SJPMS

Sphinx Journal of Pharmaceutical and Medical Sciences

e-mail: sjpms@sphinx.edu.eg

SPHINX UNIVERSITY

MAGNETIC NANOPARTICLES: SYNTHESIS, CHARACTERIZATION, BIOMEDICAL APPLICATIONS AND CHALLENGES

Mahmoud M. Sheha[1,2], Asmaa M. Mostafa[3], Donia G. Nasr[3] and Reem Y. Shahin[1*]

[1]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Sphinx University, New Assiut 10, Assiut, Egypt*
[2]*Department of Pharmaceutical Medicinal Chemistry, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt*
[3]*Faculty of Pharmacy, Sphinx University, New Assiut 10, Assiut, Egypt*

One of the research and development disciplines with the fastest global growth is nanotechnology. In the areas of energy, electronics, data storage, food, and healthcare, it brings about revolutionary technologies and drives revolutions. Magnetic nanoparticles (MNPs) show different properties from their bulk counterparts due to their large ratio of surface to volume, increasing their reactivity. Different methods are utilized for their synthesis, these methods include physical, chemical, and biological synthetic methods. The obtained MNPs are then characterized using variable characterization techniques. The fusion of nanotechnology and medical applications, or so-called biomedical applications of nanotechnology, is a field for development, allowing for their biological applications in many fields as drug delivery systems, gene therapy, use as antibacterial drugs, and utilization in tissue engineering. Various types of MNPs whether mono component or coated ones have been synthesized serving such mentioned purposes, but a few reviews have dealt with such topic The growing interest in MNPs has inspired us to design this review focusing on the composition, synthesis, characterization, and recent applications of MNPs.

Keywords: Magnetic nanoparticles, synthesis, characterization, biological applications, challenges.

1. Introduction

In recent years, magnetic nanoparticles (MNPs) have gained much interest in many application fields such as biomedicine, agriculture, environment, and catalysis in addition to their applications in extraction from complex matrices.

Certain metals such as cobalt, nickel, iron and oxides are used either alone; in the form of mono-component MNPs, or as coated MNPS. Iron oxides, mainly maghemite and magnetite (γ-Fe_2O_3 and Fe_3O_4) are the most commonly used as magnetic cores due to their biocompatibility and low level of toxicity[1].

It was found that the properties of MNPs are completely different from their bulk materials, this is mainly due to that as the size of MNPs decreases, their size-to-volume ratio increases, this is the main reason for MNPs' unique mechanical, chemical, and physical properties. Mechanical properties of MNPs include hardness and strength, while chemical properties include a high chemical reactivation rate and physical properties comprise magnetic, optical, and electric properties[2]. Consequently, small-sized MNPs are preferred in biomedical and biological applications, but MNPs always tend to aggregate and thus lose magnetism[3]. So,

Received in 25/4/2023 & Accepted in 25/5/2023

*Corresponding author: Reem Y. Shahin, E-mail: reem.shahin@sphinx.edu.eg

variable methods are employed to attain MNPs of appropriate size, stability, morphology, and biocompatibility. These methods include physical, chemical, and biological synthetic methods. The obtained MNPs are then characterized using variable characterization techniques.

The growing interest in MNPs has inspired us to design this review focusing on the composition, synthesis, characterization, and recent applications of MNPs.

2. Synthesis of MNPs

Different synthesis methods are used to obtain MNPs with the required morphology, size, biocompatibility, and stability. These methods are classified into physical, chemical, and biological methods (Fig. 1).

2.1. Physical methods

Physical methods for synthesis of MNPs include two main techniques: 1- top-down technique where nanosized particles are obtained from the bulk material by using a ball mill in high energy conditions, the produced NPs are not usually of an appropriate size and shape[4], 2- bottom-up technique produces NPs with good dispersion properties. The ball milling mechanical method uses top-down technique, while laser evaporation and wire explosion methods use bottom-up technique[5].

2.1.1. Ball mill mechanical method

It is an example of top-down technique for the synthesis of MNPs where bulk material is placed in a jar together with balls of steel for grinding of the bulk material by the applied kinetic energy that results from the collisions of the balls with the bulk material. The size of the produced particles depends on the ratio of powder to balls, size of the balls, time of milling, and time of vibration, but this synthesis method has a major drawback that is producing contaminated particles with non-uniform size[6].

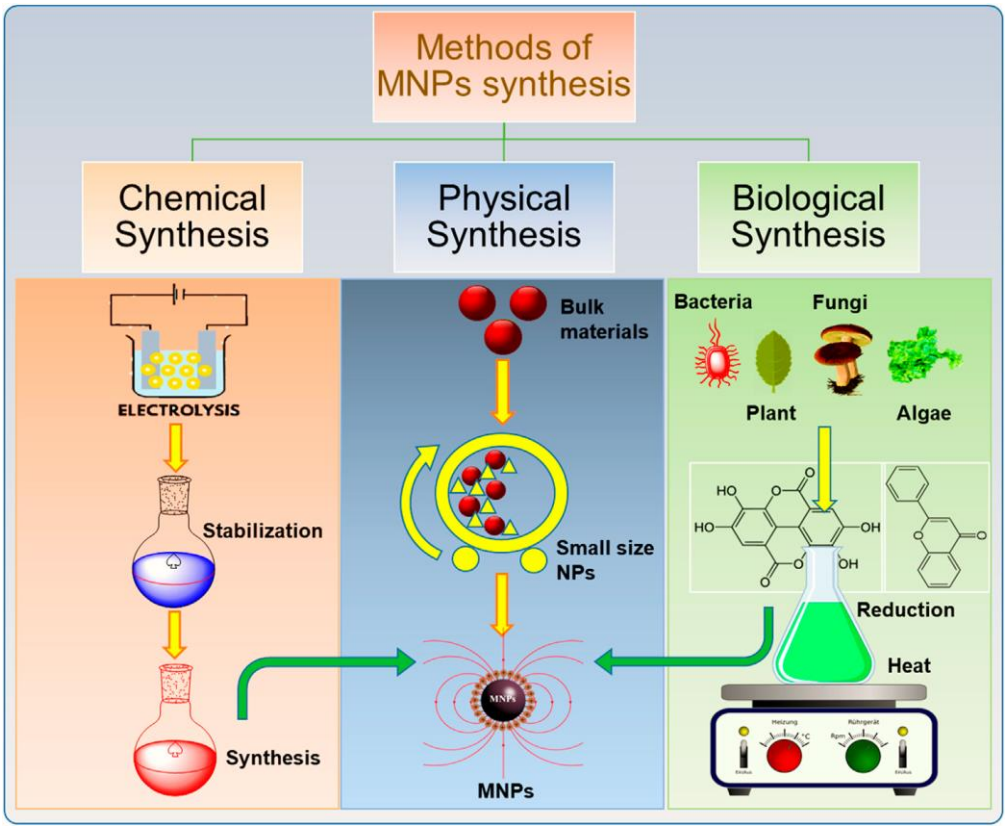

Fig. 1: A schematic presentation of the techniques utilized for the synthesis of MNPs[1].

2.1.2. Laser evaporation physical method

An example of the bottom up technique, it is assumed to be a laser ablation method where the size of the particles of the bulk material is in the mm or μm size and is evaporated after exposure to a highly energetic laser beam then it is cooled by gas phase, the cooling process leads to fast nucleation and condensation of the material leading to the formation of the NPs[7]. This method uses a low cost, environmentally friendly experiment the contrary to the chemical synthesis method but the laser system is expensive and the method requires high energy[8].

2.1.3. Wire explosion physical method

An example of bottom-up technique, it depends on passing high-density electric pulse in the required metal wire, this leads to the boiling of the metal to explosion[9&10], oxygen penetrates the exploded particles causing their evaporation and burning followed by condensation into particles of oxides, this was verified by the production of Al_2O_3[10] ZnO_2 and TiO_2 NPs where the particles of their wires decomposed into micro size then burned while scattering in the oxidizing gas and the particles of nano size are then formed, particles of 15 to 20 nanometer were possible to synthesize[11], the wire explosion method is environmentally friendly, gives high yield and clean method but the produced NPs may be contaminated[9]. Figure 2 shows the wire explosion technique utilized for the synthesis of iron oxide MNPs[12].

2.2. Chemical methods

All chemical methods for the synthesis of NPs utilize the bottom-up technique in different approaches[1]. Controlling the size and shape of the NPs produced by the physical method is generally difficult[13], while producing NPs of uniform size and shape by the chemical methods is easily approached by controlling the chemical reaction conditions[14].

2.2.1. Co-precipitation chemical method

A very simple chemical method to produce NPs of uniform size and shape, good dispersion properties, and in large amounts that are widely used in the biomedical field[15&16]. For the production of $MgFe_2SO_4$, co-precipitation of Mg^{+2} and Fe^{+3} is achieved by sodium hydroxide[17], Fe_3O_4 NPs were synthesized by the co-precipitation of Fe^{+3} and Fe^{+2} [18]. Certain factors such as metal concentration, pH, and temperature of the reaction must be controlled to obtain NPs of controlled size and shape[19], the produced NPs despite having uniform size and shape may be contaminated and the process suffers from being time-consuming[16].

2.2.2. Thermal decomposition chemical method

A method for synthesis of MNPs that depends on using precursors of organometallic nature under conditions of extremely high temperature, in the presence of surfactants of organic nature and stabilizing agent as oleic

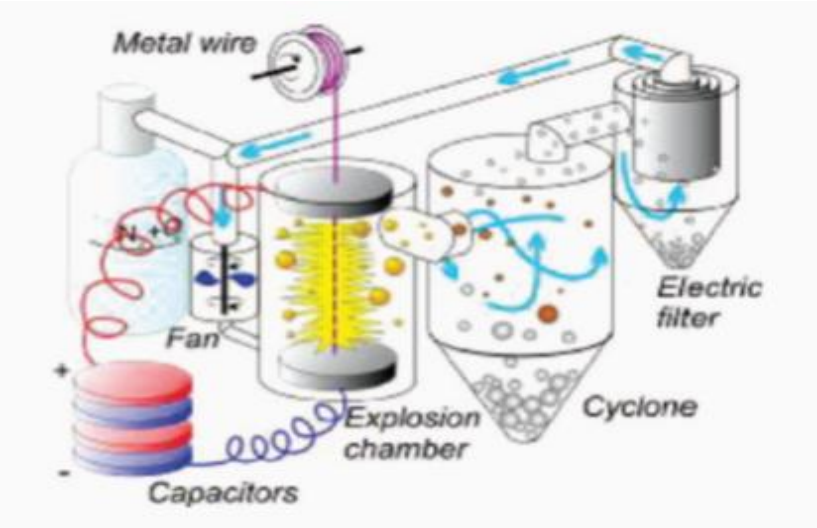

Fig. 2: Wire explosion technique utilized for the synthesis of iron oxide MNPs.

acid, hexadecylamine and fatty acids[20], under these conditions thermal decomposition method, is superior to other methods in producing MNPs of uniform size and shape[21] but this method has a major drawback of using toxic solvents[22], the method can be used to produce iron NPs using $Fe(CO)_5$ as precursor followed by thermal decomposition leading to direct formation of iron NPs but if oxidation is done, Fe_3O_4 NPs would be formed. Direct formation of the metal oxide could be done if the metal precursor was decomposed in the presence of cationic metal centers[23&24].

2.2.3. Micro-emulsion synthesis chemical method

Micro-emulsions are thermodynamically stable phases that consist mainly of two immiscible ingredients and an amphiphilic ingredient, the surfactant[25&26]. Micro-emulsions are classified into three classes: o/w which consists mainly of water enclosing droplets of oil, w/o which consists mainly of oil enclosing droplets of water, and the third type contains water and oil in relatively equal amounts[19&27]. Okai *et al.*[28] have suggested two methods for the synthesis of iron oxide MNPs using the micro-emulsion synthesis method, in the first method two micro-emulsions were used the first one was obtained from the mixing of $FeCl_3$ and $FeCl_2$ precursors with surfactant, the second micro-emulsion was obtained by mixing precipitating agent with surfactant, then the two micro-emulsions were mixed, an external magnet was used to separate the formed iron oxide MNPs. The second method uses only one micro-emulsion containing the metal precursors to which ammonia was added as precipitant followed by fast stirring until the desired pH was obtained, the MNPs are then washed with a mixture of water, chloroform, and methanol for removal of oil and surfactants from the system (Fig. 3). These two methods were used to synthesize silica-coated iron oxide MNPs which were also functionalized by amino groups[29]. Produced MNPs by the micro-emulsion method are usually uniformly dispersed, and thermodynamically stable but of low yield[30].

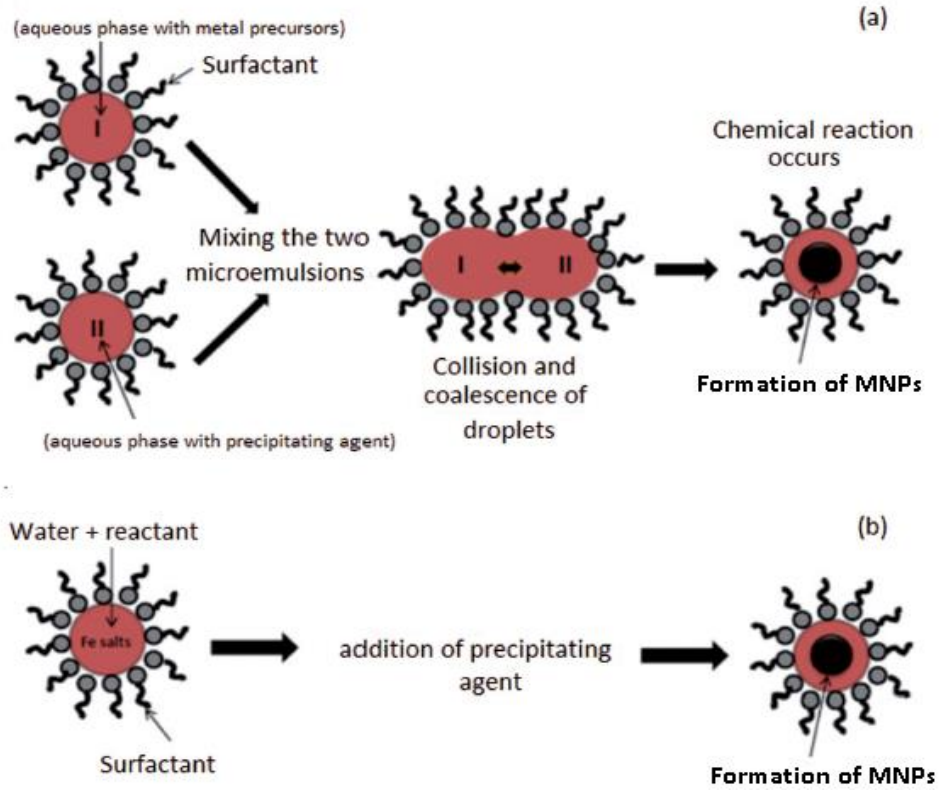

Fig. 3: Schematic presentation of two methods for synthesis of iron oxide MNPs[19].

