

Review

An Overview of Iron Oxide (Fe₃O₄) Nanoparticles: From Synthetic Strategies, Characterization to Antibacterial and Anticancer Applications

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Abstract: Magnetic nanoparticles have been discovered to be promising materials for various biomedical applications; for example, they have been used for cancer detection, screening, and chemotherapy studies during the last few decades. Likewise, magnetic nanoparticles have significant antibacterial properties, and similarly, they can be applied for magnetic resonance imaging purposes. These sensors are meant to detect certain biomarkers, which are substances that can be linked to the beginning or progression of cancer both during and after therapy. Magnetic nanoparticles have several unique properties that are being employed widely in cancer therapy as drug delivery agents to precisely target the targeted spot using an external magnetic field in vivo. Magnetic resonance imaging can also be used in conjunction with antineoplastic drug treatment personalized to the individual. We have presented an overview of the different applications of magnetic nanoparticles as well as current breakthroughs in their development as antibacterial and cancer therapies in this review. In addition, the cancer targeting, possible toxicity, and degradability of these nanomaterials are briefly discussed.

Keywords: NPs MNPs; antibacterial properties; drug delivery; cancer therapy



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1. Introduction

The study of science, engineering, and technology in the nanoscale, which extends from 1 to 100 nanometers, is known as nanotechnology [1]. The study and use of tiny things can assist all other science areas, including biology, chemistry, physics, material science, and engineering. Nanoscience and nanotechnology are the terms for this [2–4]. In his conversation, an American physicist named “Richard Feynman” uncovered the notions and concept of nanoparticles and nanoscience for the first time. On 29 December 1959, at the physical society meeting at the California Institute of Technology, there was plenty of room at the bottom. Professor Norio Taniguchi invented the term “nanotechnology” in 1974 while researching ultra-precision machining. Eric Drexler used the word “nanotechnology” in his 1986 book *Engine of Creation: The Coming Era of Nanotechnology*. The scanning tunneling microscope, which was invented in 1981, allowed for the observation of individual atoms and bonds. Second, fullerenes were discovered in 1985 by Harry Kroto, Richard Smalley, and Robert Curl, earning them the Nobel Prize in Chemistry in 1996 [5]. Sumio Iijima (Japan) developed carbon nanotubes in 1991 and was awarded the Kavli Prize in Nanoscience in 2008 [6]. A 3 nm MOSFET was developed in 2006 by a Korean researcher from the Korea Advanced Institute of Science and Technology (KAIST) and the

National Nano Fab Center (metal-oxide-semiconductor-field-effect transistor [7,8]. “Nano” is derived from the ancient Greek word “nanos”, which meaning “dwarf” (small) [9]. The only units of measurement for length are meters and centimeters. One billionth of a meter is a nanometer. One nanometer equals 0.000000001 m or 9–10 m. A particle is a tiny component of stuff that makes up everything in the cosmos. The term “elementary particle” refers to anything that cannot be broken down any further [10]. There are several varieties of particles, each with its own size and features. As stated in Table 1, one of the important particles is nanoparticles. Any substance with at least one dimension in the range of 1–100 nm is referred to as a nanoparticle. It is invisible to the naked eye. The physical and chemical characteristics of nanoparticles can vary greatly.

Table 1. Particle types and its diameter size.

Particle Type	Diameter Size
Small molecules and/or atoms	0.1 nm
Nanoparticles (NPs)	1–100 nm
Fine particles	100–2500 nm
Coarse particles (dust)	2500–10,000 nm
Thickness of paper	100,000 nm

Nanomaterials are classified into the following groups based on their size, morphology, physical, and chemical characteristics [11]. Carbon nanotubes (CNTs) and fullerene are the two basic components in carbon-based nanomaterials [12]. Carbon nanotubes are nothing more than rolled-up graphene sheets. Single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) are two types of carbon nanotubes (MWCNTs) [13]. Fullerenes are carbon allotropes with a hollow cage structure containing sixty or more carbon atoms. Ceramic-based nanoparticles, on the other hand, are inorganic solids made composed of oxides, carbides, carbonates, and phosphate. Ceramic nanoparticles can be used as effective drug delivery agents by manipulating certain properties, such as the size, surface to volume ratio, and so on [14]. The third kind is metallic nanoparticles, which are nanoparticles made from metal precursors and are referred to as metal nanomaterials. Chemical, electrochemical, and photochemical processes can all be used to make it. Semiconductor nanomaterials are materials that have characteristics that are similar to metals and non-metals [15]. They belong to the groups II–VI, III–V, or IV–VI of the periodic table. GaN, GaP, CdS, ZnO, and other semiconductor nanoparticles are examples [16]. Similarly, polymeric nanomaterials are organic-based nanomaterials with structures such as nanocapsules or nanospheres, depending on the technique of synthesis. Lipid-based nanomaterials are spherical nanomaterials with diameters ranging from 10 to 100 nanometers. It is made up of a solid lipid core and a matrix of soluble lipophilic molecules. It is employed in cancer therapy as a medication delivery system and to release RNA [17–20]. This review summarizes the fundamentals of metallic nanoparticles, their synthetic strategies, and their characterization in detail. Moreover, the application of nanoparticles as an antibacterial agent and as a drug delivery system for cancer therapy has been discussed here. The novelty of this review is that it covers all aspects of metallic nanoparticles, including their drug delivery ability and bactericidal properties, in one article. We hope that the topics covered in this review will be of great interest to nanoparticle researchers and general readers and will inform them of the multiple directions metallic nanoparticle research has taken and its many achievements to date.

1.1. Properties of Nanoparticles

1.1.1. Physical Properties

Physical properties include optical properties such as the shading, light entrance, ingestion and reflection capacities and UV retention and reflection capacities in an answer or covered onto a surface. The mechanical properties, for example, versatility, malleability, elasticity and adaptability, play a critical element in their application. Hydrophilicity,

hydrophobicity, suspension, dispersion, and settling properties have led to their use in numerous cutting-edge regular things. The conductivity, semiconductivity, and resistivity make the nanoparticles utilized in present-day gadgets useful in environmentally friendly power applications [21].

1.1.2. Chemical Properties

The reactivity of nanoparticles with the target, as well as their stability and susceptibility to moisture, environment, heat, and light, dictate their applicability. The nanoparticles' antibacterial, antifungal, sterilization, and toxicological capabilities make them ideal for biomedical and environmental purposes. The nanoparticles' corrosive, reduction, anti-corrosive, oxidation, reduction, and flammability capabilities dictate their everyday usage.

1.2. Synthesis Techniques of Nanoparticles

Different techniques are accessible to orchestrate nanoparticles, composite materials, metal oxides, and polymers [22]. There are two fundamental techniques for the blending of nanoparticles: for example, the base-up technique, which incorporates biosynthesis, chemical fume deterioration (CVD), pyrolysis spinning, and sol-gel. The hierarchical strategy involves mechanical processing, thermal decay, laser removal, sputtering and nanolithography [23].

2. Magnetic Materials

Magnetic materials are the materials which can draw in or repulse different materials. Attraction traces all the way back to old Greeks who likewise gave attraction its name, which was derived from "Magnesia" [24]. Magnet signifies "the stone from Magnesia". The stone consists of magnetite (Fe_3O_4). A few magnets were consolidated to frame a huge magnet for lifting power then in the eighteenth century. Then, in the twentieth century, physicists laid the premise of current innovation in light of attraction. Currently, the presentation of novel electrical, optical, or photochemically appealing qualities is likely the most exciting and trying subject in nano-research [25].

