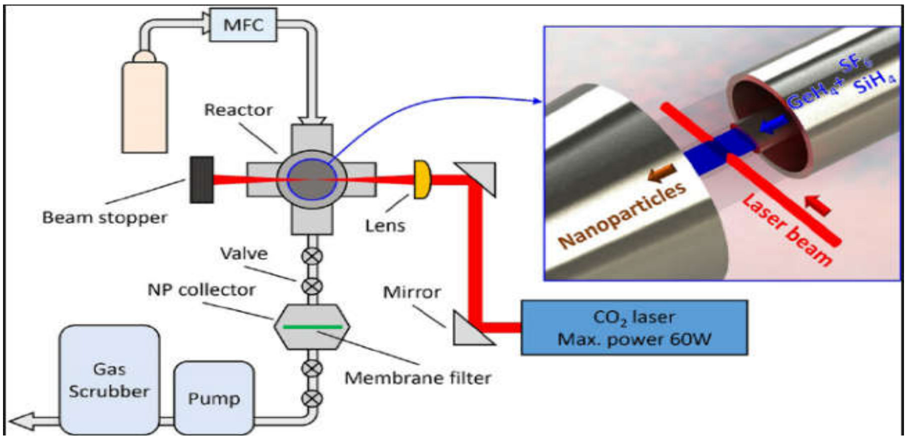


Figure 5. Schematic diagram for Laser Pyrolysis

1.3.1.1 Electro chemical methods*:* The electrochemical methods for iron oxide nanoparticles present some advantages over other methods, the crucial one being the high purity of the product, and the control of particle size is achieved by adjusting the current or the potential applied to the system. Magnetite nanoparticles with sizes between 20 and 30 nm by Fe electro-oxidation in the presence of an amine surfactant, which acted as a supporting electrolyte and coating agent for particle size and aggregation control during the synthesis process. The distance between electrodes is critical for the successful synthesis of iron oxide nanoparticles.

1.3.2 Physical methods: Physical methods can be divided into “top down” and “bottom up” procedures. Top down methods are based on the size reduction of macroscopic magnetic materials to the nanometre range, e.g., by means of milling. A major drawback of these methods is the difficulty of adjusting the desired particle size and shape. Furthermore, the milling procedure leads to lattice defects that cause deviations in the magnetic properties compared to regular particles of the same size. Bottom up methods use the condensation of nanoparticles from either a liquid or gaseous phase. A promising bottom up method for the synthesis of iron oxide nanoparticles powders is laser evaporation. Starting materials are coarse metal oxide powders of a few m sized particles, which are evaporated by means of a laser. As a result of the steep temperature gradient outside of the evaporation zone, a very fast condensation and nucleation takes place from the gas phase and nanoparticles are formed. The resulting mean particle sizes (20 to 50 nm) and magnetic phase are tuned by laser power and composition of the atmosphere in the evaporation chamber.

1.3.3 **Biological methods or bio mineralization:** some living organisms prepare magnetic particles for use for their sense of direction. Magneto tactic bacteria is a classic example which are capable of preparing magneto some. Magneto some are Nano sized crystals of magnetic iron oxide coated with proteins. The bacteria use the particles as a compass to find their preferred habitat in anaerobic areas at the bottom of the sea. Under anaerobic synthesis conditions similar to the conditions of their habitat produce uniform particles of 20 to 45 nm core diameter. Magneto some has medical application like hyperthermia as they show excellent magnetic properties but they have found no application in medicine until now due to their bacterial protein coating[12-15].

1.4 SURFACE FUNCTIONALISATION OF IRON OXIDE NANOPARTICLES:

A prerequisite for every possible applied structure is the proper surface protection or functionalization of such magnetic composite Nanoparticles.Iron oxides with bare surface tend to agglomerate due to strong magnetic attraction among particles, Vander Waals forces, and high energy surface. Consequently, the reticula endothelial system eliminates the agglomerated iron oxide Nanoparticles. High concentration of local Ferrous ions is also toxic to organisms from Ferrous dissolution. Magnetic nanoparticles have hydrophobic surface with large surface -area -to- volume ratio. These particles agglomerate and form large clusters and increase the particle size and also increases the saturation magnetisation.