2.2.4. Hydrothermal (solvothermal) chemical synthesis method

This method is based on the production of MNPs in an aqueous solution under conditions of high temperature and pressure[29] where oxidation and hydrolysis reactions are involved in the production of MNPs[31]. The produced MNPs by this method are uniform in size and of good crystallinity[14], where the crystallinity and morphology of the produced MNPs depend on the amount of pressure, appropriate mixing of solvents, and temperature, when these conditions are well controlled, the produced NPs were as good as that produced by the micro-emulsion method[32]. The solvothermal method was used for the production of Fe_3O_4 MNPs that is used in MRI of tumors, these NPs were of 15 nm size and spherical shape[33] also Fe_3O_4@chitosan MNPs used in the immobilization of enzymes were also produced by this method[34] but the major drawback of this method is that it needs a special equipment and requires high temperature and pressure[32].

2.2.5. Sol-gel chemical method

The Sol-gel method involves polycondensation and hydrolysis reaction of metal hydroxides present as an aqueous solution or dissolved in organic solvents[35], this solution is heated to remove the solvent followed by drying the solution leading to gel formation, Sol gel method does not require special equipment and is carried out at room temperature producing particles of controlled size, shape, and composition in a simple cheap way. but the produced particles may be contaminated from the reaction byproducts and require pretreatment[36] the method is also time-consuming and uses toxic organic solvents. This method was utilized for the synthesis of Fe_3O_4 MNPs and MNPs coated with silica in controlled size and shape and large amounts[37].

2.3. Biological methods

Micro-organisms like bacteria, viruses, fungi, and actinomycetes have been utilized to synthesize MNPs[38]. This method provides biocompatible MNPs that are widely used in biomedical applications, the produced MNPs are also environmentally friendly and are of good yield but they suffer from weak dispersion properties[39]. The extract of the tissues of multicellular plants and the unicellular micro-organisms have been reported as sources of synthesis of MNPs[40], MNPs produced by micro-organisms are produced either intracellularly or extracellularly, the latter method is economical and easily handled. Fe_3O_4 NPs are produced by magnetotactic unicellular bacteria[41&42]. For the transformation of the ions of metals into zero valence NPs, the bottom-up technique[43] is employed where bio-macromolecules such as polysaccharides, phenols, sugars, proteins, and others are utilized and the main mechanisms involved in this conversion are the oxidation and reduction[44]. The reported enhanced biocompatibility of the produced MNPs by biological synthesis is mainly due to encapsulation of the toxic core of MNPs with biomolecules which are non-toxic. Figure 4 shows a summary of the biological synthesis of MNPs and their biomedical applications[43].

In general, the selection criteria of the method employed for the synthesis of MNPs are mainly based on their application, yield, size, morphology, and cost, so there is no single optimal method employed for the synthesis of MNPs[1].

2.4. Comparison between different synthesis methods of MNPs

When comparison is made between physical and chemical approaches of MNPs synthesis, it was found that obtaining NPs in the nanoscale size is difficult to achieve by the physical approach[13] also particle size and shape are not easily controlled by the physical method[4]. On the other hand, chemical approaches allow controlling NPs shape and size by modification of reaction conditions[14]. Hydrothermal method as one of the chemical methods of MNPs synthesis; is the most efficient method in producing NPs with controlled shape and size, homogenous composition and high crystallinity, particles produced are monodispersed and have uniform size[32]. Co-precipitation method is always a favored synthesis method being easily applied, simple method but despite producing high yield of NPs, shape control is unsatisfactory. Sol-gel method produces highly pure NPs with good crystallinity, the method can be carried out at room temperature, which is always an advantage. Micro-emulsion method produces low yield of monodispersed particles with non-

uniform morphology. However, the thermal decomposition method is considered the best approach to produce controlled size NPs[22]. Biological methods are green, low cost, reproducible and high yield methods for producing NPs. Table 1 shows a brief comparison between methods of synthesis of MNPs.

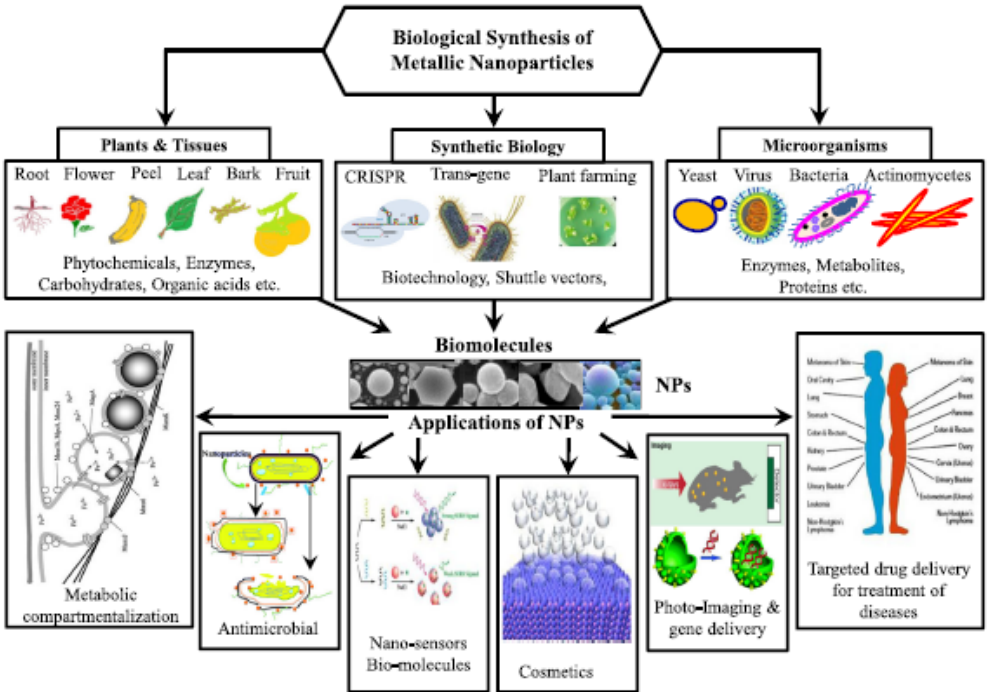

Fig. 4: Biological methods of synthesis of MNPs and their applications.

Table 1: Merits and demerits of different synthesis methods of MNPs.

Synthesis method	Merits	Demerits
Ball mill	Popular, simple method, produces fine powder	Product is contaminated
Laser evaporation	Cheap experimental cost, green method	Expensive laser instrument, requires high energy
Wire explosion	Green , safe, produces high yield	Product may be contaminated
Co-precipitation	Simple, produces high yield	Product may be contaminated, time consuming method
Thermal decomposition	High yield, produced particles have controlled size	Hazardous solvents
Micro emulsion	Thermodynamically stable	Low yield
Hydrothermal	Particles of good crystallinity	Need high pressure and temperature
Sol- gel method	Good crystallinity and high purity	Hazardous solvents, long synthesis time
Biological methods	Green , efficient method	Low dispersion

3. Composition of MNPs

3.1. Mono-component MNPs

3.1.1. Iron, nickel, and cobalt-based MNPs

Iron MNPs are the most widely studied NPs because of their application in biological and biomedical fields, this is mainly due to their excellent biocompatibility, magnetic properties, low cost, chemical and physical stability, and being environmentally friendly. [Fe $(CO)_5$] iron carbonyl is decomposed in the presence of oleic acid to form iron NPs[45]. Since iron NPs are sensitive to oxygen, PVP was utilized in their synthesis through the aqueous phase synthesis method, PVP was found to be an excellent antioxidant for the iron NPs surface[46]. Nickel NPs with an average particle size of 3.7 mm were prepared by reduction of nickel (II) bis (acetylacetonate), the medium should contain hexadecylamine[47]. Cobalt NPs may have an average size of 2-6 nm or 7-11 nm, for the first type, is prepared using bulky alkyl phosphine as a reductant, while the second type is prepared using another trialkyl phosphine which is less bulky and has a neutral surface metal sites[48].

3.1.2. Metal alloys MNPs

the alloys of iron-platinum, iron-palladium, and cobalt platinum NPs (FePt, FePd, and CoPt respectively) show high chemical stability, and high symmetrical magnetism of the crystals(magnetocrystalline anisotropy) which make them preferred over their counterparts[49] and highest saturation magnetization[50]. FePt MNPs are mainly done by vacuum deposition, but this method was found to result in particles with wide size distribution and agglomeration. The solution phase method was thus preferred to the vacuum deposition method and resulted in the successful preparation of monodispersed MNPs[45&51-53]. Recently, the synthetic method was introduced[54] based on reducing platinum acetylacetonate and decomposition of iron pentacarbonyl, stabilizers (oleyl amine and oleic acid) should be present. Such a method resulted in tunable particles of (3-10 nm) in diameter. The vacuum deposition method has been used to prepare FePd MNPs. Recently, the wet chemical method is utilized to prepare monodispersed NPs using two or more surfactants as adamantyl carboxylic acid-hexadylamine[45], and trioctylphosphine oxide oleic acid[55]. To stabilize FePd MNPs, a modification of Sun *et al.* method[54] was carried out by using hexadecandiol as a reducing agent for palladium acetyl acetonate, while $Fe(CO)_5$ was thermally decomposed[49].

Such metal alloy MNPs are susceptible to corrosion or oxidation hindering their applications in biomedicine, protecting these particles by a biocompatible outer shell is the answer to that problem[56-60]. FeCO NPs coated with silver or gold shell were fabricated first using a nanocluster gun containing $Fe_{60}CO_{40}$ as starting material, that gun produced FeCO NPs, and their size was controlled by changing the preparation conditions of the source of nano particles already present in the gun, then Au or Ag particles are deposits on the surface of FeCO NPs during their flight by online evaporation or sputtering[61].

3.1.3. Metal oxide MNPs

Metal oxide MNPs have recently got much interest due to their high magnetic properties and chemical stability[1]. Iron oxide NPs are classically prepared by co-precipitation of Fe^{+2} and Fe^{+3} salts[62]. Stoichiometric mixing of aged inorganic salts in an aqueous medium is used to obtain iron oxide NPs on a large scale, where parameters such as reaction temperature, pH, and precursors have to be optimized, also the solvothermal process in high pressure is used to obtain well-shaped crystals of iron oxide MNPs. But, the previous two methods did not result in MNPs with a close size distribution. So, the decomposition of metal complexes at high temperatures (thermal decomposition) is used to obtain MNPs of narrow size distribution and controlled morphology[63&64]. The method depends on dissolving the metal complex with the surfactant in a high boiling point organic solvent where precursors are added either by direct heating up or by hot injection[65]. In the heating up procedure, heating and mixing of the precursors are carried out with the thorough adjustment of their temperature and concentration, while in the hot injection method, thermally unstable metal complexes are injected quickly in a hot solution containing surfactants to allow for the nucleation to occur followed by the controlled growth of MNPs. In both methods, olyelamine and oleic acid surfactants are used to control

the MNPs' size and morphology, metal oleates and metal acetylacetonates are usually used as metal precursors[66]. To produce Fe_2O_3, $COFe_2O_4$, and $MnFe_2O_4$ MNPs, their metal acetylacetonate was thoroughly mixed with 1,2-hexadencandiol, oleylamine, and oleic acid in benzyl ether, the mixture was heated to 300°C, this reaction resulted in monodispersed NPs of size range from 4-8 nm. Direct heating of iron (III) acetylacetonate and oleylamine dissolved in benzyl ether - without using alkyl diols - was found to be successful in producing monodispersed MNPs[67]. FeO NPs (Wüstite) were also produced by the thermal decomposition of iron (III) acetylacetonate in an oleylamine and oleic acid mixture. Where, according to their molar ratio, the produced FeO NPs had a size range from 14-100 nm, and their size was octahedral or polyhedral. The produced FeO Nps by this method can be converted into hematite (α-Fe_2O_3), maghemite (γ-Fe_2O_3), magnetite, or Fe/Fe_3O_4, thus they can be generally used to synthesize different iron oxide NPs[68].

3.1.4. Metal carbides MNPs

Iron carbides (Fe_2C, Fe_3C, Fe_5C_2) show great stability and magnetism, but they face difficulty in synthesis due to challenges in their morphology and size control. Different synthetic routes including laser ablation, sonochemical methods, solid state, and biotemplated methods were used for the synthesis of iron carbides, but the produced particles suffered from being polydispersed and aggregated[69-74]. The accurate supply of reactants, and modification of particles by nucleation bursting were utilized in solution chemistry for controlling the growth and generation of the NPs[75]. In general, penetrating carbon atoms are used to produce crystalline iron carbides[76]. Carbonization of iron NPs was used for the synthesis of Fe_5C_2 where bromide was used for surface energy tuning of carbide nanoparticles, the produced iron carbide NPs had a particle size of 20 nm and an amorphous shell[77]. This chemical synthetic route produced NPs of iron carbides with different crystalline forms, but they showed weak magnetic properties, which lead to a conclusion that iron carbides produced by the synthetic route are of different kinds and that the introduced halide affects carbon penetration by selective absorption[1].