Magnetic substances/materials are arranged into two kinds: for example, delicate attractive (materials that is not difficult to charge by applying the outer field and can be demagnetizing effectively) and hard attractive (materials that gain their attraction and are challenging to demagnetize).

The previous utilization of the magnetic materials was in mass structure, yet in mass structure, a portion of the properties cannot be used in various applications. Material researchers achieved an extraordinary accomplishment tracking down materials at the miniature and nano level. These are the nanoparticles that normally make up components displaying attractive properties. They are in particular iron, nickel, cobalt and their synthetic mixtures. The attractive properties of these components exist because of the revolution of electrons around the core and twisting in an outside magnetic field [26].

2.1. Magnetism

Attraction emerges in materials because of the twist and orbital precise movements conveyed by electrons. The net attractive snapshot of an iota is the amount of the net attractive snapshots of each of the electrons in the molecule. As a rule, the orbital attractive snapshot of an iota is practically insignificant in contrast with the twist magnetic moment. In numerous molecules, the twists of adjoining iotas pair up, counterbalancing each other on a nuclear scale. For a molecule to have a twist magnetic moment, it should have electrons with unpaired twists [27]. Because of the arrangement of magnetic moments, attraction emerges in materials. Whenever an magnetic field (H) is subjected to the material, the magnetic moments in the material will generally adjust and in this way bring about the increments of the size of the strength field (B). This expansion is provided by a boundary known as polarization, (M), to such an extent that

$$B = \mu_0 H + \mu_0 M \quad (1)$$

$$M = \chi_m H \quad (2)$$

where μ_0 represents the permeability of vacuum and is given by $\mu_0 = 4\pi \times 10^{-7} \text{ H/m}$, and χ_m is called the magnetic susceptibility.

2.2. Classification of Magnetism

Magnetic materials are further classified into different types depending upon their response to applied magnetic field such as diamagnetism, paramagnetism, ferromagnetism and antiferromagnetism.

2.2.1. Diamagnetism

The magnetic moment is because of turning, and the orbital movement of electrons is zero in diamagnetic material. It is an exceptionally feeble type of attraction since they are pitifully repulsed by the magnetic field. This sort of magnetism continues just when an outside field is being applied. It emerges because of the progressions that happen in the orbital movement of electrons when an outer magnetic field is applied. There is no dipole movement without even a trace of outside magnetic field, yet with the use of an outer magnetic field, the magnetic moments adjust themselves toward the path inverse to that of the applied field. Along these lines, the worth of relative penetrability is not as much as solidarity, and the attractive vulnerability is negative. In addition, the greatness of the B field is not exactly like a vacuum in a diamagnetic material. Al_2O_3 , Cu, Au, Si and Zn are diamagnetic materials.

2.2.2. Paramagnetism

For materials having paramagnetic properties, every particle holds an extremely durable dipole second as an aftereffect of deficient wiping out of electron turn and orbital magnetic moments. Along these lines, the magnetic moments are arbitrarily adjusted without even a trace of an outer magnetic field, having no net perceptible charge. By applying an outer magnetic field, every one of the magnetic moments is adjusted toward the applied field. In paramagnetic material, the magnetic helplessness is small yet present. For example, B in a said material is somewhat more prominent than that of vacuum. Al, Cr, Mo, Ti, and Zn are paramagnetic materials. As both diamagnetic and paramagnetic materials have charge just in the presence of an outer field, they are viewed as nonmagnetic in light of the fact that for both, the motion thickness B inside them is practically something very similar to that in a vacuum.

2.2.3. Ferromagnetism

Materials that are emphatically drawn to magnets are called ferromagnetic. Iron is the most widely recognized material of this sort, since the Latin prefix Ferro implies iron. Ferromagnetic materials are those metallic materials that have a super durable magnetic moment without an outside field. These long-lasting magnetic moments in ferromagnetic materials result due to the uncanceled electron turns as an outcome of the electron structure. The commitment from the orbital magnetic moment additionally exists, which is extremely minor in contrast with the twist moment [28]. In addition, in a ferromagnetic material, coupling associations starts the net twist magnetic snapshots of neighbor particles to line up with each other even without any an outer field. The common twist arrangement exists over moderately huge volume locales of the precious stone called areas [29]. Ferromagnetic materials incorporate lodestone, iron, nickel, and cobalt.

2.2.4. Antiferromagnetism

On account of antiferromagnetism, the peculiarity of magnetic moment coupling between neighboring particles or particles happens. This coupling of electron turns brings about enemies of equal arrangement because of which the contrary twists will drop one another, and this design will yield a zero net polarization. This arrangement of the twist snapshots of adjoining molecules or particles in inverse bearings is known as antiferro-

magnetism. Manganese oxide (MnO) is a notable illustration of antiferromagnetism. The temperature at which this coupling is annihilated and the material re-visitations of paramagnetic conduct is named as Néel temperature (T_N), which is comparable to the Curie temperature for ferromagnetism.

2.2.5. Superparamagnetism

Another significant quality of the magnetic material is the superparamagnetism where the material has more noteworthy magnetic powerlessness than ordinary paramagnetic materials. The magnetic material, particularly ferromagnetic in a mass structure, has unconstrained polarization called areas, ranging from 10 to 100 nm. In this area, the magnetic moments are adjusted in the same request. It is not required for all spaces to possess the same arrangement. Hence, these materials have net polarization. Whenever an outer field is applied, the space is adjusted to the field applied. At the point when there is the most extreme arrangement, immersion polarization is obtained. The polarization stays in the material after the expulsion of the outside field in view of the contact, the Weiss space unwinding does not happen totally. The distinction among the subjected magnetic field and the polarization of material is called hysteresis. A great deal of data can be obtained by dissecting a hysteresis circle. This chart is in the middle of the subjected magnetic field " H " versus the prompted attractive motion thickness " B ".

The hysteresis circle is obtained by varying the polarizing power H while estimating the incited attractive motion thickness. The speckled line shows the prompted motion thickness of the ferromagnetic material that has neither polarized nor been demagnetized as the charging power is expanded H . The curve shows that the transition thickness is expanded $B+$ as the polarizing power is expanded H . Any increment in the polarizing power H produces a little incited attractive motion thickness $B+$ at point "a", which exhibits that all areas generally adjusted. This point is the immersion point [30]. While the charging power becomes zero, the motion thickness B line scopes to point "b", showing the remaining motion thickness in the material. This point on the diagram shows the remaining polarization level. At point "c", the prompted motion thickness becomes zero where the charging power H is turned around and is called a coercivity point. As the power is expanded in regrettable bearing, the motion thickness is additionally expanded and arrives at its immersion point in inverse heading at point "f". While the polarizing power is expanded in a sure bearing, the diagram line comes again to point after some time elapsing to point "e" inverse retentivity. Meanwhile, the point "d" is inverse coercivity, along these lines, contending a hysteresis circle. If the material is put in a magnetic field of intensity H , the magnetic induction is the ratio of individual moment response to total response as shown in the inset of Figure 1.