These can be avoided by coating a shell on the iron oxide Nanoparticles surface which makes them hydrophilic, compatible to bio environments, and functionalized. The appropriate surface coating allows a targetable delivery with particle localization in a specific area and is considered biocompatible and non toxic.There are different types of coating techniques.

1.4.1 **Organic Materials:** Several approaches have been developed to functionalize iron oxide nanoparticles, including in situ coatings and post-synthesis coating, which are the common routes for organic material coating on the iron oxide nanoparticle surface. iron oxide nanoparticles are functionalised either with small molecules or surfactants and polymers

1.4.1.1 **Small molecules and surfactants:** For surface modification magnetic nanoparticles should be functionalised by special groups (e.g. hydroxyl, carbonyl, amide, sulfanide groups), which are suitable for the attachment of different bioactive molecules for various applications. A small molecule silicane is often used to modify and endow the functionalized end groups to the surface of bare iron oxide nanoparticles directly for post-connecting with metal ions, polymers, biomolecules or other biological entities. However, fabrication of oil-soluble type iron oxide nanoparticles is very important for obtaining monodisperse iron oxide nanoparticles. The most common organic compounds are oleic acid and oleyamine are used. oleic acid is widely used in iron oxide nanoparticle synthesis because it can form a dense protective monolayer, thereby producing highly uniform iron oxide nanoparticles. Generally, the oleic acid and oleyamine are often used in the high-temperature thermal decomposition reaction process. To synthesize water-soluble magnetic iron oxide nanoparticles directly, one way is to use small molecules (such as amino acid, citric acid, vitamin, cyclodextrin, etc) in the reaction process. Generally, surface of magnetic nanoparticles is hydrophobic in order to change the polarity to hydrophilic excess of ligand should be added to the Nano particulate solution, resulting in the displacement of the original ligand on the surface of nanoparticles. Examples Nitrosonium tetrafluoroborate ($NOBF_4$) is used to replace the original organic ligands attached to the nanoparticles surface, stabilizing the nanoparticles in various polar and hydrophilic media for years, without aggregation or precipitation.

1.4.1.2 **Natural and synthetic polymers*:*** Compared with small molecules and surfactants, polymer functionalization not only provides multifunctional groups and more colloid stability, but also plays a significant role in pharmacokinetics and bio distribution. Polymers are the most common surface coating used in iron oxide nanoparticles, since they can prevent oxidation and confer stability to the nanoparticles and the polymers get attached to the surface of magnetic nanoparticles by either adsorption by covalent bond linkage or by cross linker like glutaldehyde. The polymers can be synthetic, polyethylene glycol, poly(vinylpyrrolidone), polyvinyl alcohol and poly (lactic-co-glycolic acid), or natural like chitosan.

1.4.1.2.1 **Poly Ethylene Glycol (PEG):** Poly ethylene glycol is a hydrophilic, uncharged polyether polymer well known for its biocompatibility. It has been commonly used as iron oxide nanoparticles-coating due to reduced blood proteins opsonization,non-fouling properties and, as a result, escapes recognition by the immune system. These properties increase its time in blood circulation and the accumulation in the target cells/organ.Water-soluble synthetic polymers include polyvinyl pyrrolidine and polyvinyl alcohol. N-vinyl pyrrolidone is the monomer from which polyvinyl pyrrolidine is generated. Polyvinyl pyrrolidine is widely utilized in pharmaceutical and biomedical applications because of its safe, stable, and biocompatible qualities. Conversely, polyvinyl alcohol demonstrates emulsifying and adhesive qualities, utilizing hydrogen bonds between the polymer chains to generate a hydrogel structure that incorporates the iron oxide nanoparticles. This prevents the particles from clumping together by increasing the contacts between the polymer and the surface.