3.2. Coated magnetic nanoparticles

Coating the surface of MNPs with certain inorganic or organic coating material is carried out to counteract problems of mono-component MNPs such as non-uniform size or morphology, low stability at highly acidic and highly alkaline media, irregular binding properties, and improves their compatibility in biological and solid matrices[78]. The coating could be Inorganic coatings such as graphene, manganese oxide, alumina, or silica, while molecularly imprinted polymers, divinyl benzene, chitosan, or surfactants are examples of organic coating.

Coating the core of MNPs increases their lifetime and prevents their oxidation. Modification of the coating materials by certain functional groups enhances the dispersion, mechanical, physicochemical properties, and surface activity of MNPs.

The selection criteria for both core and surface modification is based on the purpose of those particles[66,79&80]. The coating of iron oxides (whether maghemite or magnetite) being the most commonly used MNPs' core will be discussed in the following discussion.

3.2.1. Silica

The most commonly used coating of iron oxide NPs is silica. Silica is generally available and has specific binding characters[81] so it can be modified with various functional groups. The binding of organic or inorganic particles to the silane groups is utilized for functional group modification of the silica coating, thus increasing its thermal and mechanical stability, coating of silica also reduces the agglomeration of MNPs, enhances their stability, and reduces MNPs' cytotoxic effects[82]. For the synthesis of iron oxide NPs@SiO, the Stöper method is the most widely used method, this method is based on the dispersion of iron oxide NPs in ethanol, then tetraethoxysilane is added followed by addition of ammonia solution[83&84]. Using ammonia lead to the formation of particles with uniform morphology and large size[85]. Highly crystalline iron oxide NP@SiO_2 was synthesized by the micro-emulsion method which is classified into oil in water or water in oil methods. the methods, by definition,

comprise oil, water, and a surfactant. Such a method produced particles of controlled size, the thickness of the shell, and dispersion, but the major drawbacks of this technique are the time-consuming step of separating surfactant from NPs, low yield, and high solvent consumption[86]. Aerosol pyrolysis in a flame environment was recently used to synthesize iron oxide@SiO_2 NPs, where superparamagnetic iron oxide (Fe_2O_3) NPs with low content of SO_2 were obtained by synthesis of iron oxide at first by acetylacetone iron fame spraying in acetonitrile / xylene solution, the resulting aerosol was then coated with SiO_2, this was done using oxidized vapors of hexamethyldisiloxane[87].

When unmodified silica is used for extraction, the free silanols will absorb polar compounds irreversibly. While modification of silane groups by certain functional groups reduces the degree of absorption of polar compounds allowing ease of extraction of polar compounds (e.g. binding of free silanols to –NH_2 group). On the other hand, binding silanols with octadecyl group(C_{18}) makes their surface of very low polarity and facilitates reversible extraction of non-polar or compounds of low polarity[88]. Sol-gel process is used to add certain functional groups to the silica-coated MNPs (for example –NH_2 groups) where ammonia water used as a catalyst is added together with deionized water and ethanol to the magnetic core at a controlled temperature. To this mixture, ethanol, and tetraethoxysilane (TEOS) are added, then mixing is done by sonication or vigorous stirring. TEOS causes hydrolysis of Si-O bonds with subsequent formation of –OH groups, these hydroxyl groups can be replaced by other functional groups as amino groups for the extraction of drugs. It should be noted that the synthesis is carried out in an inert atmosphere of nitrogen gas[89] (Fig. 5).

3.2.2. Carbon

Carbon is an extraordinary material, being biocompatible, easily surface modified, and stable over a wide pH range, such features make carbon an excellent coating for Fe_3O_4 NPs which are stable in both acidic and alkaline medium, show a low level of toxicity and an excellent magnetization[90-93]. The carbon shell is formed by strengthening at high temperatures leading to the reduction of iron oxide NPs and carbonation of precursor of hydrocarbon[94-96].

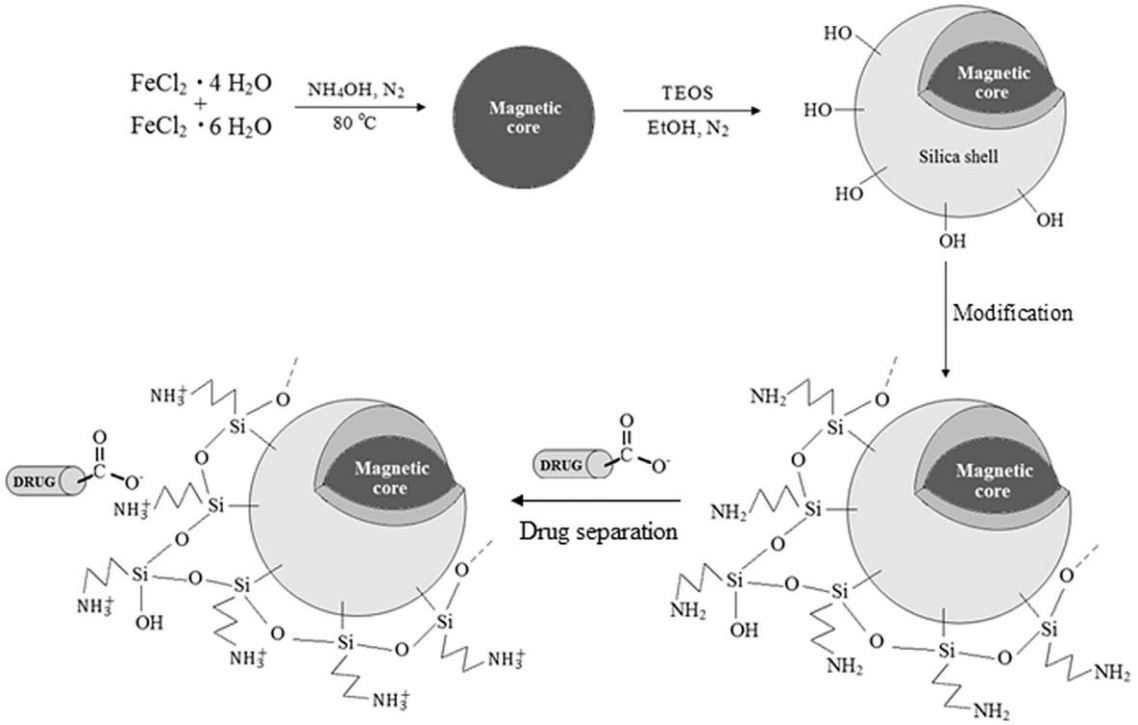

Fig. 5: Synthesis of silica-coated magnetic nanoparticles (MNPs) with surface modification by amino groups to separate drugs[89].

3.2.3. Metal

Metallic coating or iron oxide NPs can be used to provide an inert outer layer, it also facilitates the addition of functional groups to iron oxide NPs. improving their biocompatibility and stability[97]. The most commonly used noble metal for coating iron oxide NPs is gold which can be applied to their surface by either direct or indirect methods[98]. The direct method is carried out in an aqueous or organic solution, the method is based the on reduction of the trivalent gold ions by a reducing agent. Sodium borohydride or sodium citrate the common reducing agents used in the aqueous solution[99&100], while oleylamine is commonly used in the organic synthesis route serving as a capping and reducing agent[101]. The indirect method used to produce iron oxide@Au NPs is based on the formation of a layer between Fe_3O_4 NPs and the shell of gold, such a layer will act as a glue binding the core and the shell together. Such a glue layer must be able to increase the core stability and should have functional groups to bind the gold shell to the iron oxide core[102]. Materials acting as glue are usually silica, carbon-based materials, or polymers[103]. Another noble metal that can be used as a coating for iron oxide is silver, Fe_3O_4@Ag NPs have very promising applications in biomedicine since they have peroxidase-like catalytic activity[104], they also show antibacterial properties[105-108]. Chen *et al.*[109] used the solvothermal method to synthesize Fe_3O_4@Ag, where a pronounced improvement in the antibacterial activity was reported for Fe_3O_4@C@Ag NPs when compared to Fe_3O_4@AgNPs, the introduced layer of carbon has opened a new area of applications of these particles as antibacterial, catalysts and adsorbents[110].

3.2.4. Metal oxides and sulfides

Using metal oxides and sulfides as a coat of iron oxide NPs gives them unique physicochemical properties. According to the valence of the metals employed, metal oxides and sulfides can be classified into six classes: monovalent metals (e.g. Ag_2O, Cu_2O), divalent metals (e.g. CdS, ZnS, CoO, MgO, ZnO), trivalent metals (e.g. Bi_2S_3, Y_2O_3, Al_2O_3), tetravalent (e.g. TiO_2, SnO_2), pentavalent metals (V_2O_5) and hexavalent metals (MoO_3, WO_3). Fe_3O_4@ZnO NPs were found to be superparamagnetic, they were found to have a photocatalytic activity that is superior to ZnO NPs[111]. Fe_3O_4@Al_2O_3 NPs were perfectly used for the adsorption of ions from water-when doped with sulfate ions- it adsorbed fluoride ions from the water, where 90% of the fluoride content was adsorbed in 20 minutes. Uranium (VI) was also effectively adsorbed by Fe_3O_4@TiO_2 NPs[112]. It was found that when particles of soft magnetic origin are smaller than the particles of hard origin, they will act as a single phase. Based on theoretical calculations, the exchange coupling effect is produced when the soft magnetic phase is smaller than double the thickness of the hard magnetic phase which can be achieved by controlling synthesis conditions. Using a soft magnetic shell to coat the hard magnetic core is a very effective method to produce an exchange coupling effect, which would ultimately lead to increased magnetization[113]. Fe_3O_4@Co Fe_2O_4 NPs is an example of core-shell NPs combining soft and hard magnetic compound respectively, such combination was found to have many applications[14] such as in data storing apparatus, devices of microwave, and also as magnets

3.2.5. Polymers

Coating of iron oxide NPs with polymers is utilized to reduce particle aggregation since that the presence of polymer provides steric stability[114]. Polymer-coated iron oxide NPs can be synthesized by the inclusion of the polymer coat during the synthesis of iron oxide NPs, such process is called *in-situ* coating[115] or polymer@ iron oxide NPs can be prepared by using functionalized polymer as a coat for iron oxide NPs that are already prepared[116]. Many polymers are used as a coating for iron oxide NPs depending on the intended application, commonly used polymer coatings include: dextran, chitosan, starch, polyethylene glycol, and polyvinyl alcohol.

Dextran when used as a coat for iron oxide NPs, it acts as a non-magnetic shell reducing iron oxide NPs' magnetic saturation, it was also found to be a very good nanocarrier with reduced cytotoxicity and excellent biocompatibility[115] making such coated NPs ideal candidates in the biomedical field[113]. Dextran is a polysaccharide composed of α-D-glucopyranosyl units with different degrees of

branching and lengths[117]. The interactions between dextran and iron oxide NPs occur mainly by hydrogen bonds and chelation, such interactions are enabled by the appropriate size of dextran chains, the large number of hydroxyl groups over the entire length of dextran chain enables multiple hydrogen bonding with a high bonding energy despite the fact that a single hydrogen bond is a relatively weak bond[118]. But, it was found that dextran coat is easily desorbed from the surface of iron oxide NPs by dilution or by heating at 120°C[119]. However, when using epichlorohydrin as cross-linking agent, it prevented dextran desorption[120&121]. Dextran-coated iron oxide NPs can be synthesized by co-precipitation or laser pyrolysis method[119]. Chitosan is an excellent polymer for coating iron oxide NPs, being biodegradable, naturally occurring chitin, having a large number of primary amino groups capable of binding to many other agents, chitosan is also a linear biocompatible polysaccharide, thus iron oxide NPs coated with chitosan are widely used in hyperthermia and tissue engineering. Coating with chitosan is done by an *in-situ* coating method or by co-precipitation in an alkaline medium of ferrous and ferric precursors of chitosan hydrophilic polymers in an aqueous solution, the use of these polymers prevent iron oxide NPs overgrowth that may occur during synthesis leading to steric hindrance during dispersion of nanoparticles in the aqueous medium[122]. Derivatives of chitosan are preferred as a coating material of iron oxide NPs because pure chitosan has poor solubility in acidic medium, in addition to low mechanical and thermal stability. N-, O- carboxy methyl chitosan is a common derivative of chitosan used to overcome the abovementioned problems, the produced NPs show enhanced anti-fouling and hydrophilic properties[123]. Polyethylene glycol (PEG) is used as iron oxide NPs coat where such NPs are applied as contrasting agents in the MRI for imaging cancer cells *in-vivo* or when used in biosensors[124], PEG is soluble in aqueous solutions, hydrophilic, and a biocompatible polymer[121&125] so when it is used as a coat for iron oxide NPs, it increases its dispersion and decreases the time required for blood circulation, and proved to have superparamagnetic properties[126-128]. Coated particles with sizes (20-35 nm) or (60-100 nm) were prepared by aqueous hydrolysis of $FeCl_3.6H_2O$ followed by a reaction with PEG-poly aspartic acid polymer[129], the produced NPs proved to have good stability and solubility in the physiological system and aqueous medium[116]. Alginate is a polysaccharide with electrolytic properties containing many carboxylate groups, it was assumed that repulsions occurring between the carboxylate groups and iron oxide NPs make such coated iron oxide NPs more stable and superparamagnetic[130-133], the classical method for synthesis of such coated NPs includes three steps: first, the formation of gel of ferrous ions and alginate then alkaline treatment of the alginate leading to precipitation of iron as ferric hydroxide finally, the resulted ferrous hydroxide is oxidized by an oxidizing agent like H_2O_2 or O_2, modification of this complicated procedure was carried out[134] using co-precipitation technique in two steps producing monodispersed iron oxide@alginate NPs, such particles of controlled size and superparamagnetic properties make them excellent candidates in drug controlled delivery targeted systems and also as adsorbents[135]. Other polymers used as a coating for iron oxide NPs include many polymers with variable applications as polyethylenimine (PEI) which is applied in hyperthermia and separation of cancer cells, polyacrylic acids that are used in the targeting of cancer cells, polydopamine applied in biosensors, as adsorbent and as a catalyst, starch is applied in imaging and is contrasting medium, flavonoids are applied as nano carriers for nano drugs and cell imaging, amino acids are applied in the detection of cancer cells, as adsorbents, in biosensors and as radio labels, lipid coatings are applied in dual modal imaging and in gene therapy[124]. Recently, polymer gels were used as coating of iron oxide NPs, their use enables easy control of growth and nucleation of the core NPs by the polymer gel rigid architecture[136&137]. It was found that controlling the ratio of the monomer to iron oxide NPs controls the morphology of the coated NPs and increasing MNPs content in coated particles will improve the dispersion properties[116]. Spin coating was used for deposition of poly(methylacrylate polypyrolle) from solution, the co-precipitation was used to prepare FE_3O_4 NPs, then the MNPs coated with

surfactant and fatty acids were mixed with the dissolved polymer leading to formation of uniformly dispersed NPs[138].