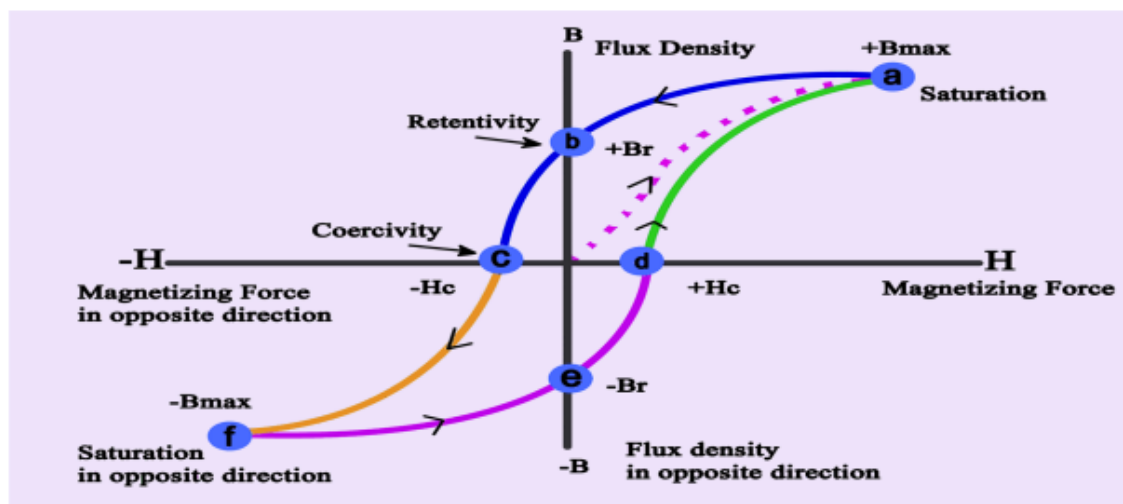


Figure 1. Hysteresis loop of magnetic material.

2.3. Unit of Magnetization

$$B = \mu \cdot H \quad (3)$$

$$B = \mu \cdot (H + M) \quad (4)$$

Here, μ represents the permeability of available space and the magnetic moment per unit volume ($M = m/v$) is magnetization, where “ m ” stands for the magnetic moment on volume. To some extent, all materials are magnetic, with their response dependent on the atomic structure and temperature. They can be described in terms of volumetric magnetic susceptibility (X).

$$M = X H \quad (5)$$

The magnetization caused by the magnetizing force H is seen in Equation (5). X is dimensionless in S.I, whereas B and H are expressed in Am^{-1} .

2.4. Magnetic Material at Nano Level

As indicated by logical terms, those having a size below 100 nm are considered as “nano” and have unexpected properties in comparison to the mass material. These materials exist in the middle nuclear and mass degree of the material. As the material size varies, variation in the properties of nanomaterials also occurred. As of now, magnetic nanomaterials are a focal point of analysis because of their remarkable properties. Most of the research has been carried out for the synthesis of 1D nanostructures such as nanotubes [31–34], nanorods [35,36], nanobelts [37–39], nanowires [37,40], nanofibers [41,42], nanosheets [43,44], and many more structures.

3. The Magnetic Nanoparticles

The MNPs have attractive conduct within the sight of the magnetic field. They have a solid connection with the magnetic field as well likewise with magnetic materials. The nanocrystal and NPs with inorganic base have ended up being crucial for the advancement of modern nanotechnology [43]. Due to nanoscale peculiarity, they have extraordinary properties [37]. Fe_3O_4 (magnetite) and Fe_2O_3 (maghemite) have appeared in different fields, for example, material science, medication, mechanical designing and science because of their amazing properties such as small size, superparamagnetism, enormous surface region, low poisonousness, and numerous others [45,46].

3.1. Physics of Magnetic Nanoparticles

The magnetic nanoparticles (MNPs) show attractive conduct according to the magnetic field. The MNPs are plentiful in nature and can exist in various living beings such as the human mind, birds, honey bees, green growth, subterranean insects and microbes. Additionally, MNPs are found in natural articles such as platelets, nerves and shockingly, a few vertebrates [45–47]. The magnetic material has a few properties such as coercive power, immersion polarization and Curie temperature, and this large number of properties are because of the compound and gem construction of the materials. The different parameters such as the size and shape play no part in the attractive property of the materials. Then again, MNPs have properties depending on the size and shape as well as synthetic creation, level of imperfection of the cross-section, and their association with encompassing material and particles [48]. The MNPs bring together two important SSP (strong state material science) and QC studies. The QC investigates the particle’s synthetic framework and union, whereas the SSP investigates the material’s design, morphology, electric, and attractive properties. At this point, the majority of sciences has merged or, at the very least, are assisting one another in the advancement of materials and their applications. The science plays an important role in material mixtures and clarifies the substance reactions of distinct materials. Physical science, on the other hand, clarifies the real state of the substance. The gem structure, mill operator indexes, planes, grain size, optical and electrical characteristics

are all clarified. For material depictions, we use several types of amalgamation operations as well as diverse methodologies.

3.2. Metal Oxide

There are many different types of materials, which are divided into metallic and non-metallic categories. Ferrous and non-ferrous metals are also separated from the metallic materials. Ferrous materials, such as steel, have iron as an important component, whereas non-ferrous materials, such as polymers, do not. Metal oxides are oxygen-containing compounds that contain at least one metal. Metal oxide is the main component of clay materials, and it has unique features at high temperatures, including resistance to oxidation and synthetic reactions.

3.3. Iron and Iron Oxide

In the intermittent table, iron is a hard and brittle component known as metal. When in an unadulterated structure, it eats the most abundant metal of all metals and consumes sodden air and high temperatures. Iron is the fourth normal component in the earth hull in terms of weight, and it makes up the great bulk of the planet's core. Excavators estimate that people have been working with iron for over 5000 years. Hematite and magnetite are the most common sources of iron. It may also be obtained in smaller amounts from the minerals taconite, limonite, and siderite. Iron has four separate allotropic structures, which means it has four different basic structures in which particles connect under different situations. These structures are known as ferrites, and they are classified as alpha (attractive), beta, gamma, and omega. In the period table, the image of iron is Fe, which has a nuclear number of 26 and a normal nuclear weight of 55.845. Iron has a strong period at room temperature, with a thickness of 7.874 g/cm^3 . The temperatures at which iron focuses liquefy and bubble are 1538°C and 2862°C , respectively. The total number of isotopes is 33, yet there are only four stable isotopes. Iron-56, with 91.75% normal overflow, is the most well known. Lately, iron has been the focus of a number of research projects. This iron is lithophile and chalcophile, resulting in the formation of pyrite FeS_2 , magnetite Fe_3O_4 , hematite Fe_2O_3 , siderite FeCO_3 , and many other stone-framing minerals.

3.4. Magnetite Fe_3O_4 (Iron Oxide)

Magnetite was discovered in the region of Magnesia in Asia Minor, which is a common occurrence. This magnetite comprises iron species that are both ferrous in reduced state and ferric in oxidized state. This appealing chemical possesses a variety of fascinating characteristics and has the potential to be used in a variety of applications. According to the paper, the characteristics of magnetite alter from bulk to nanoscale material, as well as with regard to the mix processes [49]. The improved on response shows the substance cosmetics of the magnetite in condition A



Equation (6): Oversimplified magnetite synthesis reaction.

In 1995, X-ray diffraction was used for the first time to determine the structure of magnetite. Because of the alternating lattices of iron (II) and iron (III), magnetite has an inverted spinal structure and is ferromagnetic in nature. It differs from other iron oxides in that it contains both divalent and trivalent iron [50,51].