1.4.1.2.2 Poly (lactic-co-glycolic acid): Poly (lactic-co-glycolic acid) is a copolymer of poly lactic acid and poly glycolic acid with great potential for use in drug delivery and tissue engineering. Besides presenting solubility in most of common solvents, Poly (lactic-co-glycolic acid) can take different shapes and sizes, and encapsulates molecules of all sizes. Generally, higher rates of poly glycolic acid (which contains methyl site groups) lead to a highest degradation of the polymer and hydrophobicity. On the other hand, lactide-rich poly (lactic-co-glycolic acid) are less hydrophilic and degrade more slowly, since it absorbs less water. Moreover, physical properties of poly (lactic-co-glycolic acid)are known to vary depending on different factors such as the molecular weight, which plays an important role in the drug-loading capacity on the polymer surface.

1.4.1.2.3 Chitosan: Iron oxide nanoparticles have also been coated with Chitosan. This material is a natural, long-chain polymer, generated by the combination of 2-amino-2-deoxy -D-glucan with glycosidic linkages, which can be obtained by chitin deacetylation. Its positive charge drives the Chitosan carriers to the cell membrane (negatively charged) and its mucoadhesive properties extend the Chitosan retention in the target sites, making it interesting for application in drug delivery systems. Furthermore, Chitosan is biocompatible, biodegradable and presents low toxicity.

Many Chitosan-Nano systems have been developed over the last few years, relying on the aforementioned advantages and water solubility. Coating of iron oxide nanoparticles with this polymer does not change the thermal and magnetic properties of the nanoparticles, serving as support for drug binding. Also, a one-pot synthesis in the presence of Chitosan of low molecular weight showed that it was capable of protecting iron oxide nanoparticles from aggregation due to the electrostatic repulsion between the positively charged nanoparticles.As a coating polymer this polymer has certain limitations, mainly associated with the partial protonation of its amino groups in water at physiological pH, which reduces Chitosan solubility. To overcome such issues, chemical changes can be performed in order to make Chitosan derivatives more water-soluble-carboxymethyl Chitosan, forms hydrogen bonding between water and the polymer in combination with carboxyl group to obtain watersolubilisation is a practical example. Also, a polyelectrolyte complex of carboxymethyl starch-Chitosan can be used as a coating for iron oxide nanoparticles, producing stable, biocompatible and mucoadhesive Nano systems.

1.4.1.2.5 Biomolecules: Because of their increased biocompatibility, biomolecule-functionalized magnetic iron oxide nanoparticles have recently emerged as a popular and successful technique in biological separation, detection, sensors, and other bio-applications. Iron oxide nanoparticles have been coated with a variety of biomolecules, such as enzymes, proteins, antibodies, biotin, bovine/human serum albumin, avidin, and polypeptides.

1.4.2 Inorganic Materials:

1.4.2.1 Silicon: Silica-coatediron oxide nanoparticles is a classical and important composite material for both fundamental study and bio-applications. Silica coating can enhance the dispersion in solution and also stabilise the nanoparticles and protect from acidic environment. Three different approaches have been explored to generate Silica-coated iron oxide nanoparticles. The first method relied on the well-known Stober process, in which the iron oxide nanoparticles were homogeneously dispersed in the alcohol, then the silane was added, and finally the water or ammonia aqueous solution was dropped into the mixed solution and Silica-coated iron oxide nanoparticles areformed.Tetraethoxysilane, Vinyltriethoxysilane, Octadecyltrimethoxy silane are the most common used silanes, which easily bind on the surface of iron oxide nanoparticles through hydroxyl groups.

The second approach was based on microemulsion synthesis, in which micelles or inverse micelles were used to confine and control the coating of silica on core nanoparticles.

It is noteworthy that this method requires much effort to separate the core–shell nanoparticles from the large number of surfactants associated with the microemulsion system.

The third approach is aerosol pyrolysis, in which Silica-coated iron oxide nanoparticles were prepared by aerosol pyrolysis of a precursor mixture composed of silicon alkoxides and metal compound in a flame environment.