4. Characterization of MNPs

Many instruments are employed to characterize MNPs and examine their physical structure. It was found that MNPs' size is the key factor in the determination of their physicochemical properties which are affected by even a small variation in size[1]. The biological properties of MNPs are also affected by their size, shape, dispersion, charge and coating[116]. Many instruments are employed for the purpose of characterization of these physicochemical properties.

Characterization of MNPs size includes determination of: the core crystalline part, the amorphous and the crystalline iron core, core as a whole and the shell. MNPs are usually poly dispersed so many values could be obtained for the same size of the particles based on the technique's expression method being expressed either as a volume, number or intensity weighted mean size[116]. When the technique gives access to intensity-weighted mean size or volume, high values are obtained even in the case of small amounts of big-sized NPs. *TEM (transmission electron spectroscopy)* is used to characterize the composition, size, and morphology of the MNPs[1], it determines the core (the amorphous and the crystalline parts) particle size, it also gives information about shape and size distribution of the particles, but the preparation steps of the sample in TEM cause aggregation of the particles, so the measured distribution and size of the particles may not be accurate[139&140]. So *high resolution TEM (HR-TEM)* can be used alternatively to examine the surface arrangement, lattice vacancies, glide plane, lattice fringe and screw axis[141&142]. *Scanning electron microscope (SEM)* defines composition and topography of the MNPs, it is mainly concerned with the outer structure, while TEM is concerned with the internal ultra or micro structure and can also be applied in studying the interaction of cells with the MNPs[143]. Sample preparation in TEM involves the MNPs dispersion in an inert organic solvent as hexane which is then evaporated, when water is used, sample is subjected to a heating lamp and a desiccant[144]. But TEM suffers from: being time consuming technique, being applied only to small sized samples, need to take many images with zooming out of the background to show as much particles as possible and to obtain statistically accurate measurements, a program (e.g. Image J) should be used to analyze the images[145]. The preparation step of particles in TEM involves using a desiccant, so it can only applied to dry MNPs, it is also applied only to electron rich materials and provides a 2D image rather than a 3D one[146]. *XRD (X-ray diffraction)* technique is used to describe the atoms crystalline order, the crystals structure and size[147] where size can be easily determined for crystalline NPs by applying Scherrer equation, while non crystalline NPs give broader peaks which makes the Scherrer equation inapplicable[148&149], in that case using Willianson-Hall equation is more appropriate. The major drawback of XRD application in size determination is that it does not discriminate between maghemite and magnetite NPs as it gives the same spectrum for both of them since they both have structure of inverse spinel, in that case other techniques as Mössabur spectroscopy at low temperature can be used where magnetite gives Verwey transition[150]. *Small angle x-ray scattering (SAXS)* is a scattering technique at low angles as the particles are exposed to high density x-rays which are then scattered by the particles at variable small angles (from 0.1° to 5°) and the scattering is measured at these angles taking into consideration that scattering is inversely proportional to distance[151]. SAXS is employed for determination of particle size, shape and size distribution. XRD, SAXS and TEM were employed to study PVP@Pt NPs particles and crystals size changes with temperature[152], it was found that different sizes were obtained for the same NPs measured by XRD and SAXS, this is mainly because XRD measures the crystalline size while SAXS measures particle size being sensitive to the region of fluctuation in the electron cloud while XRD responds to size of the region of long range, compared to TEM, SAXS gave bigger size NPs this is mainly because the studied NPs were coated with PVP and the scattering intensity caused by this coat cannot be removed. The major drawback of SAXS is that it provides low resolution images, and sometimes complementary techniques as electron

diffraction and/or XRD should be done[147]. *Localized surface plasmon resonance (LSPR)* studies are used to detect the interactions of molecules close to the surface of NPs, when performing such studies, SAXS is usually accompanied to measure the length of aggregates of NPs, compared to SEM and TEM, SAXS is the most suitable technique to measure such a parameter because it is non-invasive, while the first two techniques require drying the solvent and involve interactions of the substrate with the particles leading to invasion of the studied NPs, so both techniques cannot be used in conjugation with LSPR to study the behavior of NPs on the contrary to SAXS[153]. *XPS (x-ray photon spectroscopy)* is widely used to characterize nano-sized particles based on photoelectric properties[154]. It is also used to describe elemental composition, electronic structure, the elemental oxidation state in a material, surface functional groups of the NPs and to study the exchange interaction of ligands, it can be used to study the heterogeneous internal structure of the NPs[155]. When XPS is compared to other microscopic techniques (e.g. TEM), such techniques can recognize elements vertical to the reference beam of electros while XPS recognizes elements in the same direction as the reference beam of electrons. XPS has the advantage of providing information about the depth of the NPs up to 10nm from the surface and being a non-invasive technique, while the preparation of samples in a dry solid form that is free from any contamination and interpretation of the findings represent the two major limitations of XPS analysis[147].

FTIR (Fourier transform infrared spectroscopy) is a method based on the measurement of the electromagnetic radiation's absorption at wavelengths between 4000 and 400 cm^{-1}. When a molecule absorbs IR light, the dipole moment is changed in some way, so it becomes IR active. The position of bands associated to the strength and kind of bonds, as well as certain functional groups, is revealed by a recorded spectrum. By this technique FTIR can be used as a tool to provide information about molecular structures and interactions[156]. Highly crystalline ferrite superparamagnetic NPs (MFe_2O_4, where M is CO, Mn, Zn and Ni) with size smaller than 10 nm were synthesized by a straightforward polyol method[157] were characterized by FTIR, that showed tetrahedral frequency (u_1) that confirmed the ferrite spinel structure, the existence of diethylene glycol in the coating of the NPs was confirmed by the presence of -OH and C-O groups characteristic bands, indicating that the coating of ferrite NPs was successful. In a different study, FTIR studies of hydrophobic iron nanoparticles that had been converted into water soluble iron oxide core shell NPs by the use of ligands treated with alkyl phosphoric acid revealed the presence of Fe-O-P bands[158]. *Nuclear magnetic resonance (NMR)* is also used for NP structural determination, it is based on the NMR phenomenon that occurs in non-zero spin nuclei in a strong magnetic field, which results in a minor energy difference between the spin up and spin down states. The interaction or co-ordination between the ligand and the surface of antiferromagnetic or diamagnetic NPs is frequently investigated using NMR. The characterization of ferro or ferrimagnetic NPs, however is not feasible due to the substantial saturation of magnetization of such materials, which results in a change in the local magnetic field and shifts in the frequency of the signal leading to noticed shortened relaxation time. Consequently, the signals broaden rendering measurement practically useless and unexplained[159]. NMR is an essential technique complementary to other sizing methods as dynamic light scattering (DLS) and TEM, because it can be used for measuring the NPs hydrodynamic radius. Like DLS, NMR determines the NPs size through determination of the diffusion of particles, it can measure sizes bugger than 100 nm for hybrid polymer particles and particles within the range of 1-5 nm for metallic NPs[160&161]. A popular method for determination of NPs size in a colloidal suspension id the *DLS (dynamic light scattering)*. In a colloidal solution, NPs usually exhibit Brownian motion. DLS together with the assumptions of Stokes-Einstein are used to calculate the hydrodynamic diameter which is the diameter of molecules of solvent and NP molecules that have the same diffusion rate as the colloid, this is crucial in DLS to avoid multiple scattering effect[162]. Values of NPs size delivered from DLS are affected by concentration of the suspension, shape of the particles, stability of the colloid and nature of the coating on the MNPs. When different size

measuring techniques (TEM and DLS) were compared, discrepancies were found for both small and large particles. When studying NPs of small size, there is a noticed difference in diameter measured by both techniques, this was mainly attributed to effect of curvature radius, while for middle sized NPs of Fe_3O_4 coated with oleilamine and oleic acid, an agreement was found between size measurement taken by DLS and TEM[163]. DLS is an important tool for studying the process of aggregation and for quantitative measurement of the particles clusters size, in addition DLS being sensitive to large sized particles can be used as a method for detecting aggregation in the first place. The quick, simple and accurate measurement of NPs of the same size in suspension and the idea that DLS gives strong representation of the statistics of each NP in the sample, represent the two major advantages of using DLS, also for homogenous, monodispersed samples, it is incredibly sensitive and repeatable. But, for DLS techniques to be performed, particles should be suspended and have Brownian motion. The presence of large and small particles will scatter light unevenly, so, the resolution of heterogeneous sized particles is low, also the interpretation of DLS data requires special care especially for heterogeneous samples. In general, DLS is useful in determination of NPs' hydrodynamic radius very accurately but it lacks accuracy for aggregates of small size[164]. To overcome such abstacle, DSC (differential centrifugal sedimentation) should be done prior to DLS, when DSC data show that sample does not contain any aggregations, we can simply rely on results obtained from DLS[165]. *NTA (nanoparticle tracking analysis)* is a novel method that is adopted fast, it can detect NPs of smaller size than those detected by DLS, based on both Brownian motion and light scattering, making it suitable for NP size determination in liquid dispersions[147]. When NTA is compared to other size measurement techniques, NTA is found to be an excellent technique for poly-dispersed samples, it also offers no preference for big NPs or for aggregates[166]. Comparing DLS and NTA, the latter gave accurate results for the size distribution of both poly and monodispersed particles, size results obtained by NTA were more accurate and of smaller values than those obtained from DLS, but NTA operation is difficult and is slower than DLS. NTA examines particles individually, so it is able to examine different NPs size distributions, on the other hand, DLS investigates a group of particles as a whole and it greatly favors large particles[167]. In contrast to TEM, NTA enables size measurement of vast quantities of particles, it is also able to distinguish particles made of different materials within a specified range of size by measuring the scattered light intensity of each particle[168]. *MS (mass spectrometry)* has attracted attention as a potent method for accurate analytical evaluation of the NPs, when it comes to understanding structure, chemical state, composition and NPs conjugation to the specific biomolecules, MS provides crucial molecular and elemental data[169]. In addition, MS could be combined with a separation technique giving a more detailed information on the NPs nature that could be utilized for selection of the appropriate applications and uses of NPs. *(ICP-MS) inductively coupled plasma MS* is a sensitive, robust and a highly selective technique. It can be used for the elemental characterization of metallic NPs and the determination of impurities of metallic nature in the non-metallic NPs. Characterization of the protective ligands can be obtained by using molecular characterization MS techniques such as MALDI (matrix assisted laser desorption/ionization) and ESI (electron spray ionization)[147]. *Zeta Potential* is used to measure colloidal NPs dispersions stability. A colloid with high concentration of positively and negatively charged NPs is highly stable due to repulsions between particles that inhibit agglomeration. a stable colloidal dispersion will have a zeta potential values between ±20 and ±30 mV, while lower values of zeta potential indicate the colloidal agglomeration and thus reduced colloidal stability. In such case, modification of the NPs surface chemistry should be done to enhance the colloidal stability and increase the repulsions. DLS being a useful tool for detecting aggregates in NPs solution can be combined with zeta potential for comprehensive characterization of NPs in solution[170]. Both zeta potential and DLS offer a common advantage over TEM and SEM that sample preparation step does not include solvent evaporation which itself leads to

aggregation of the NPs[171]. *DSC (differential scanning calorimetry)* can be used for characterization of NPs based on the fact that particles melting point vary according to their grain size, since that surface to volume ratio is greater for NPs, so their melting point would be 10-100 k less than the corresponding bulk material[172]. DSC is a thermal analytical technique which is quick, accessible and simple, a reference material and the sample are put within holders, where they are either kept at a specified temperature or temperature is increased gradually in a predetermined manner, the device then computes the differential flow of heat between the sample and the reference[173]. *VSM (vibrating sample magnetometry)* is used to study the magnetic properties of MNPs and their relation to temperature, magnetic field and time. VSM was used to study the magnetic properties of $FeCO@SnO_2$ NPs on graphene polyaniline, and it was found thatthey show powerful dipolar magnetic interaction and that their magnetic moment is in the same direction of an applied external magnetic field[147].

5. Biomedical applications of MNPs

Magnetic nanoparticles (MNPs) are a commonly utilized system in biomedical applications owing to their non-toxic nature, biocompatibility, and unique magnetic properties that enable their directed localization or heating through an external alternating electromagnetic field[174-176]. Iron oxide-based nanoparticles with a size smaller than 100 nm and a coating are the primary commercialized magnetic nanoparticles utilized in the biomedical applications due to their durability and biological compatibility. Nanoparticles can be encapsulated within shells that are either inorganic (such as silica, gold or hydroxyapatite) or organic (such as polyvinyl alcohol, dextran, or polyethylene glycol)[174]. The application of coated MNPs prevents aggregation of particles which is attributed to the combined effects of hydrophobic interaction and ferromagnetic behavior. Nanoparticles that possess an appropriate surface coating have the ability to escape detection by the immune system, specifically the reticuloendothelial system (RES), thereby prolonging their circulation time[177].