3.4.1. Properties of Magnetite (Fe_3O_4)

As magnetite is significant and of distinct fascination of the researcher because of its outstanding properties, writing shows that the properties of the magnetite are not something very similar for the mass and that of the nanoparticles. A few of the properties of the magnetite are examined here.

Structural Properties

The construction is opposite winding with an octahedral and tetrahedral layer on the other hand. Because of the more prominent precious stone field adjustment energy, the ferrous species have half of the octahedral site (CFSE). The ferric species are made up of half of the octahedral and any remaining tetrahedral sites. It is intended that an equal number of Fe^{2+} and Fe^{3+} particles constructed with oxygen are present at the octahedral site, whereas oxygen is only implicated by Fe^{3+} particles at the tetrahedral site. Additionally, a magnetite unit cell with a concentrated cubic sample is shown.

Physical Properties

Magnetite, whether naturally occurring or added, has the same metallic luster and a dull dark tone. The magnetite has a thickness of 5.18 g/cm^3 . Magnetite is hard and has a hardness of 5.5 at room temperature, making it indistinguishable from glass, which can be shattered when pounded. The surface region fluctuates as indicated by the amalgamation strategy as a specific method producing fine particles having different scopes of distance across according to the required application [52]. The magnetite structure is thermodynamically perfect, since the typical Gibbs free energy of development is 1012.6 kJ/mol . The magnetite arrangement's standard enthalpy and entropy are 1115.7 kJ/mol and 146.1 kJ/mol , respectively. The disintegration reaction affects the magnetite's solvency. In any case, the breakdown of magnetite is faster than that of other iron oxides.

Thermal Properties

The softening and limitations are seen around 1590 and 2623°C , respectively, according to the writing. At a temperature of 2623°C , the fieriness of combination and vaporization is 138.16 and 298.0 kJ/mol , respectively.

Electrical Properties

As previously stated, magnetite contains ferrous (Fe^{3+}) and ferric (Fe^{2+}) species at the octahedral site, which are facilitated by electrons. When these electrons are thermally delocalized, creating high conductivity, the temperature inside magnetite rises steadily from -28 to 3 J.K between the octahedral and tetrahedral destinations. Magnetite has an organized game plan of ferrous and ferric species at the octahedral site at Vewry's change temperature (118 K). As the temperature falls below Vewry's change temperature, electrons delocalize at the octahedral site, causing metal to become insufficient and thus allowing magnetite for n-type and p-type semiconductors.

Conductivity

It is the estimation of passing current in any arrangement or material. For conveying current, it is important to hold charged molecule or particles inside it. The SI unit assumes that the conductivity is Siemens per centimeter (S/cm). Resistivity is proportional to the conductivity.

$$\rho = RA/L \quad (7)$$

where ρ is the resistivity of the specimen. " L " is the length and " A " is the cross-sectional area.

$$\sigma = 1/\rho \quad (8)$$

Conductivity is the inverse of the resistivity [53].

3.5. Uses of Magnetite (Fe_3O_4)

Fe_3O_4 possesses a variety of features, including small size, superparamagnetic properties, a large surface area, exceptional electrical, optical, and low toxicity, to name a few. It has been used in distinguished work in fields including magnetoresistance detection, drug delivery, bio-practical materials, ferro liquid, mineral detachment, and viable heat transfer.

4. Synthetic Strategies

Techniques utilized for the combination of different magnetic nanoparticles, polymer nanoparticles, composites and metal oxides are classified fundamentally into compound and actual strategies [54]. The blend strategies are mostly sol–gel method, thermal vapor deposition (TVP), chemical vapor deposition (CVD), co-precipitation, and physical vapor deposition (PVD) [55,56].

4.1. Physical Vapor Deposition Technique (PVD)

This technique is used to preserve frail metal films on a variety of surfaces. The following are the three venture processes. Sublimation is the process of a substance disappearing and transiting from a source to a substrate, and nucleation is the process of developing a thin layer [57].

4.2. Chemical Vapor Deposition Technique (CVD)

In the semiconducting industry, this chemical interaction is commonly used. In this method, the substrate is exposed to unsteady chemicals that decompose at a very high temperature on the substrate, forming the optimum slender layer. The transportation of reactants on the development surface, chemical reaction on the development surface, and evacuation of products formed on the development surface are all part of the process [58].

4.3. Sol–Gel Technique

In this technique the arrangement is continuously changed over to a gel. This gel contains fluid and strong stages, too. Both the two stages range from discrete particles to polymer organizations. The fluid stage can be taken out to acquire the necessary gel. It is a moderately low-temperature modest and controlled strategy. It is exceptionally utilized in ceramics handling and flimsy movies of metal oxides. Nanoparticles delivered by this procedure are generally utilized in applications such as medication, hardware and optics [59].

4.4. Co-Precipitation Technique

It is easiest in a sound and climate cordial procedure to deliver wanted nanoparticles from fluid arrangement. A blend of controlled and wanted measured nanoparticles has forever been used as a experimental challenge [60]. Co-precipitation strategies are used to design nanoparticles of ideal behavior for many application. Upon expansion of the base to fluid arrangement, the size, shape and piece of magnetic NPs can be controlled. These boundaries additionally rely on the sort of salts utilized (for example, chlorides, sulfates, nitrates and so on), salt proportions, response temperature and pH upsides of the arrangement. Hydroxides, carbonates, oxalates, and other metal cations are co-encouraged from normal medium [61]. The dried co-encourages are drudgery to fine powder for various applications. Drying at low temperature results in more modest estimated NPs in the co-precipitation procedure [62].

4.4.1. Comparison of Co-Precipitation Technique with Other Techniques

Every strategy has its own benefits and bad marks relying on the variables such as vacuum necessities, temperature, pressure, surface morphology and grain size to control cost for the amalgamation of materials. The fume stage cycle and fly affidavit technique need the classification and blended material mass. The processing procedure meets this lack yet creates particles of measurement just in the scope of sub-microns. Furthermore, the morphology of the integrated nanostructures are likewise unconfined. Techniques having low cost and low temperature such as sol–gel and micro-emulsions are more feasible; high-temperature calcination and strengthening are required. These strategies additionally miss the mark on controlling the surface morphology and size of the items. Hydro-warm and solvo-warm techniques give different nanomaterials yet are incapable of creating super unadulterated items and furthermore cause contamination [62]. Various combination

procedures are accounted for to deliver different nanostructures; however, a large portion of them are either restricted to create one kind of material or the other.

4.4.2. Method of Co-Precipitation Technique

Metal cations are co-encouraged in this technique from a normal media such as hydroxide, carbonate, or oxalate, and so on. This accelerates calcination at appropriate temperatures [63]. In an exceptionally homogenous item, the encourages of metal cations are nearer to one another [64]. Since co-precipitation brings about nuclear scale blending, consequently, the temperature prerequisite for the eventual outcome is exceptionally low [65]. Subsequently, lower measured nanostructures are effectively orchestrated at lower temperature. The end result of desired properties can be obtained by controlling the temperature, pH and mixing rate of the blend [66].

4.4.3. Advantages and Disadvantages of Co-Precipitation Technique

The homogenous blending of reactants decreases the response temperature. The most straightforward procedure is to blend the metal oxide powders. No all-inclusive experimental conditions are accessible to blend the different kinds of metal oxides.