1.4.2.2 Carbon: Iron oxide nanoparticles shielded by carbon have good chemical and thermal stability in addition to their inherent high electrical conductivity. The carbon coating in magnetic core materials prevents corrosion and serves as an oxidation barrier. A hydrophilic carbon coating on iron oxide nanoparticle cores improves stability and dispersibility compared to bare iron oxide nanoparticles. Three processes make up the usual procedure: first, magnetic iron oxide nanoparticles are created as seeds using a number of methods; next, the polymer is covered using the polymerization process; and finally, iron oxide nanoparticle carbon composite materials are created by annealing.

1.4.2.3 Metals: Surface modification of iron oxide nanoparticles with metallic elements can provide an inert layer, which typically exhibit a core-shell, core-satellite or dumbbell structure. Metallic coatings facilitate further functionalization of the iron oxide nanoparticles to improve stability and compatibility. Gold and silver are the most common noble metal element used for surface coating.

In general, the core–shell, core–satellites and dumbbell structures of iron oxide nanoparticles can be formed by microemulsion and thermal decomposition methods and then direct and indirect method are the two routes used to achieve the gold shell coating on the surface of the magnetic iron oxide nanoparticles.

In direct method, a gold or silver shell is formed on the surface of Ferrous oxide nanoparticles by reduction of gold or silver ions in the presence of reducing agents. Direct gold coating is carried out in aqueous or organic solutions. Sodium citrate and sodium borohydride are used as reducing agents in the aqueous phase. In the organic phase, oleic acid and oleylamine are used as reducing agents.

In indirect method, Gold/silver coated iron oxide nanoparticles are synthesised by forming a “glue layer” between the iron oxide nanoparticles core and the gold shell. The “glue” layer should be capable of enhancing the magnetite magnetic nanoparticles stability, and also have metal binding groups to attach gold seeds to promote the formation of gold shell. Materials used as “glue” layer are polymers like silica and carbon.

1.4.2.4 Metal oxides and sulphides: More and more metal oxides or sulphides have been used to protect or functionalize iron oxide nanoparticles, mainly because of the fantastic magnetic properties of iron oxide nanoparticles and other unique physical or chemical properties of metal oxides and sulphides.

Oxide and sulphide semiconductors are the most common compounds that are used to functionalize magnetic iron oxide nanoparticles, such as Titanium oxide, Zinc oxide, stannic oxide, tungsten trioxide, cuprous oxide, Cadmium sulphide, zinc sulphide, Lead sulphide, Bismuth sulphide etc .

1.5 CHEMICAL PROPERTIES OF IRON OXIDENANO PARTICLES

- Iron NPs are extremely reactive with oxidizing agents, particularly with air.
- 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.
- Iron oxide NMs have great importance because of their magnetic properties and wide applications
- They are biocompatible and non-toxic also. The **Iron oxide nanoparticle** shows improved quality in terms of size tunability, monodispersity and crystalline structure as compared to that of traditional **iron** oxides.

1.6 FACTORS ENHANCING THE EFFICIENCY OF IRON OXIDE NANOPARTICLES:

- High magnetic susceptibility for an effective magnetic enhancement.
- The property of super paramagnetic crystal suspension to absorb energy of an oscillating magnetic field.
- The most effective, cheap, and simplest pathway (technique) to obtain magnetic particles, e.g. the simplest one is the precipitation technique to obtain iron oxide particles
- 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.

- Size of NPs, i.e., small size gives a high surface-area-to-volume ratio that enables interaction with various types of chemical species, both aqueous and gaseous. The materials at Nano scale are potentially highly efficient for binding metal ions.
- Controlled shape, nucleation, growth, durability, reproducibility, scalability, dispersibility (particularly for building complex magnetic nanostructures). 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.
- 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.
- High magnetic susceptibility for an effective magnetic enhancement. Further, the diameter of coated (with metallic or non-metallic) iron oxide NPs is prone to tailoring, and the indispensable diameter can be attained by adjusting reduction and the repeat times.
- Characteristics associated with the use of magnetically responsive and magnetically guided NPs in magnetofection and drug delivery.
- Particles should be Nano sized (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 high saturation magnetization values. These Nano sized range particles are rapidly removed through eructation and renal clearance.
- The property of super paramagnetic 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.
- Tailored surface chemistry for specific biomedical applications.