5.1. MNPs for biological separation

Recent advances in biological research have made it more important than ever to be able to quickly and thoroughly separate biological components including DNA, proteins, antibodies, and antigens. Due to their distinctive magnetic characteristics, magnetic nanoparticles (MNPs) are a highly suitable option for bio separation. The utilization of magnetic bio separation presents several benefits in comparison to alternative bio separation methods, including centrifugation, precipitation, and chromatography. This is due to its intrinsic magnetic properties and its minimal toxicity towards biological molecules. Separation by MNPs is characterized by its versatility and robustness. It operates through interaction between MNPs or the ligand present on the surface of NPs, which is subsequently isolated from unwanted particles with the aid of a magnetic field from outside. The utilization of coated MNPs is a viable approach for the tracking of particular molecules, including antibodies and antigens. Magnetic Nanoparticles have the potential to selectively isolate bacteria, lung and breast cancer cells, as well as red blood cells from biological specimens. The MNPs are subjected to modification in order to achieve biocompatibility, colloidal stability and biological targeting. The coated magnetic nanoparticles (MNPs) are subsequently thoroughly blended and subjected to incubation with the biological specimen, together with the desired molecules present in the solution, for a specific duration. Following the incubation phase, a magnetic field of external origin is employed to differentially isolate the molecules present in the solution. The magnetic particles, which have been conjugated with the targeted biomolecules via surface ligand, are subjected to multiple washes with a washing buffer in order to eliminate any unwanted molecules that might have been adsorbed. A buffer is then employed for elution subsequent to the washing procedures for the retrieval of the targeted molecules. Finally, the magnetic nanoparticles undergo a recycling process to restore their binding ability before being reused[178] (Fig. 6).

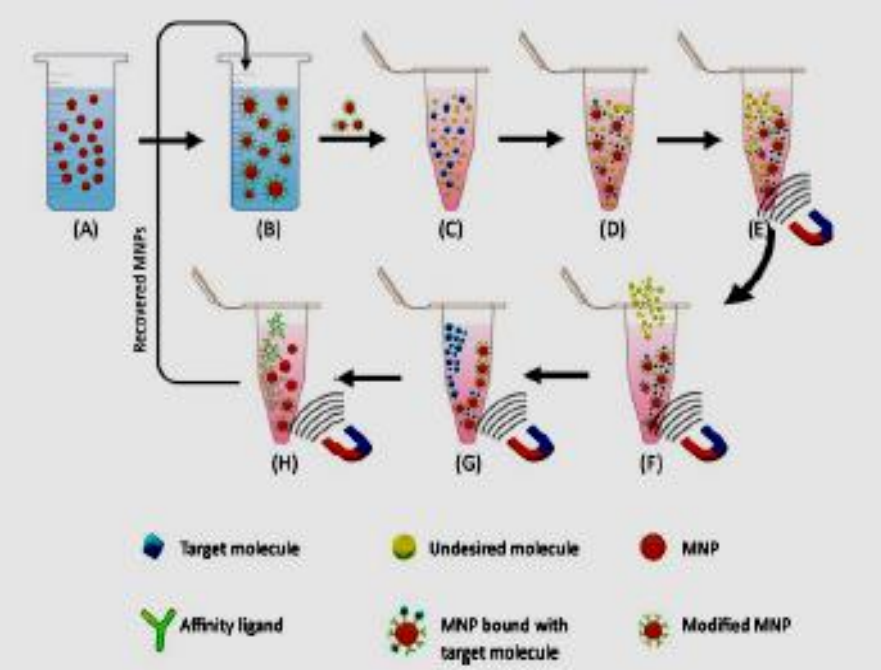

Fig. 6: An illustration to steps employed for biological separation of targeted molecules by MNPs[179].

Proteomics is one of the most widely used applications of MNPs, such a process involves purifying native and recombinant proteins. Traditionally, proteomics is a tedious process that involves the utilization of a range of chromatographic and electrophoretic techniques, among which, affinity chromatography was the most popular technique. This method is not appropriate for the early phases of the purification process when suspended solid and fouling components are present in the sample since it is unable to handle samples containing particle debris[180]. Hence, magnetic separation presents an appealing option owing to its uncomplicated manipulation, economical nature, and superior efficacy for unrefined specimens. FePt MNPs modified with Ni(II)-chelated nitrilotriacetic acid (NTA-Ni^{2+}) as surface functional groups have 6 sites for coordination on their surface, so they demonstrated a strong affinity for 6-histidine-tagged proteins. This protein was efficiently isolated from the lysate of cells and the preparation step was omitted. The capacity of binding of the abovementioned functionalized MNPs to such protein was found to be superior to marketed magnetic microbeads (2-3 mg proteins for each1 mg of MNPs)[181&182]. Another intriguing application of MNPs is *the separation of bacteria*[183]. Vancomycin is an antibiotic that binds to the terminal D-Ala-D-Ala dipeptide of bacterial cell wall precursors, was attached to the surface of FePt MNPs. Such modified MNPs might be magnetized apart by combining Vancomycin-FePt MNPs with a solution containing Vancomycin-sensitive bacteria for 10 minutes. A technique was presented by Hei and Cai[178], for the concentration and purification of RNA of COVID-19 (from the SARS-CoV strain), where researchers employed a method involving the use of nucleotide capture probe streptavidin-coated magnetic particles which covalently attach to the RNA of the coronavirus, followed by an external magnetic field separation of the bound RNA. This method was found to be 10 times more sensitive than the traditional PCR method.

5.2. MNPs utilized in imaging techniques

Timely and precise diagnosis of diseases is crucial in preventing disease progression, determining optimal therapy options, assessing treatment effectiveness, and reducing therapy costs. Current biomedical applications of magnetic nanoparticles (MNP) as methods for imaging include MRI, MPI, CT (Computed tomography), and PET (Positron emission tomography), of which MRI and MPI will be discussed briefly in the following section.

5.2.1. Magnetic resonance imaging (MRI)

Magnetic Resonance Imaging (MRI) offers a noninvasive way to penetrate deep into the body using magnetic fields, which could be applied for diagnostic purposes. MRI operates by the concept of field penetration, based on the fact that protons, abundantly present in water are being nuclearly magnetized, and since that water constitutes a significant portion of the human body, this allows for feasibility in the utilization of MRI, where magnetization of hydrogen-1 is carried out by an external radio frequency that causes free protons in solution to experience rotational motion and aligns itself in an antiparallel orientation with respect to the externally applied magnetic field. Once the applied RF is turned off, this horizontal magnetization breaks apart, and as it does, protons emit radiation as they return to their original state. Transverse relaxation (T2) which leads to dark contrast and longitudinal relaxation (T1) which leads to light contrast are two separate processes that make up the relaxation process. The MR image may be built using either contrast[184]. Such contrast enables MRI images to discriminate between red diseased tissues and healthy tissues (Fig. 7).

5.2.2. Magnetic particle imaging (MPI)

This technique is able to produce high-quality images of tissues and cells without radioactive labels. This has made it a valuable tool for applications as cancer cell imaging and cell tracking tool. Magnetic Particle Imaging (MPI) exhibits superior resolution in comparison with traditional imaging modalities, such as MRI and Computed Tomography (CT). The underlying operational mechanism is based on the generation of a point free of magnetic field within the sample region by making use of two magnets. Such a point is generated by utilizing the distinct irregular magnetization response exhibited by superparamagnetic iron oxide nano-particles when subjected to the magnetic field supplied by the two external magnets, the magnetization of the superparamagnetic iron oxide NPs reaches a plateau and is saturated beyond a specific magnetic field, only the particles present in the field free point are not fully saturated, so when subjected to a time-varying magnetic field, the magnetic particles located at that point exhibit a response by altering their magnetization and aligning themselves to 180 degrees. Conversely, other saturated magnetic particles show no response to the magnetic field, the detector identifies only magnetization changes in the field free point. The signals obtained from the detector coil are subsequently analyzed to generate a visual representation of the magnetic particles' influence (Fig. 8). MPI was used for diagnosing perfusion of the brain in acute stroke cases[185], The MPI's excellent temporal resolution enables single-beat accurate real-time heartbeat monitoring[185&186].

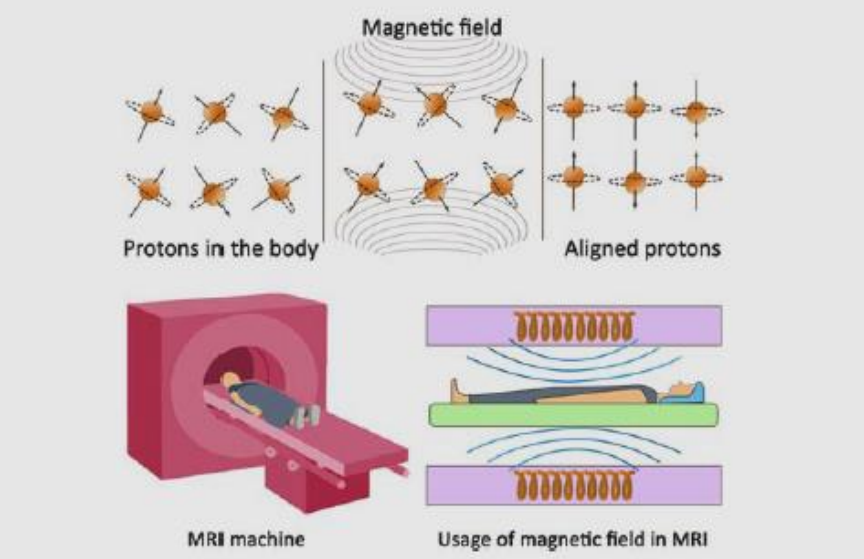

Fig. 7: Schematic representation of the MRI device[179].

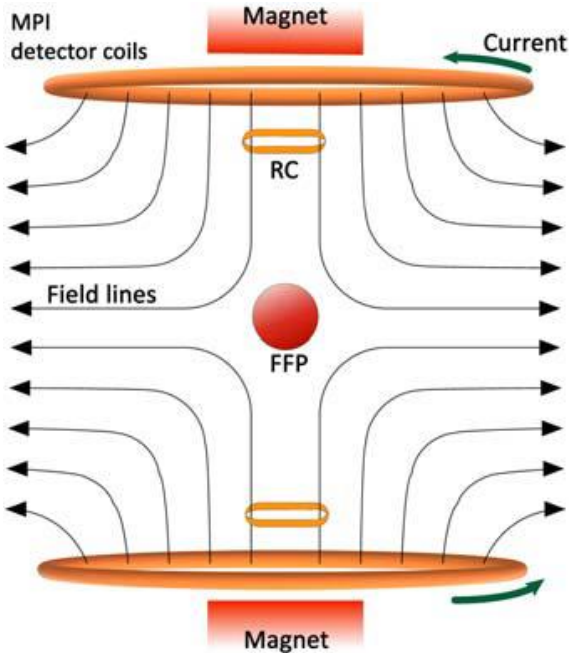

Fig. 8: Schematic representation of the MRI device setup[179].

5.3. MNPs in therapeutic applications

5.3.1. MNPs as drug delivery systems

Utilizing MNPs as site-specific drug delivery systems was first proposed in the 1970s[187]. But, this methodology has not yet materialized into a viable clinical implement-ation. One of the contributing factors is the limited load capacity of current magnetic nanoparticles (MNPs), as the attachment of drugs is restricted to the surface or the coating of the MNPs, thus limiting their use as *drug carriers in treatment of tumors*. As a method for increasing the loading capacity of the MNPs, Fe_2O_3 MNPs were replaced by hollow porous MNPs, where cisplatin was loaded in the interior of the MNPs cavities and herceptin the targeting agent was loaded on the surface, such hollow porous MNPs was found to be 24% more efficient in delivering cisplatin to the breast cancer cells than traditional Fe_2O_3 MNPs, a further improvement in the efficiency of cisplatin delivery to breast cancer cells was found when the pores of the hollow MNPs were acid etched (pH below 6) which lead to faster release of cisplatin with subsequent destruction of the cancer cells[188].

Iron (Fe) and zinc (Zn) deficiencies are significant health concerns worldwide[41]. Iron deficiency leads to the development of anemia, whereas zinc deficiency affects growth and immunity. Since that iron and zinc deficiency usually come together, drugs given for treatment of anemia usually contain both elements[189]. Electrolytic iron recommended by WHO for treatment of anemia was found to suffer from limited bioavailability. When poorly soluble nanosized (approximately 11 nm) Fe alone or Fe together with Zn elements were synthesized employing scalable flame aerosol technology, this lead to improved bioavailability by 40-80% compared to electrolytic iron in rats, without any observed buildup in tissues. Such NPs offer the advantages of reduced unwanted taste and color of traditional $FeSO_4$, also they can be used to provide dose specific drug that comply with each patient needs[190]. Superparamagnetic NPs coated with carbohydrate shell called ferumoxytol were given by intravenous administration for treatment of iron deficiency in patients suffering from kidney disease, such route of administration was found to be superior to oral route in patients with kidney problems, but its major drawback was localized sensitivity reaction at injection site[191].