4.5. Synthesis Process of Fe_3O_4 Nanoparticles

Ferric chloride hexahydrate and ferrous chloride tetrahydrate were mixed in a 2:1 ratio. Ferrous chloride tetrahydrate 0.05 M and ferric chloride hexahydrate 0.1 M watery arrangements were ready. Both arrangements were merged and mixed on a visually appealing mix plate at 40 °C and 400 rpm. In a nitrogen environment, the pH of the solution was preserved at 9.5 by the addition of ammonium hydroxide, and the orange color of the solution changed to dark brown. The arrangement was centrifuged for 15 min at 2000 rpm to extract the nanoparticles. Fe_3O_4 nanoparticles were dried for 24 h in an 80 °C stove.

5. Characterization Techniques

Various portrayal methods are utilized to distinguish and evaluate the integrated material. The first step in trial research is the portrayal of the orchestrated material for its affirmation. It decides the various primary properties that help the choice of materials be more reasonable for a particular application. XRD, SEM, VSM and FT-IR are a portion of the normal rehearsing portrayal procedures [60].

5.1. X-ray Diffraction (XRD)

It is notable method to describe the glasslike materials. Practically 95% of the solids show glasslike conduct not entirely settled by utilizing XRD. Its logical method is used to decide the stage immaculateness and kinds of stages present in the combined material [67]. This strategy utilizes the dispersing peculiarities of light. The X-ray frequency is equivalent to bury nuclear dividing. The occasional course of action of the iotas in the gem plane diffracts the light beams delivering productive obstruction designs. These examples and force tops contain data about the nuclear game plan and gem structure. Undefined material such as glass having unpredictable gem planes does not diffract the occurrence beams.

Working Principle of XRD

Max van Laue clarified the X-beam diffraction interestingly. He proposed that the precious stones could diffract X-beams. Bragg's proposed gems planes carry on like mirrors to diffract X-beams as shown in the inset of Figure 2. He gave an exceptionally basic clarification of diffraction peculiarities. The internal shell progress of the designated material exposed to electron barrage produces high energy X-beams. The change from different shells results in X-beams of longer frequency and lower energy, which are inadmissible for diffraction peculiarities. Copper (Cu) and Molybdenum (Mu) are for the most part utilized as objective materials to deliver X-beams. They produce X-beams running in 0.8–1.54 Å individually allow us to consider a precious stone comprising various equal

planes of molecules known as Bragg planes. Whenever a beam (a) of an X-ray is incident on a precious stone, it will diffract from the outer layer of the gem at a point θ , and when a beam (b) of an X-ray is incident on a gem and enters inside the gem, then, at that point, it will diffract from the inward plane of the gem at a point θ . On the off chance that the diffracted radiates are in stage, they will give valuable obstruction, yet on the off chance that the diffracted radiates are out of stage, they will give disastrous impedance [68].

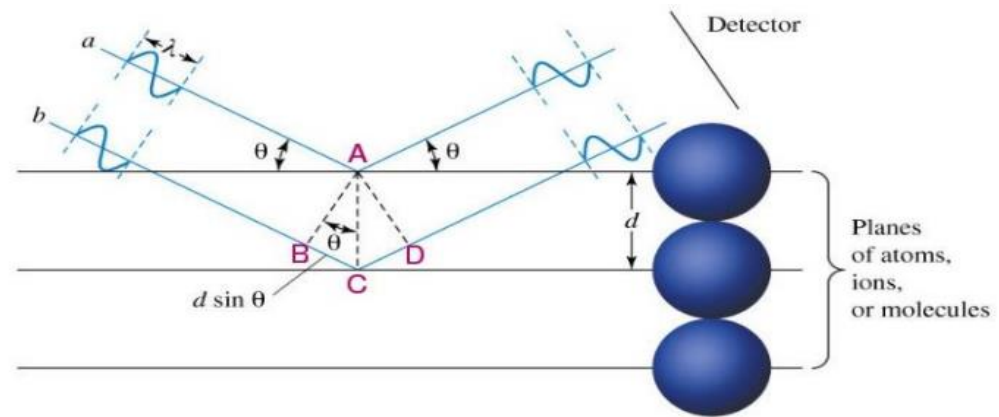


Figure 2. Bragg's reflection from first crystal plane.

Constructive interference $\theta_i = \theta_r$ (In phase)

Destructive interference $\theta_i \neq \theta_r$ (out of phase)

From the right angled triangle, BAC, the length BC is perpendicular and AC is the hypotenuse.

$$\begin{aligned} BC/AC &= \sin\theta \\ BC &= AC \sin\theta \\ BC &= d \sin\theta \end{aligned} \quad (9)$$

DC is perpendicular to the right-angled triangle, DAC, and AC is the hypotenuse.

$$\begin{aligned} DC/AC &= \sin\theta \\ DC &= AC \sin\theta \\ DC &= d \sin\theta \end{aligned} \quad (10)$$

Add Equations (9) and (10) to find a path difference

$$BC + DC = d \sin\theta + d \sin\theta \quad n\lambda = 2d \sin\theta \quad (11)$$

Bragg's equation is represented by Equation (11) in which "d" is the interplanar spacing, "n" is the order of diffraction, and " λ " is the wavelength of the X-ray used. The rotating crystal method and the powder approach with unique orientations are used in X-ray diffraction. The powder method was used in our study. The powdered sample is exposed to the X-rays of known wavelength and diffracted rays are analyzed to determine the crystal planes and structure [69]. Briefly the various peaks were observed for Fe_3O_4 at 21.230, 30.470, 35.570, 43.370, and 62.810 with reflection phases (200), (220), (311), (400), (440). The peaks are compared to a normal card (JCPDS card No. 01-071-6338). The five typical peaks seen in Figure 3 indicate that magnetite has a cubic inverse spinel structure [70].

The XRD (X-ray Diffraction) examination was utilized to determine the crystallinity level of this magnetite synthesis product. The XRD examination was carried out to determine the composition of the sample as well as the characterization of the crystals. Diffraction peak data from an XRD examination show the number of crystals and crystal size of the substances in the sample. The greater the diffraction peak, the more crystal compounds there were in the sample. The smaller size of the crystalline compounds in the sample was indicated by the breadth of the diffraction peak.

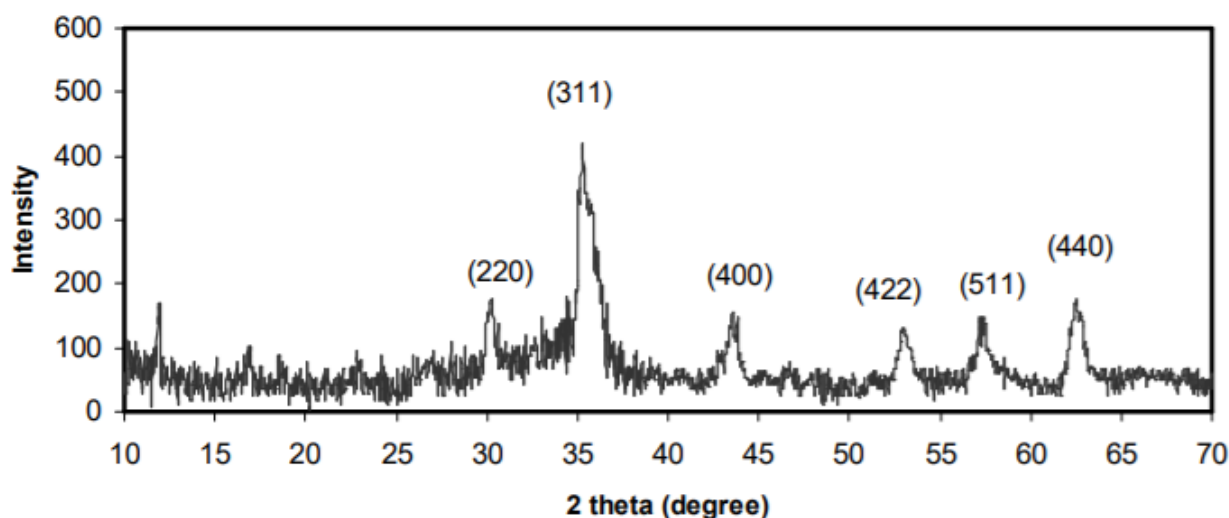


Figure 3. XRD analysis of Fe_3O_4 .