- Development of iron oxide NPs that should be characteristically suitable for optimal cell labelling 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.
- 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.
- High coactivity and low Curie temperature

1.7APPLICATIONS OF IRON OXIDE NANOPARTICLES:

1.7.1 Targeted drug delivery

- Nanostructure-mediated targeted drug delivery, a key technology for the realization of Nano carriers, has the potential to enhance drug bioavailability, improve the timed release of drug molecules, easily functionalize with targeting ligands, and enable precision drug targeting (sensitivity to an external magnetic field). In particular, magnetic composite iron oxide nanoparticles are currently recognized as one of the most promising modalities of such drug carriers. Furthermore, nanostructure targeted iron oxide nanoparticles carriers can not only serve as a vehicle for drug delivery, but also for gene delivery. A high drug loading efficiency and drug-release rate are essential parameters for therapy, while mesoporous functional layers (such as Silicon dioxide and carbon) and iron oxide nanoparticles with hollow or mesoporous structure are enabling the promotion of drug loading.
- Moreover, carriers comprising coated magnetic iron oxide nanoparticles loaded with an anti-cancer drug are injected into the patient’s body via the human circulatory system. An external magnetic field localize the drug loaded carriers to the target site and the drug can then be released from the carriers either via enzymatic activity or changes in physiological conditions such as pH, osmolality, or temperature, and be taken up by target cells.
- Smart control release systems have been developed to meet the changed physiological conditions, enhance accumulation, and control drug release at the intended sites. The

stimulus pH-/thermo-/photo-magnetic targeted drug delivery systems are the common smart control release systems. Generally, the pH of body tissue is maintained around 7.4 in a healthy human. However, there exist several mechanisms to modulate pH inside the body. The gastrointestinal tract changes the pH along the tube, which is ∼1–3 in the stomach and ∼7 in the intestine. Each mechanism has been used as a triggering signal for pH-responsive targeted drug delivery. Basically, ionisable moieties, such as carboxylic acid, amine, azo, phenylboronic acid, imidazole, pyridine, sulphonamide, and thiol group functionalized iron oxide nanoparticles can afford pH-sensitivity drug loaded carriers. A thermo sensitive polymer obtained by simple aliphatic modification of biocompatibility/biodegradable block copolymers exhibited a low critical solution temperature of ∼38 °C, thus the functionalized iron oxide nanoparticles released the drugs in response to a variation in external temperature

- The drug release is primarily influenced by a triggered drug release mechanism. The acidic medium favours drug release because of the acid-labile linker. Additionally, targeted delivery of therapeutic agents to the brain has enormous potential for the treatment of several neurological disorders such as Alzheimer’s disease and brain tumours. However, the blood–brain barrier significantly impedes the entry of drug molecules into the brain from the bloodstream. Iron oxide nanoparticles-based targeted delivery represents a promising alternative strategy in overcoming the BBB.

The potential application in medicine is currently further enhanced by the creation of multifunctional magnetic iron oxide nanoparticles that have been functionalized or coated with polymers, lipidic, or inorganic shells. These multipurpose iron oxide nanoparticles have uses in fluorescence/luminescence imaging, targeted thermosensitive chemotherapy, and magnetic resonance imaging in addition to being a medium for targeted drug administration.[16–22]