Upon exposure to temperatures above 41°C, cells with cancer go through either necrosis or apoptosis, such method is called *hyperthermia* which involves exposure to elevated temperature to manage cancer cells[192]. Research has shown that cancer cells are more sensitive to heat as a result of their elevated rates of metabolism. a point that explains the potency of hyperthermia in management of tumor cells[174]. Magnetic nanoparticles have the ability to produce thermal energy when subjected to an alternating magnetic field. This phenomenon is attributed to Brown and Neel relaxations resulting from frictions due to particles movement and magnetic moment rotations with each magnetic field oscillation, respectively[193]. Making use of hyperthermia in cancer treatment is highly encouraging due to its non-invasive nature and the absence of limitations in the magnetic field's penetration depth. The aforementioned approach additionally offers magnetic resonance imaging capabilities for particle monitoring and serves as a foundation for the integration of chemotherapy through the use of magnetic nanoparticles that have been linked with other pharmaceuticals. Superparamagnetic NPs

containing 112 mg/ml of iron and coated with aminosilane were used as a hyperthermia therapy for glioblastoma multiforme, such particles were injected into the tumor at a varying dose of 0.1-0.7 ml/ml tumor, then patient went into heat therapy under alternating magnetic field, where MRI and CT were employed to compute the thermal profile of cancer cells in response to the alternating magnetic field. The administration of MNPs was found to be very well tolerated with no side effects[194].

5.3.2. MNPs for gene therapy

Magnetofection is a technique employed in molecular biology, which utilizes a magnetic field to concentrate magnetic nanoparticles that pass nucleic acids into cells. Such MNPs have the potential to be integrated into both non-viral and viral systems, thereby enhancing the efficacy of gene delivery. In recent times, there has been a conjugation of recombinant adeno-associated virus onto magnetic nanoparticles with the aim of achieving therapeutic levels of expression of the transgene. The efficacy of transfection was improved by this platform. It has been observed that the utilization of 1% of vector-conjugated MNPs can result in achieving an equivalent level of transfection as that of a free vector[195]. Magnetic nanoparticles coated with polyethyleneimine were used for non-viral delivery, such a system reduces polyethyleneimine cytotoxicty while enabling effective protection and loading of the gene[196].

5.3.3. Application of MNPs as antibacterial

Infections associated with medical devices are a common occurrence. Biofilm formation is a contributing factor that arises from bacterial adhesion to medical equipment, leading to the formation of a biofilm, followed by creating a composite structure consisting of proteins, DNA, and additional polysaccharides (a matrix is formed). The formation of biofilm serves as a protective mechanism for pathogenic bacteria against antibiotics, leading to the development of chronic infections[197]. In general, antibacterials should possess the ability to specifically eradicate bacteria in a localized manner, while avoiding any potential toxicity to the adjacent tissue. The significant antibacterial activity of silver nanoparticles has led to their recognition as promising antimicrobial agents. Nevertheless, it is worth noting that these particles possess two limitations, namely their adverse impact on human cells and their limited efficacy in penetrating bacterial biofilms. Therefore, scholars claim that the utilization of magnetic nanoparticles as a delivery mechanism for antibacterials, including but not limited to ZnO, TiO_2, MgO, copper, and silver, may result in a specific antibacterial impact (via magnetic field applied externally) and the elimination of bacterial biofilms. The utilization of $Ag@Fe_3O_4$ and γ-Fe_2O_3@Ag NPs has been suggested as a means of achieving site specific delivery of silver NPs. In a recent study, it was discovered that superparamagnetic iron oxide NPs were conjugated with zinc, iron, and silver via a chelation process. The results indicated a reduction in both biofilm development and the growth of plankton[198].

5.3.4. NPs in tissue engineering

Nanoparticles have been utilized in tissue engineering for a variety of purposes, including but not limited to augmenting electrical, biological as well as mechanical properties, also facilitating gene delivery, viral transduction, DNA transfection, and cell patterning. Additionally, nanoparticles have been employed to promote development of diverse types of tissues and to enable the detection of molecules and biological sensing. The utilization of appropriate NPs in tissue engineering has the potential to substantially augment the characteristics of the arena whether biologically, electrically, or mechanically, yet fulfilling many functions based on their particular applications[199].

5.4. Challenges for MNPs

At present, the FDA has granted approval to no less than 12 nano-structured medicines, it is to be noted that there are many others under development[200]. Undoubtedly, studying NPs' toxicity is a crucial matter and requires additional research. However, reporting toxicity is challenging due to the presence of many variables that lead to toxicity, such as dosage, route of administration, composition, size, being biodegradable, the ability to dissolve, pharmacokinetics, biological distribution, and framework[201]. One of the

primary methods for minimizing toxicity is through manipulation of the surface characteristics of magnetic nanoparticles. Fe_2O_3 nanoparticles were extensively investigated by the researchers. Such particles are extensively utilized in magnetic resonance imaging (MRI) because of their biocompatibility. Application of dextran@Fe_2O_3 NPs in combination with different polyvinyl acetates did not result in cytotoxicity towards EC219 endothelial-derived brain cells and microglial cells[202]. The interaction of iron oxide NPs with macrophages / monocytes in human was studied[203] where it was found to be non-toxic at 1 mg/ml and showed little toxicity at 10 mg/ml.

In addition, the major problem concerning MNPs based drug delivery systems is the capacity to effectively guide the drug carriers toward the required site of action. Many studies were conducted for development of suitable drug carriers. However, the most commonly used system for controlling NPs is a permanent magnet positioned in proximity to the intended location[204&205] which, of course, is not the ideal system for focusing on the MNPs. Additionally, permanent magnets produce a magnetic field with limited tissue penetration ability (8-12 cm), thus such an approach is non-applicable to deep tumors[206&207]. To overcome such obstacles, magnetic implants that possess the ability to attract magnetic nanoparticles are required. A specially designed magnetic mode equipped with 8 magnets and controlled by a specific algorithm enabled MNPs carriers to reach deeper tissues[208]. The findings of the study indicate that the utilization of magnetism under dynamic control has the potential to propel a magnetic fluid towards the center, thereby generating a region of elevated temperature at intended destination. Whilst the aforementioned approach exhibited considerable potential, it is imperative to acknowledge that regulating NPs *in-vivo* might be more complex. However, further research is required in order to create a method that allows for deep penetration of NPs carriers despite of the complexity of vascularity[174].

REFERENCES

1- A. Ali, T. Shah, R. Ullah, P. Zhou, M. Guo, M. Ovais, Z. Tan, Y. Rui, "Review on recent progress in magnetic nanoparticles: Synthesis, characterization, and diverse applications", ***Front. Chem.,*** 2021, 9, 1-25.

2- B. Issa, I. M. Obaidat, B. A. Albiss, Y. Haik, "Magnetic nanoparticles: Surface effects and properties related to biomedicine applications", ***Int. J. Mol. Sci.,*** 2013, 14 (11), 21266-21305.

3- L. Chen, T. Wang, J. Tong, "Application of derivatized magnetic materials to the separation and the preconcentration of pollutants in water samples", ***Trends Analyt. Chem.,*** 2011, 30 (7), 1095-1108.

4- C. L. DeCastro, B. S. Mitchell, "Nanoparticles from Mechanical Attrition in Synthesis, Functionalization, and Surface Treatment of Nanoparticles", In: C. A. Valencia, M. I. Baraton (Eds.), American Scientific Publishers, 5, 2002.

5- P. Biehl, M. von der Lühe, S. Dutz, F. Schacher, "Synthesis, characterization, and applications of magnetic nanoparticles featuring polyzwitterionic coatings", ***Polymers,*** 2018, 10 (1), 91-119.

6- A. E. Mohamed, M. A. Mohamed, "Magnetic Nanostructures: Nanoparticles: Magnetism and Applications", Springer, 2019, pp. 1-12.

7- H. D. Kurland, J. Grabow, G. Staupendahl, W. Andrä, S. Dutz, M. E. Bellemann, "Magnetic iron oxide nanopowders produced by CO_2 laser evaporation", ***J. Magnetism Magn. Mater.,*** 2007, 311 (1), 73-77.

8- G. Yang, "Laser ablation in liquids: Applications in the synthesis of nanocrystals", ***Prog. Mater. Sci.,*** 2007, 52 (4), 648-698.

9- Y. A. Kotov, "Electric explosion of wires as a method for preparation of nanopowders", ***J. Nanoparticle Res.,*** 2003, 5, 539-550.

10- Y. A. Kotov, E. I. Azarkevich, I. V. Beketov, T. M. Demina, A. M. Murzakaev, O. M. Samatov, "Producing Al and Al nanopowders by electrical

explosion of wire", ***Key Eng. Mater.,*** 1997, 132-136, 173-176.

11- I. V. Beketov, A. P. Safronov, A. I. Medvedev, "Iron oxide nanoparticles fabricated by electric explosion of wire: Focus on magnetic nanofluids", ***AIP Advances,*** 2012, 2 (2), 022154.

12- G. V. Kurlyandskaya, S. M. Bhagat, A. P. Safronov, "Spherical magnetic nanoparticles fabricated by electric explosion of wire", ***AIP Advances,*** 2011, 1 (4), 042122.

13- B. R. Cuenya, "Synthesis and catalytic properties of metal nanoparticles: size, shape, support, composition, and oxidation state effects", ***Thin Solid Films,*** 2010, 518 (12), 3127-3150.

14- W. Wu, Q. He, C. Jiang, "Magnetic iron oxide nanoparticles: Synthesis and surface functionalization strategies", ***Nanoscale Res. Lett.,*** 2008, 3, 397-415.

15- T. Indira, P. Lakshmi, "Magnetic nanoparticles – A review", ***Int. J. Pharm. Sci. Nanotechnology,*** 2010, 3 (3), 1035-1042.

16- W. Jiang, H. C. Yang, S. Y. Yang, H. E. Horng, J. C. Hung, Y. C. Chen, "Preparation and properties of superparamagnetic nanoparticles with narrow size distribution and biocompatible", ***J. Magnetism Magn. Mater.,*** 2004, 283 (2-3), 210-214.

17- Q. Chen, A. J. C. Rondinone, B. Chakoumakos, Z. John Zhang, "Synthesis of superparamagnetic $MgFe_2O_4$ nanoparticles by coprecipitation", ***J. Magnetism Magn. Mater.,*** 1999, 194 (1-3), 1-7.

18- L. Shen, Y. Qiao, Y. Guo, S. Meng, G. Yang, M. Wu, "Facile co-precipitation synthesis of shape-controlled magnetite nanoparticles", ***Ceramics. Int.,*** 2014, 40 (1), 1519-1524.

19- J. Mosayebi, M. Kiyasatfar, S. Laurent, "Synthesis, functionalization, and design of magnetic nanoparticles for theranostic applications", ***Adv. Healthc. Mater.,*** 2017, 6 (23), 1700306.

20- F. B. Effenberger, R. A. Couto, P. K. Kiyohara, G. Machado, S. H. Masunaga, R. F Jardim, L. M. Rossi, "Economically attractive route for the preparation of high quality magnetic nanoparticles by the thermal decomposition of iron(III) acetylacetonate", ***Nanotechnology,*** 2017, 28 (11), 115603.

21- J. Kudr, Y. Haddad,L. Richtera, Z. Heger, M. Cernak, V. Adam, "Magnetic nanoparticles: From design and synthesis to real world applications", ***Nanomaterials,*** 2017, 7 (9), 243.

22- M. Faraji, Y. Yamini, M. Rezaee, "Magnetic nanoparticles: Synthesis, stabilization, functionalization, characterization, and applications", ***Jics.,*** 2010, 7, 1-37.

23- N. A. Frey, S. Peng, K. Cheng, S. Sun, "Magnetic nanoparticles: Synthesis, functionalization, and applications in bioimaging and magnetic energy storage", ***Chem. Soc. Rev.,*** 2009, 38 (9), 2532-2542.

24- F. B. Effenberger, R. A. Couto, P. K. Kiyohara, G. Machado, S. H. Masunaga, R. F. Jardim, "Economically attractive route for the preparation of high quality magnetic nanoparticles by the thermal decomposition of iron(III) acetyl-acetonate", ***Nanotechnology,*** 2017, 28 (11), 115603.

25- J. B. Hayter, "Physics of Amphiphiles: Micelles, Vesicles and Microemulsions", In: V. Degiorgio, M. Corti (Eds.), Proceeding of the International School of Physics, North Holland, Amsterdam, 1985, p. 59.

26- S. H. Chen, R. Rajagopal (Eds.), "Micelles, Solutions and Microemulsions; Structure, Dynamics and Statistical Thermodynamics", New York: Springer, 1990.

27- J. A. Lo´pez Pe´rez, M. A. Lo´pez Quintela, J. Mira, J. Rivas, S.W. Charles, "Advances in the preparation of magnetic nanoparticles by the microemulsion method", ***J. Phys. Chem. B,*** 1997, 101 (41), 8045-8047.

28- C. Okoli, M. Boutonnet, L. Mariey, S. Järås, G. Rajarao, "Application of magnetic iron oxide nanoparticles prepared from microemulsions for protein purification", ***J. Chem. Technol. Biotechnol.,*** 2011, 86 (11), 1386-1393.

29- P. Zhang, Y. Zhang, M. Gao, X. Zhang, "Dendrimer-assisted hydrophilic magnetic nanoparticles as sensitive substrates for

rapid recognition and enhanced isolation of target tumor cells", ***Talanta,*** 2016, 161, 925-931.

30- J. Vidal-Vidal, J. Rivas, M. A. López-Quintela, "Synthesis of monodisperse maghemite nanoparticles by the microemulsion method", ***Colloids Surf. A: Physicochemical Eng. Aspects,*** 2006, 288 (1-3), 44-51.

31- L. H. Reddy, J. L. Arias, J. Nicolas, P. Couvreur, "Magnetic nanoparticles: Design and characterization, toxicity and biocompatibility, pharmaceutical and biomedical applications", ***Chem. Rev.,*** 2012, 112 (11), 5818-5878.

32- M. Zahid, N. Nadeem, M. A. Hanif, I. A. Bhatti, H. N. Bhatti, G. Mustafa, "Magnetic Nanostructure. Metal Ferrites and Their Graphene-Based Nano-composites: Synthesis, Characterization, and Applications in Wastewater Treatment", In: K. A. Abd-Elsalam, *et al.* (Eds.), Springer, 2019, pp. 181-212.