5.2. Scanning Electron Microscopy (SEM)

The filtering electron microscopy is utilized for analyzing the surface elements of example with extremely high amplification at nano-scale. It is realized that the more modest the frequency of light, the more prominent the goal achieved will be. An electron-magnifying instrument has a lot higher amplification than the optical magnifying instrument as the frequency of green light ($=0.55 \mu$) is 1, which is 10,000 times longer than that of the electron bar. An electron-magnifying instrument can resolve a picture from 50 up to 106X. The SEM structures a 3D picture of an item by centering the electron bar across the article. SEM is regularly utilized for the investigation of bond disappointments, pressing breaks, actual deformities, and so forth. The fundamental components required for SEM are sample stage, electron source (gun), power supply, cooling framework, electron lenses, display/data yield gadgets, vacuum system, detectors for signs and place with no attractive and electric fields [71].

Working Principle

Because air or fumes induce contortion in the electron passage, the checking electron-magnifying device operates in an exceptionally high vacuum. The information about the example is transferred by auxiliary electrons from the surface layer whenever the example is given to a very high energy electron pillar. The surface layer has a request thickness of 5 nm. The data about the example are also provided by the backscattered electrons communicated from the example. The appropriately organized locator collects the scattered electrons. Optional electrons are commonly used for imaging morphology and geography, for example. In multiphase instances, back-dissipated electrons are used to highlight differences in arrangement [72].

The magnetite product and the uneven surface have agglomerated, according to the SEM results of Fe_3O_4 . The influence of stirring rate on magnetic morphology is seen in Figure 4a,b. Increasing the stirring rate lowers the size of magnetite particle clumps, as seen in the picture. In addition, they are irregularly formed. The shape of magnetite nanoparticles is also affected by temperature changes. Increased temperatures improve the uniformity of magnetite particle size; however, there are certain downsides. The agglomeration has not gone away. The size of magnetite particles was evaluated by measuring them in an SEM test picture: 2.7 to 3.3 μm . Agglomeration in magnetite synthesis is particularly difficult to avoid due to its magnetic properties. In addition, poor sample preparation might result in particle agglomeration. The temperature and speed rate have an impact on the crystallinity of magnetite [73,74].

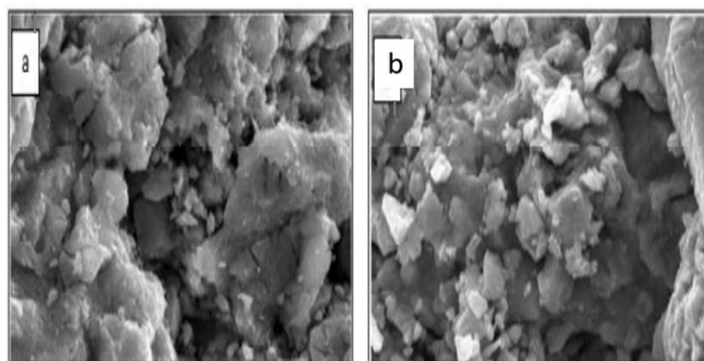


Figure 4. SEM Image of Magnetite synthesized sample. (a) stirring rate (b) temperature.

5.3. Vibrating Sample Magnetometer (VSM)

The attractive properties of MNPs are examined by utilizing basic vibrating test magnetometer (VSM) estimation methods. To concentrate on the attractive property of magnetic materials and its estimation, VSM is one of the most utilized portrayal methods. To deliver essential thoughts, first, the estimation guideline and the properties of ferromagnetic materials will be perceived, and afterward, we will talk exhaustively about the attractive anisotropy of ferromagnetic materials [75].

Working Principle

The essential standard of VSM in light of Faraday's regulation. state as an electromagnetic power is produced in a curl when there is an adjustment of transition through the loop. The attractive example is moving between two vicinity curls. The oscillator delivered a sinusoidal single. The sign interprets with the assistance of a transducer get-together into an upward vibration. The proper example in example bars vibrates with a steady recurrence and abundance. The magnetic field is created by two shaft bits of electromagnet. Fixed pickup loops are mounted on the posts of the electromagnet. Their balance place agrees with the attractive focus of the static example. Consequently, the adjustment of attractive transition beginning from the upward development of the polarized test instigates a voltage [76].

5.4. Fourier Transform Infrared Spectroscopy (FT-IR)

Infrared spectroscopy is a fundamental tool for investigating instances at any level. This framework is mostly used to confirm the example's creation. On the example, FTIR radiations are used to determine which fraction of the event radiations is consumed at a certain force. The absorption of energy considers the model's piece of vibration repeating. Every one of the covalently energized blends, for the most part, osmoses diverse frequencies between the perceptible and microwave areas, such as in the infrared region. The vibrational separation of the IR region is of relevance for compounding reasons. It gathers radiations with frequencies between 2.5 and 25 μm ($1 \mu\text{m} = 10^{-6} \text{ m}$) or between 4000 and 400 cm^{-1} . Two oppositely plane mirrors are used in an FTIR spectrometer, one of which may move in a beeline for the plane.

Working Principle Fourier Transform Infrared (FT-IR)

In order to generate an interferogram, spectroscopy relies on the possibility of radiation impedance between two support points. The operating approach of an IR spectrometer is depicted schematically in Figure 5 The IR radiations that travel through the example have an effect on the particles' vibrational techniques, and the sent radiations include beneficial stuff that is subsequently supplied in the design-ingesting gathers. IR spectroscopy is a technique that relies on the vibrations of a molecule's bits. Broadening and bending are two important types of nuclear vibrations. The co-collaborated life is transformed into the previously specified types of advances by osmosing infrared radiation. Discrete, quantized

energy levels are used in the maintenance. Nonetheless, numerous rotational changes are usually inextricably linked to the single vibrational development. The above-mentioned mixes aid ingesting groupings rather than separate lines to obtain an IR range. The IR radiations ingested by the model explanation cause network particle vibrations to alter. The infrared approach should be employed only with materials whose network vibrations accelerate changes in the dipole moment of the iotas in the example. In general, the model does not osmose IR radiations and is considered IR inactive. Nuclear vibrations are divided into two categories: broadening and bending. Osmosing infrared radiation transforms the co-collaborated life into the previously specified types of advancements. In the maintenance, discrete, quantized energy levels are employed. Nonetheless, a single vibrational development is frequently intimately related to many rotational modifications. To obtain an IR range, the above-mentioned blends help in ingesting groups rather than distinct lines. The network particle vibrations change as a result of the IR radiations swallowed by the model explanation. Only materials whose network vibrations accelerate changes in the dipole moment of the iotas in the example should be used with the infrared technique. The model is called IR inactive since it does not osmose IR radiations. The 1624 cm^{-1} top for NH twisting vibration moved to 1565 cm^{-1} , and the FeO bond moved to 573 cm^{-1} in the range of Fe_3O_4 covered with chitosan compared to the range of iron oxide coated with chitosan and Gallic corrosive nanoparticles. Chitosan and gallic corrosive were efficiently coated onto the Fe_3O_4 nanoparticles, and the negative ions on the iron oxide surface had a propensity for chitosan and protonated it. The coating was achieved by electrostatic cooperation and a synthetic response including glutaraldehyde cross-linking [70,77].