1.3.4 The use of ferromagnetic nanoparticles for magnetic hyperthermia and thermo ablation therapies has attracted considerable attention as one of the promising treatments for cancer. Hyperthermia is the heating of cells in the range of 41–47 °C, which causes the preferential death of tumour cells. When magnetic iron oxide nanoparticles are subjected to an alternating magnetic field, heat generation is a result of a combination of internal Neel fluctuations of the particle magnetic moment, hysteresis, and the external Brownian fluctuations that all rely on the magnetic properties of iron oxide nanoparticles. However, the temperature of the thermo ablation method should be greater than 47°C, which causes the rapid death of tumour cells due to the high temperature. Thus, some difficulties are faced when heating the tumour part to a sufficiently high temperature while simultaneously maintaining the normal tissues at a lower temperature. Modern techniques generally employ localized hyperthermia for cancer therapy.[23] Many techniques have been developed for the localized heating treatment of cancers, for example, radio-frequency waves microwaves and ultrasounds.Hence, increased heating rates of magnetic iron oxide nanoparticles are an important challenge in order to minimize dosages of magnetic iron oxide nanoparticles needed to reach therapeutic temperatures in magnetic hyperthermia or thermo ablation. Possible approaches to increase heating rates are increasing the anisotropy of the nanoparticles (shape or magneto crystalline) or increasing the field strength. An alternative approach to increase the heating rates would be to increase the monodispersity of a sample of magnetite nanoparticles.Supra magnetic iron oxide nanoparticles can be considered as a very promising agent for hyperthermia therapy, but this new field of application requires an improvement of the reproducibility, size and shape controlling in the preparing process and its biocompatibility. Moreover, how to apply the cancer treatment of fine tissues (such as brain and kidney) is also an ongoing challenge.[24]

1.7.2 Bio-separation: As a successful application of magnetic iron oxide nanoparticles, bio-separation is also an important kind of application, especially for *in vitro* DNA, antibody, protein, gene, enzyme, cell, virus and bacteria separation. Compared with the traditional separation procedures, magnetic separation has many advantages of being able to be quickly localized or retrieved with a common magnet), which is faster and more cost-effective than traditional column affinity chromatography. Generally, surface functionalized magnetic iron oxide nanoparticles with suitable intermediates are commonly used to enhance the separation efficiency with such modification of surfactants, polymers, and ligands for introducing functional end groups (such as hydroxyl, amino, sulphanide, carboxyl groups etc.) through the selective adsorption to the target biomolecules.Additionally, Iron oxide nanoparticle-based magnetic separation applications involve strict requirements such as chemical composition, particle size and size distribution, stability of magnetic properties, morphology, adsorption properties and low toxicity, and so on. Magnetic iron oxide nanoparticles with a core–shell structure may enable this development of bio-separation fields, especially silica coated iron oxide nanoparticles

1.7.3 Biosensor. In order to identify biomolecules and cells with great sensitivity and perhaps facilitate early disease diagnosis, biosensing has been created as an effective diagnostic platform. High specificity and biocompatibility are demonstrated by magnetic nanosensors that are synthesized for the detection of molecular interactions both in vitro and in vivo.Furthermore, the super paramagneticiron oxide nanoparticles core of an individual nanoparticle becomes more efficient at dephasing the spins of surrounding water protons, enhancing T_2relaxation times so that the nanoparticles act as magnetic relaxation switches in the cooperative assembly process.[25]Magnetic biosensors for diagnosis have not only been based on the properties of iron oxide nanoparticles, but also on functionalized coated materials. The magnetic bead-based biosensors are functionalized iron oxide nanoparticles by conjugating targeting ligands, which endow new specificity to the magnetic bead–based biosensors. Simultaneously, the iron oxide nanoparticles, together with targeted receptors and functionalized layers/materials, act as the generator or detector of a signal, assigning the sensitivity of magnetic bead-based biosensors. Optical-magnetic bead-based biosensors exhibit excellent optical performance because of the unique interactions between light waves and the surface coating materials (such as gold, silver and fluorescent molecules), which displayed excellent localized surface plasmon resonance (LSPR), surface-enhanced Raman scattering (SERS), and fluorescence. One-dimensional nanostructures (such as carbon nanotube, nanowires, and grapheme) have been applied as functional components for electrochemical magnetic bead-based biosensors. Those are usually based on a field-effect transistor (FET) where analyte molecules act as a gate, which controls the electrical resistance by causing depletion or accumulation of charge carriers and the electrochemical–magnetic bead-based biosensors in clinical diagnosis are based on glucose, lactate, cholesterol, urea, creatine, and creatinine biosensors.

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