33- J. Li, L. Zheng, H. Cai, W. Sun, M. Shen, G. Zhang, X. Shi, "Polyethyleneimine-mediated synthesis of folic acid-targeted iron oxide nanoparticles for *in-vivo* tumor MR imaging", ***Biomaterials,*** 2013, 34 (33), 8382-8392.

34- G. Y. Li, Y. R. Jiang, K. L. Huang, P. Ding, J. Chen, "Preparation and properties of magnetic Fe_3O_4-chitosan nano-particles", ***J. Alloys Compd.,*** 2008, 466, 451-456.

35- S. Ansari, E. Ficiarà, F. Ruffinatti, I. Stura, M. Argenziano, O. Abollino, Magnetic Iron Oxide Nanoparticles: Synthesis, Characterization and Functionalization for Biomedical Applications in the Central Nervous System, Materials, 2019, 12 (3), 465.

36- S. F. Hasany, I. Ahmed, Rajan J, A. Rehman, "Systematic review of the preparation techniques of iron oxide magnetic nanoparticles", ***Nanoscience and Nanotechnology,*** 2012, 2 (6), 148-158.

37- A. H. Lu, E. L. Salabas, F. Schüth, "Magnetic nanoparticles: Synthesis, protection, functionalization, and application", ***Angew. Chem. Int. Edn.,*** 2007, 46 (8), 1222-1244.

38- R. Verma, S. Pathak, A. K. Srivastava, S. Prawer, S. Tomljenovic-Hanic, "ZnO nanomaterials: Green synthesis, toxicity evaluation and new insights in biomedical applications", ***J. Alloys Comp.,*** 2021, 876, 160175.

39- A. Komeili, "Molecular mechanisms of compartmentalization and biomineralization in magnetotactic bacteria", ***FEMS Microbiol. Rev.,*** 2012, 36 (1), 232-255.

40- S. Rajesh, D. P. Raja, J. M. Rathi, K. Sahayaraj, "Biosynthesis of silver nanoparticles using Ulva fasciata (Delile) ethyl acetate extract and its activity against xanthomonas campestris pv. Malvacearum", ***J. Biopesticides,*** 2012, 5, 119-128.

41- O. Strbak, P. Hnilicova, J. Gombos, A. Lokajova, P. Kopcansky, "Magnetotactic bacteria: From evolution to bio-mineralization and biomedical applications", ***Minerals,*** 2022, 12, 1403.

42- L. Marcano, A. García-Prieto, D. Muñoz, L. Fernández Barquín, I. Orue, J. Alonso, A. Muela, M. L. Fdez-Gubieda, "Influence of the bacterial growth phase on the magnetic properties of magnetosomes synthesized by Magnetospirillum gryphiswaldense", ***Biochim. Biophys. Acta Gen. Subj.,*** 2017, 1861 (6), 1507-1514.

43- F. Ahmad, N. Ashraf, T. Ashraf, R. B. Zhou, D. C. Yin, "Biological synthesis of metallic nanoparticles (MNPs) by plants and microbes: Their cellular uptake, biocompatibility, and biomedical applications", ***Appl. Microbiol. Biotechnol.,*** 2019, 103 (7), 2913-2935.

44- M. Ovais, A. T. Khalil, N. U. Islam, I. Ahmad, M. Ayaz, M. Saravanan, Z. K. Shinwari, S. Mukherjee, "Role of plant phytochemicals and microbial enzymes in biosynthesis of metallic nanoparticles", ***Appl. Microbiol. Biotechnol.,*** 2018, 102 (16), 6799-6814.

45- K. S. Suslick, M. Fang, T. Hyeon, "Sonochemical synthesis of iron colloids", ***J. Am. Chem. Soc.,*** 1996, 118, 11960-11961.

46- Y. L. Hou, S. Gao, "Solvothermal reduction synthesis and magnetic properties of polymer protected iron and

nickel nanocrystals", ***J. Alloys Compd.,*** 2004, 365 (1-2), 112-116.

47- Y. Hou, S. Gao, "Monodisperse nickel nanoparticles prepared from a monosurfactant system and their magnetic properties", ***J. Mater. Chem.,*** 2003, 13 (7), 1510-1512.

48- S. Sun, C. B. Murray, "Synthesis of monodisperse cobalt nanocrystals and their assembly into magnetic superlattices", ***J. Appl. Phys.,*** 1999, 85 (8), 4325-4330.

49- Y. Hou, H. Kondoh, T. Kogure, T. Ohta, "Preparation and characterization of monodisperse FePd nanoparticles", ***Chem. Mater.,*** 2004, 16 (24), 5149-5152.

50- J. Bansmann, S. H. Baker, C. Binns, "Magnetic and structural properties of isolated and assembled clusters", ***Surface Science Reports,*** 2005, 56 (6-7), 189-275.

51- G. Schmid, "Large clusters and colloids: Metals in the embryonic state", ***Chem. Rev.,*** 1992, 92 (8), 1709-1727.

52- S. Murray, C. B. Sun, "Synthesis of monodisperse cobalt nanocrystals and their assembly into magnetic superlattices", ***J. Appl. Phys.,*** 1999, 85, 4325-4330.

53- H. Doyle, "Nanoparticles and colloidal self-assembly", ***Mat. Res. Soc. Symp. Proc.,*** 577, 1999, 385, 306-356.

54- S. Sun, C. B. Murray, D. Weller, L. Folks, A. Moser, "Monodisperse FePt nanoparticles and ferromagnetic FePt nanocrystal superlattices", ***Science,*** 2000, 287 (5460), 1989-1992.

55- V. F. Puntes, K. M. Krishnan, A. P. Alivisatos, "Colloidal nanocrystal shape and size control: The case of cobalt", ***Science,*** 2001, 291 (5511), 2115-2117.

56- X. B. Chen, Y. B. Lou, A. C. Samia, C. Burda, "Coherency strain effects on the optical response of core/shell heteronanostructures", ***Nano Lett.,*** 2003, 3 (6), 799.

57- D. G. Gutierrez, C. G. Wing, M. M. Yoshida, M. J. Yacaman, "HAADF study of Au-Pt core-shell bimetallic nanoparticles", ***Appl. Phys. A,*** 2004, 79 (3), 481-487.

58- M. Chen, S. Yamamuro, D. Farrell, and S. A. Majetich, "Gold-coated iron nano-particles for biomedical applications", ***J. Appl. Phys.,*** 2003, 93 (10), 7551-7553.

59- J. Cho, J. C. Idrobo, J. Olamit, K. Liu, N. D. Browning, S. M. Kauzlarich, "Growth mechanisms and oxidation resistance of gold-coated iron nanoparticles", ***Chem. Mater.,*** 2005, 17 (12), 3181.

60- Y. Bao, K. M. Krishnan, "Preparation of functionalized cobalt nanocrystals for potential biomedical applications", ***J. Magn. Magn. Mater.,*** 2005, 293 (1), 15-19.

61- J. Bai, J. P. Wang, "High-magnetic-moment core-shell-type FeCo–Au Ag nanoparticles", ***APL,*** 2005, 87 (15), 152502.

62- Y. S. Kang, S. Risbud, J. F. Rabolt, P. Stroeve, "Synthesis and characterization of nanometer-size Fe_3O_4 and γ-Fe_2O_3 particles", ***Chem. Mater.,*** 1996, 8 (9), 2209-2211.

63- T. Hyeon, "Chemical synthesis of magnetic nanoparticles", ***Chem. Commun.,*** 2003, 8, 927-934.

64- E. Kang, J. Park, Y. Hwang, M. Kang, J. G. Park, T. Hyeon, "Direct synthesis of highly crystalline and monodisperse manganese ferrite nanocrystals", ***J. Phys. Chem. B,*** 2004, 108 (37), 13932-13935.

65- S. G. Kwon, Y. Piao, J. Park, S. Angappane, Y. Jo, N. M. Hwang, J. G. Park, T. Hyeon, "Kinetics of monodisperse iron oxide nanocrystal formation by "heating-up" process", ***J. Am. Chem. Soc.,*** 2007, 129 (41), 12571-12584.

66- S. Sun, H. Zeng, "Size-controlled synthesis of magnetite nanoparticles", ***J. Am. Chem. Soc.,*** 2002, 124 (28), 8204-8205.

67- Z. Xu, C. Shen, Y. Hou, H. Gao, S. Sun, "Oleylamine as both reducing agent and stabilizer in a facile synthesis of magnetite nanoparticles, ***Chem. Mater.,*** 2009, 21 (9), 1778-1780.

68- Y. Hou, Z. Xu, S. Sun, "Controlled synthesis and chemical conversions of FeO nanoparticles", ***Angew. Chem. Int. Edn.,*** 2007, 46 (33), 6329-6332.

69- S.I. Hirano, S. Tajima, "Synthesis and magnetic properties of Fe_5C_2 by reaction of iron oxide and carbon monoxide", ***J. Mater. Sci.,*** 1990, 25, 4457-4461.

70- H. Song, X. Chen, "Large-scale synthesis of carbon-encapsulated iron carbide nanoparticles by co-carbonization of durene with ferrocene", ***Chem. Phys. Lett.,*** 2003, 374 (3-4), 400-404.
71- Z. Schnepp, S. C. Wimbush, M. Antonietti, C. Giordano, "Synthesis of highly magnetic iron carbide nanoparticles via a biopolymer route", ***Chem. Mater.,*** 2010, 22, 5340-5344.
72- Z. Schnepp, W. Yang, M. Antonietti, C. Giordano, "Biotemplating of metal carbide microstructures: The magnetic leaf", ***Angew. Chem., Int. Edn.,*** 2010, 49 (37), 6564-6566.
73- S. I. Nikitenko, Y. Koltypin, O. Palchik, I. Felner, X. N. Xu, "Synthesis of highly magnetic, air-stable iron–iron carbide nanocrystalline particles by using power ultrasound", ***Angew. Chem. Int. Edn.,*** 2001, 40 (23), 4447-4449.
74- V. Amendola, P. Riello, M. Meneghetti, "What controls the composition and the structure of nanomaterials generated by laser ablation in liquid solution?", ***J. Phys. Chem. Chem. Phys.,*** 2013, 15 (9), 3027-3046.
75- T. Hyeon, "Chemical synthesis of magnetic nanoparticles", ***Chem. Commun.,*** 2003, 8, 927-934.
76- E. de Smit, F. Cinquini, A. M. Beale, O. V. Safonova, W. van Beek, "Stability and reactivity of ϵ–χ–θ iron carbide catalyst phases in Fischer−Tropsch synthesis: Controlling μC", ***J. Am. Chem. Soc.,*** 2010, 132 (42),14928-14941.
77- Z. Yang, T. Zhao, X. Huang, X. Chu, T. Tang, Y. Ju, "Modulating the phases of iron carbide nanoparticles: From a perspective of interfering with the carbon penetration of Fe@Fe_3O_4 by selectively adsorbed halide ions", ***Chem. Sci.,*** 2017, 8 (1), 473-481.
78- Á. Ríos, M. Zougagh, "Recent advances in magnetic nanomaterials for improving analytical processes", ***Trac-Trend. Anal. Chem.,*** 2016, 84 (A) 72-83.
79- Q. A. Pankhurst, J. Connolly, S. K. Jones, J. Dobson, "Applications of magnetic nanoparticles in biomedicine", ***J. Phys. D Appl. Phys.,*** 2003, 36 (13), 167-181.
80- V. I. Shubayev, T. R. Pisanic, S. H. Jin, "Magnetic nanoparticles for theragnostics", ***Adv. Drug Deliv. Rev.,*** 2009, 61 (6), 467-477.
81- V. Camel, "Solid phase extraction of trace elements", ***Microchim. Acta. Part B,*** 2003, 58 (7), 1177-1233.
82- J. Ding, Q. Gao, X. S. Li, W. Huang, Z. G. Shi, Y. Q. Feng, "Magnetic solid-phase extraction based on magnetic carbon nanotube for the determination of estrogens in milk", ***J. Sep. Sci.,*** 2011, 34 (18), 2498-2504.
83- W. Wu, Z. Wu, T. Yu, C. Jiang, W. S. Kim, "Recent progress on magnetic iron oxide nanoparticles: Synthesis, surface functional strategies and biomedical applications", ***Sci. Technol. Adv. Mater.,*** 2015, 16 (2), 023501.
84- C. Hui, C. M. Shen, J. F. Tian, L. H. Bao, H. Ding, C. Li, Y. A. Tian, X. Z. Shi, H. J. Gao, "Core shell Fe_3O_4@SiO_2 nanoparticles synthesized with well-dispersed hydrophilic Fe_3O_4 seeds", ***Nanoscale,*** 2011, 3 (2), 701-705.
85- L. Zhao, J. G. Yu, B. Chang, X. J. Zhao, "Preparation and formation mechanism of monodispersed silicon dioxide spherical particles", ***Acta Chim. Sin.,*** 2003, 61 (4), 562-566.
86- M. Sonmez, M. Georgescu, L. Alexandrescu, D. Gurau, A. Ficai, D. Ficai, E. Andronescu, "Synthesis and applications of Fe_3O_4/SiO_2 core-shell materials", ***Curr. Pharm. Des.,*** 2015, 21 (37), 5324-5335.
87- A. Teleki, M. Suter, P. Kidambi, O. Ergeneman, F. Krumeich, B. Nelson, S. Pratsinis, "Hermetically coated superparamagnetic Fe_2O_3 particles with SiO_2 nanofilms", ***Chem. Mater.,*** 2009, 21 (10), 2094-2100.
88- W. Stöber, A. Fink, E. Bohn, "Controlled growth of monodisperse silica spheres in the micron size range", ***J. Colloid Interface Sci.,*** 1968, 26 (1), 62-69.
89- M. Wierucka, M. Biziuk, "Application of magnetic nanoparticles for magnetic solid-phase extraction in preparing biological, environmental and food samples", ***TrAC,*** 2014, 59, 50-58.
90- A. H. Lu, X.Q. Zhang, Q. Sun, Y. Zhang, Q. Song, F. Schüth, C. Chen, F. Cheng, "Precise synthesis of discrete and dispersible carbon-protected magnetic

nanoparticles for efficient magnetic resonance imaging and photothermal therapy", ***Nano Res.,*** 2016, 9, 1460-1469.