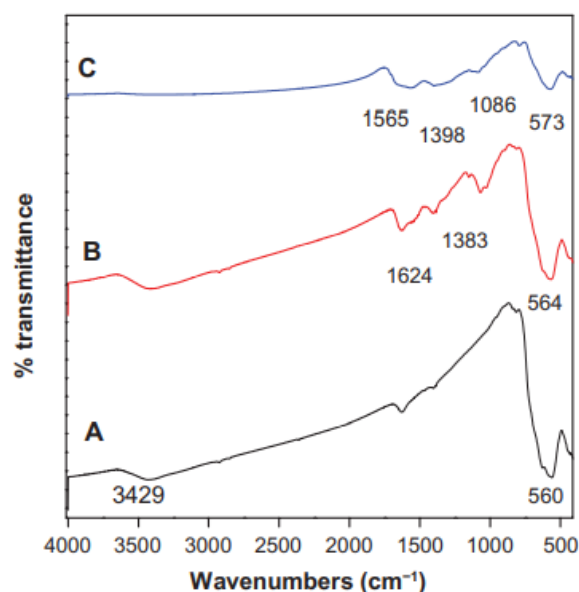


Figure 5. Fourier transform infrared spectra of (A) iron oxide nanoparticles, (B) iron oxide nanoparticles coated with chitosan, and (C) iron oxide nanoparticles coated with chitosan and gallic acid.

6. Application of Fe_3O_4 NPs

The innovative work of multifunctional nano-stages in light of magnetic nanoparticles (MNPs) is acquiring a foothold. Under the management of an outer magnetic field (MF), MNPs show uncommon reactivity, bringing about growth explicit and designated conveyance. The MNPs conduct and attractive focusing on adequacy are intensely affected by their physiochemical properties. The ideal size reach might differ across a few boundaries, especially the molecule size. As for multifunctional nanoparticles and their bio-applications, it is uncommon to find nanoparticles for outer MF-intervened designated conveyance. Fe_3O_4 nanoparticles with comparative surface qualities went in size from 10 to 310 nm, and we concentrated on their conduct and MF-helped union exhaustively. Hostile to cancer movement, our discoveries showed that more modest Fe_3O_4 nanoparticles have

more cell action. Disguise was more normal in more modest Fe_3O_4 nanoparticles; however, cancer amassing was more normal in greater Fe_3O_4 nanoparticles. Fe_3O_4 nanoparticles with a bigger size both in vitro and in vivo showed more noteworthy attractive responsiveness, which could be expected to use to expand how much nanoparticles and their payload are amassed (e.g., doxorubicin) under the oversight of an outer MF into the cancer site [78].

6.1. Antibacterial Activities of Fe_3O_4 Nanoparticles

In recent years, scientists have been especially interested in the issue of nanostructured materials since numerous types of metallic or oxide nanomaterials provide attractive properties and capabilities [79]. Both nanoparticles based on iron oxides (IONPs) and free iron ions have antibacterial capabilities; however, unlike free ions, IONPs do not have a substantial harmful impact on human cells [80]. Two elements are hypothesized to be responsible for MNPs' antibacterial mechanisms: the formation of reactive oxygen species on the surfaces of the NPs produces oxidative stress within the bacterial cell, culminating in cell death [81]. Metallic nanoparticles with sizes ranging from 1 to 100 nm constitute a new trend that is progressively being created and is being considered for use in medical research. In general, Gram-positive and Gram-negative bacteria cause human illness [82]. Different bacterial strains were discovered to be effective inhibitors of various manufactured metal oxide nanoparticles [83]. Through electrostatic interaction, iron oxide nanoparticles can interact with bacterial cell membranes, generating detrimental oxidative stress in the bacterium through the formation of free radicals known as radical oxygen species (ROS) [84]. Metal ions have the ability to bind the mecapto (-SH), amino (-NH), and carboxyl (-COOH) groups of proteins, especially enzymes, resulting in deactivation or partial suppression [85].

Iron oxide nanoparticles are magnetic as well as paramagnetic. It has been found that the utilization of an alternating magnetic field improves the bactericidal activity of Fe_3O_4 NPs against *S. epidermidis*, *P. mirabilis*, and *A. baumannii* [86]. The cell death and biofilm disintegration were caused as a result of photocatalytic ROS production and local heat and vibration damage were caused by magnetic fields [87]. All of the aforementioned circumstances cause bacteria to separate from the biofilm and caused bacterial cell wall destruction, membrane rupture, fusion of various cells' death, and others [88]. The antibacterial mechanism of iron oxide NPs has been illustrated in Figure 6.

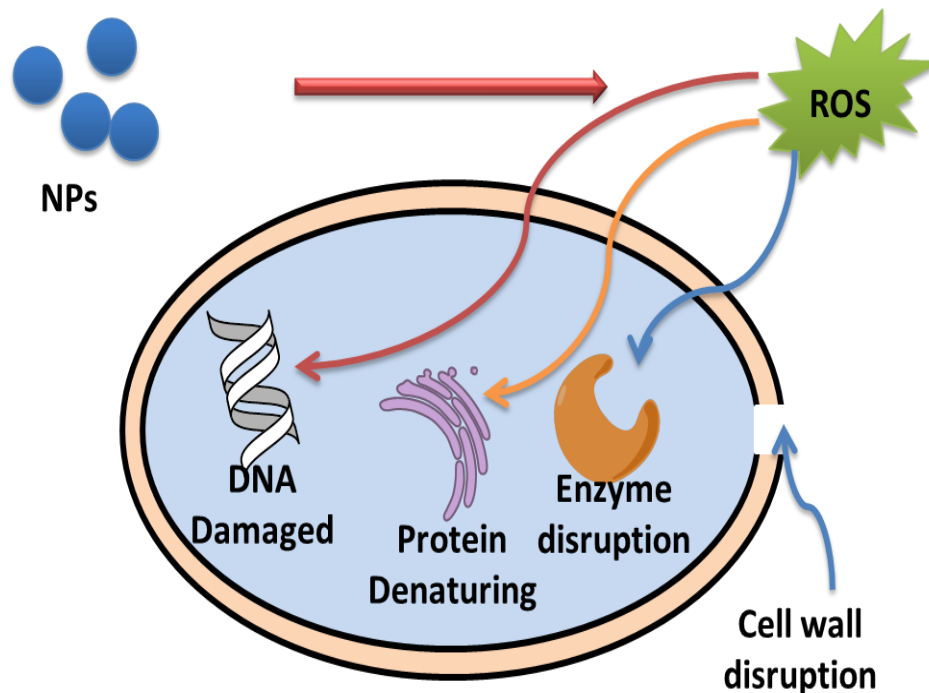


Figure 6. The antibacterial mechanism of iron oxide NPs.

6.2. Targeted Anticancer Medication Conveyance

A designated drug conveyance framework the medication stacked Fe_3O_4 -NPs is consumed by humans through parenteral medication organization. It is shown that the medication stacked Fe_3O_4 -NPs are infused into the blood and situated at the designated site (disease cells/cancer) by the guide of an outside magnetic field. This can assist with collecting the medication and delivery of the medication at the ideal site, and along these lines, it is possible to increase the viability in treating disease cells without hurting the neighboring solid cells [89].

6.3. Drug Loading and Release

Drug stacking should be performed in a manner in which the usefulness of medication is not impacted. Meanwhile, drug-stacked nanoparticles should deliver the medication at the designated site at a proper rate without hurting the sound cells. There are not many ways of stacking the medication on nanoparticles, for example, forming the medication particles on the outer layer of nanoparticles or exemplifying the medication atoms along with the covering material. For the formation of medication on the outer layer of nanoparticles, the connecting system can be separated into two gatherings, which are formation through cleavable covalent linkage and by means of actual collaborations. Covalent linkage fuses the mix of medication particles with practical gatherings present on the outer layer of nanoparticles, which have been covered with polymers. The linker can likewise be utilized to connect the medication particle to the nanoparticles. This technique can upgrade the drug-stacking limit and furthermore save the usefulness of the medication and subsequently adequacy. Actual communications, for example, electrostatic cooperation, hydrophobic and hydrophilic collaborations, can prompt the formation of medication atoms on the outer layer of nanoparticles. This peculiarity happens when there are different charges. For instance, the Fe_3O_4 -NPs covered with a cationic polymer can cooperate electrostatically with adversely charged DNA. Furthermore, lipophilic medications can interface with the Fe_3O_4 -NPs promptly if the Fe_3O_4 -NPs are covered with hydrophobic polymers, and this can improve the medication discharge as the covering debases. As a medication conveyance framework, Fe_3O_4 -NPs ought to have the option to deliver their medication payload at ideal conditions. Notwithstanding, there are a couple of disadvantages on the medication discharge which cannot be dismissed. A large portion of the medication payload was delivered quickly upon infusion into the in vivo circumstance in light of the fact that the medication is stacked on the outer layer of Fe_3O_4 -NPs, such as burst impact. Accordingly, the low capture productivity causes just a modest quantity of medication to arrive at the designated site, and the adequacy of medication in killing malignant growth cells could not perform well. Then again, profoundly stable formation between drug atoms and the surface of Fe_3O_4 -NPs could evoke a disappointment of medication discharge at the designated site. Subsequently, investigations ought to be completed to defeat these sorts of issues to kill the cancer successfully. Moreover, Fe_3O_4 -NPs should be planned so that they do not just deliver the chemotherapeutic medication in killing malignant growth cells; they ought to likewise concentrate on the non-poisonousness, biodegradability and sterility, as they will be utilized in the drug conveyance system [73].

6.4. Effect of Particle Size and Shape on Drug Delivery

The state of Fe_3O_4 -based nanoparticles is one of the significant highlights that must be thought about in drug conveyance. The issue that analysts are concerned the most with is to delay the nanoparticles at the designated site as well as perform extraordinary cell cytotoxicity. Furthermore, the blood course time, cell take-up and bio-appropriation might change in view of the state of nanoparticles. A lot of examinations had been completed to explore the nanoparticles shape especially for anticancer medication conveyance. Filomicelles is the one that was found to possess a higher anticancer medication exemplification limit and apoptotic effectiveness in correlation with round micelles. There are likewise numerous different states of nanoparticles that had been combined in a drug conveyance

study: for example, bar shape, worm shape and dab shape. In writing, non-round and pole-formed nanoparticles have a more extended blood flow time contrast and circular nanoparticles. This could be because the bar mold particles cause a lower phagocytic movement of macrophages than circular ones. Notwithstanding, circular nanoparticles show more critical benefits than bars, as per the exploration with sub-100 nm nanoparticles. The circular nanoparticles can give an even surface covering and the formation of ligands in surface alteration, which mean more medication, can be stacked on the outer layer of nanoparticles for better medication discharge at the designated site and consequently show more prominent cell harmfulness. In view of writing, the greater part of the nanoparticles orchestrated are round in shape for the in vitro concentration in treating different sorts of malignant cells. Every one of the examinations show critical cytotoxicity and adequacy in repressing disease cells development, which uncover the promising capability of nanoparticles to be utilized in drug conveyance application [74].

As a general rule, a 50 nm breadth of nanomaterial is relied upon to be the ideal one; however, this does not apply to a wide range of cells. A bigger nanoparticle, for example, bigger than 50 nm, could tie with high liking to countless receptors and could restrict the limiting of extra nanoparticles. Interestingly, a 40–50 nm nanoparticle can gather and tie adequate receptors to create film wrapping well. Nonetheless, the adequacy of size of the nanomaterial in cell take-up relies upon the sorts of cell, too, in light of the fact that every cell type claims a particular aggregate. Then again, the size of nanoparticles directs the half-life in the blood dissemination. For instance, a molecule that has a size bigger than 200 nm will move in the spleen or it will be taken up by the phagocytic cells of the body. Meanwhile, a molecule with a size more modest than 10 nm will be taken out by renal leeway. In writing, particles that lie in the size scope of 10–100 nm are accepted to be the ideal. They have more extended flow times in the body, as they can avoid the reticuloendothelial framework in the body as well as enter through tiny vessels. For the superparamagnetic nanoparticles, small sized nanoparticles are skilled to further develop the penetrability and maintenance impact, which can prompt the maximal aggregation of nanoparticles at the designated site. The size of nanoparticles must be controlled during the readiness stage with the goal that they can be used really as a medication transporter.

7. Conclusions

In recent years, the drug field has emerged, presenting numerous novel medication conveyance frameworks. The majority of them are still in the nascent stage, including Fe_3O_4 -NPs. A lot of elements make Fe_3O_4 -NPs the potential nanodrug transporter in the drug conveyance framework and as an antibacterial agent. The use of an external magnetic field that directs the Fe_3O_4 -NPs to the specific area demonstrates the promising applications of Fe_3O_4 -NPs in a variety of biomedical-related fields, such as bactericidal activity, and particularly designated drug conveyance. Regardless, there is no Fe_3O_4 -assembled nanoparticles drug conveyance item on the market. Numerous serious investigations are yet to be completed to popularize these nanoparticles as an item in the clinical space. Before these Fe_3O_4 -NPs are sent off as an item, a few restrictions should be met. The systems affecting the readiness of Fe_3O_4 -NPs should be improved, and the portrayal is the most essential part. The outcomes will show the properties of the Fe_3O_4 -NPs. The immersion polarization, size, shape, surface charge, colloidal soundness, drug stacking limit and delivery conduct, biocompatibility, and harmfulness are important factors to consider when selecting Fe_3O_4 -NPs for drug conveyance and bactericidal properties. Nonetheless, the fettle of the Fe_3O_4 -NPs in the body after drug conveyance is significant. It is safe to assume they can remove it from the body framework. Be that as it may, assuming the Fe_3O_4 center is uncovered, it can lead to a few issues connected with neurological problems. As a result, the selection of Fe_3O_4 -NPs for specific drug conveyance must be completed meticulously based on the component of formation between polymers, drug atoms, and Fe_3O_4 -NPs, or else, the burst impact will deliver poisonous synthetic substances that are harmful to the body framework.

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