91- A. H. Lu, G.P. Hao, Q. Sun, X. Q. Zhang, W. C. Li, "Chemical synthesis of carbon materialswith intriguing nanostructure and morphology", ***Macromol. Chem. Phys.,*** 2012, 213 (10-11), 1107-1131.

92- Y. Fang, D. Gu, Y. Zou, Z. Wu, F. Li, R. Che, Y. Deng, B. Tu, D. Zhao, "A low-concentration hydrothermal synthesis of biocompatible ordered mesoporous carbon nanospheres with tunable and uniform size", ***Angew. Chem. Int. Edn.,*** 2010, 49 (43), 7987-7991.

93- V. Kumar, G. Toffoli, F. Rizzolio, "Fluorescent carbon nanoparticles in medicine for cancer therapy", ***ACS Med. Chem. Lett.,*** 2013, 4 (11), 1012-1013.

94- S. N. Sun, C. Wei, Z. Z. Zhu, Y. Hou, S. Venkatraman, Z. J. Xu, S. Venkatraman, "Magnetic iron oxide nanoparticles: Synthesis and surface coating techniques for biomedical applications", ***Chin. Phys. B,*** 2014, 23 (3), 037503.

95- R. G. Mendes, "Synthesis and toxicity characterization of carbon coated iron oxide nanoparticles with highly defined size distributions", ***Biochim. Biophys. Acta (BBA) Gen. Subj.,*** 2014, 1840 (1), 160-169.

96- J. S. Lee, Y. J. Song, H. S. Hsu, C. R. Lin, J. Y. Huang, J. Chen, "Magnetic enhancement of carbon-encapsulated magnetite nanoparticles", ***J. Alloys Compd.,*** 2019, 790, 716-722.

97- C. Xu, S. Sun, "New forms of superparamagnetic nanoparticles for biomedical applications", ***Adv. Drug Deliv. Rev.,*** 2013, 65 (5), 732-743.

98- S. M. Silva, R. Tavallaie, L. Sandiford, R. D. Tilley, J. J. Gooding, "Gold coated magnetic nanoparticles: From preparation to surface modification for analytical and biomedical applications", ***Chem. Commun.,*** 2016, 52 (48), 7528-7540.

99- H. Chen, F. Qi, H. Zhou, S. Jia, Y. Gao, K. Koh, Y. Yin, "Fe_3O_4@Au nanoparticles as a means of signal enhancement in surface plasmon resonance spectroscopy for thrombin detection", ***Sens. Actuators B-Chem.,*** 2015, 212, 505-511.

100- H. Y. Sun, X. L. Jiao, Y. Y. Han, Z. Jiang, D. R.Chen, "Synthesis of Fe_3O_4-Au nanocomposites with enhanced peroxidase-like activity", ***Eur. J. Inorg. Chem.,*** 2013, 2013, 109-114.

101- L. Li, Y. M. Du, K. Y. Mak, C. W. Leung, P. W. T. Pong, "Novel hybrid Au/Fe_3O_4 magnetic octahedron-like nanoparticles with tunable size", ***IEEE Trans. Magn.,*** 2014, 50 (1), 1-5.

102- M. A. Dheyab, A. Aziz, M. S. Jameel, P. M. Khaniabadi, "Recent advances in synthesis, medical applications and challenges for gold-coated iron oxide: Comprehensive study", ***Nanomaterials (Basel),*** 2021, 11 (8), 2147.

103- Z. J. Wang, L. N. Wu, F. P. Wang, Z. H. Jiang, B. Z. Shen, "Durian-like multi-functional Fe_3O_4-Au nanoparticles: Synthesis, characterization and selective detection of benzidine", ***J. Mater. Chem. A,*** 2013, 1 (34), 9746-9751.

104- J. Z. Chen, Y. J. Liu, G. X. Zhu, A. H. Yuan, "Ag@Fe_3O_4 nanowire: Fabrication, characterization and peroxidase-like activity", ***Cryst. Res. Technol.,*** 2014, 49 (5), 309-314.

105- T. Harifi, M. Montazer, "Photo-, Bio-, and Magneto-active colored polyester fabric with hydrophobic/hydrophilic and enhanced mechanical properties through synthesis of TiO_2/Fe_3O_4/Ag nano-composite", ***Ind. Eng. Chem. Res.,*** 2014, 53 (3), 1119-1129.

106- R. Xiong, C. H. Lu, Y. R. Wang, Z. H. Zhou, X. X. Zhang, "Nanofibrillated cellulose as the support and reductant for the facile synthesis of Fe_3O_4/Ag nanocomposites with catalytic and antibacterial activity", ***J. Mater. Chem. A,*** 2013, 1 (47), 14910-14918.

107- L. Y. Wang, Y. Sun, J. Wang, J. A. Wang, A. M. Yu, H.Q. Zhang, D. Q. Song, "Preparation of surface plasmon resonance biosensor based on magnetic core/shell Fe_3O_4/SiO_2 and Fe_3O_4/Ag/SiO_2 nanoparticles", ***Colloid. Surf. B,*** 2011, 84 (2), 484-490.

108- A. Akhundi, A. Habibi-Yangjeh, "High performance magnetically recoverable g-C_3N_4/Fe_3O_4/Ag/Ag_2SO_3 plasmonic photocatalyst for enhanced photocatalytic

degradation of water pollutants", ***Adv. Powder Technol.,*** 2017, 28 (2), 565-574.
109- G. Gao, K. Wang, P. Huang, Y. X. Zhang, X. Zhi, C. C. Bao, D. X. Cui, "Superparamagnetic Fe_3O_4-Ag hybrid nanocrystals as a potential contrast agent for CT imaging", ***Crystengcomm,*** 2012, 14 (22), 7556-7559.
110- H. Q. Xia, B. Cui, J.H. Zhou, L. L. Zhang, J. Zhang, X. H. Guo, H. L. Guo, "Synthesis and characterization of Fe_3O_4@C@Ag nanocomposites and their antibacterial performance", ***Appl. Surf. Sci.,*** 2011, 257, 9397-9402.
111- J. Saffari, N. Mir, D. Ghanbari, K. Khandan-Barani, A. Hassanabadi, M. R. Hosseini-Tabatabaei, "Sonochemical synthesis of Fe_3O_4/ZnO magnetic nanocomposites and their application in photo-catalytic degradation of various organic dyes", ***J. Mater. Sci-Mater.,*** 2015, 26 (12), 9591-9599.
112- L. Tan, X. Zhang, Q, Liu, X. Jing, J. Liu, D. Song, S. Hu, L. Liu, J. Wang, "Synthesis of Fe_3O_4@TiO_2 core–shell magnetic composites for highly efficient sorption of uranium (VI)", ***Colloid Surf. A,*** 2015, 469, 279-286.
113- F. Liu, J. Zhu, W. Yang, Y. Dong, Y. Hou, C. Zhang, "Building nanocomposite magnets by coating a hard magnetic core with a soft magnetic shell", ***Angew. Chem. Int. Edn.,*** 2014, 53 (8), 2176-2180.
114- P. Majewski, B. Thierry, "Functionalized magnetite nanoparticles - Synthesis, properties, and bio-applications", ***Crit. Rev. Solid State Mater. Sci.,*** 2007, 32 (3-4), 203-215.
115- Z. Shaterabadi, G. Nabiyouni, M. Soleymani, "High impact of *in-situ* dextran coating on biocompatibility, stability and magnetic properties of iron oxide nanoparticles", ***Mater. Sci. Eng. C.,*** 2017, 75, 947-956.
116- S. Laurent, D. Forge, M. Port, A. Roch, C. Robic, L. V. Elst, "Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications", ***Chem. Rev.,*** 2008, 108 (6), 2064-2110.
117- C. C. Berry, S. Wells, S. Charles, A. S. G. Curtis, "Dextran and albumin derivatised iron oxide nanoparticles: Influence on fibroblasts *in-vitro*", ***Biomaterials,*** 2003, 24 (25), 4551-4557.
118- P. Tartaj, M. P. Morales, S. Veintemillas-Verdaguer, T. Gonzalez-Carreno, C. J. Serna, "Synthesis, Properties and Biomedical Applications of Magnetic Nanoparticles": "Handbook of Magnetic Materials", Elsevier: Amsterdam, The Netherlands, 2006, p. 403.
119- M. C. Bautista, O. Bomati-Miguel, M. P. Morales, C. J. Serna, "Surface characterisation of dextran-coated iron oxide nanoparticles prepared by laser pyrolysis and coprecipitation", ***J. Magn. Magn. Mater.,*** 2005, 293 (1), 20-27.
120- H. Holthoff, M. Borkovec, P. Schurtenberger, "Measurement of absolute coagulation rate constants for colloidal particles: Comparison of single and multiparticle light scattering techniques", ***J. Colloid Interface Sci.,*** 1997, 192 (2), 463-470.
121- C. Fournier, M. Leonard, I. Le Coq-Leonard, E. Dellacherie, "Coating polystyrene particles by adsorption of hydrophobically modified dextran", ***Langmuir,*** 1995, 11 (7), 2344-2347.
122- S. Mornet, S. Vasseur, F. Grasset, E. Duguet, "Magnetic nanoparticle design for medical diagnosis and therapy", ***J. Mater. Chem.,*** 2004, 14, 2161-2175.
123- S. Zinadini, A. A. Zinatizadeh, M. Rahimi, V. Vatanpour, H. Zangeneh, M. Beygzadeh, "Novel high flux antifouling nanofiltration membranes for dye removal containing carboxymethyl chitosan coated Fe_3O_4 nanoparticles", ***Desalination,*** 2014, 349, 145-154.
124- N. Zhu, H. Ji, P. Yu, J. Niu, M. U. Farooq, M. W. Akram, I. O. Udego, H. Li, X. Niu, "Surface modification of magnetic iron oxide nanoparticles", ***Nanomaterials, Nanomaterials (Basel).,*** 2018, 8 (10), 810.
125- Y. Zhang, N. Kohler, M. Zhang, "Surface modification of superparamagnetic magnetite nanoparticles and their intracellular uptake", ***Biomaterials,*** 2002, 23 (7), 1553-1558.
126- K. G. Paul, T. B. Frigo, J. Y. Groman, E. V. Groman, "Synthesis of ultrasmall superparamagnetic iron oxides using

reduced polysaccharides", ***Bioconjug. Chem.,*** 2004, 15 (2), 394-401.

127- L.X. Tiefenauer, A. Tschirky, G. Kühne, R. Y. Andres, "*In-vivo* evaluation of magnetite nanoparticles for use as a tumor contrast agent in MRI", ***Magn. Reson. Imaging,*** 1996, 14 (4), 391-402.

128- S. M. Moghimi, A. C. Hunter, J. C. Murray, "Long-circulating and target-specific nanoparticles: Theory to practice", ***Pharmacol. Rev.,*** 2001, 53 (2), 283-318.

129- E. A. Schellenberger, A. J. Bogdanov, D. Hogemann, J. Tait, "Annexin V-CLIO: A nanoparticle for detecting apoptosis by MRI", ***Mol. Imaging.,*** 2002, 1 (2), 102-107.

130- Y. Nishio, A. Yamada, K. Ezaki, Y. Miyashita, H. Furukawa, K. Horie, "Preparation and magnetometric characterization of iron oxide-containing alginate/poly(vinyl alcohol) networks", ***Polymer,*** 2004, 45 (21), 7129-7136.

131- F. Llanes, D. H. Ryan, R. H. Marchessault, "Magnetic nanostructured composites using alginates of different M/G ratios as polymeric matrix", ***Int. J. Biol. Macromol.,*** 2000, 27 (1), 35-40.

132- P. V. Finotelli, M. A. Morales, M. H. Rocha-Lea˜o, A. M. Rossi, "Magnetic studies of iron(III) nanoparticles in alginate polymer for drug delivery applications", ***Mater. Sci. Eng.,*** 2004, 24 (5), 625-629.

133- E. Kroll, F. M. Winnik, R. F. Ziolo, "*In-situ* preparation of nanocrystalline γ-Fe_2O_3 in iron(II) cross-linked alginate gels", ***Chem. Mater.,*** 1996, 8 (8), 1594-1596.

134- H. L. Ma, X. R. Qi, Y. Maitani, T. Nagai, "Preparation and characterization of superparamagnetic iron oxide nanoparticles stabilized by alginate", ***Int. J. Pharmaceut.,*** 2006, 333 (1-2), 177-186.

135- M. A. Morales, P. V. Finotelli, J. A. H. Coaquira, M. H. M Rocha-Lea˜o, C. Diaz-Aguila, E. M. Baggio-Saitovitch, A. M. Rossi, "*In-situ* synthesis and magnetic studies of iron oxide nanoparticles in calcium-alginate matrix for biomedical applications", ***Mater. Sci. Eng.,*** 28 (2), 253-257.

136- M. Breulmann, H. Colfen, H. Hentze, M. Antonietti, D. Walsh, S. Mann, Elastic Magnets: "Template-controlled mineralization of iron oxide colloids in a sponge-like gel matrix", ***Adv. Mater.,*** 1998, 10, 237-241.

137- R. F. Ziolo, E. P. Giannelis, B. A. Weinstein, M. P. O'horo, B. N. Ganguly, V. Mehrotra, M. W. Russell, D. R. Huffman, "Matrix-mediated synthesis of nanocrystalline ggr-Fe_2O_3: A new optically transparent magnetic material", ***Science,*** 1992, 257 (5067), 219-223.

138- J. Gass, P. Poddar, J. Almand, S. Srinath, H. Srikanth, "Superparamagnetic polymer nanocomposites with uniform Fe_3O_4 nanoparticle dispersions", ***Adv. Funct. Mater.,*** 2006, 16 (1), 71-75.

139- C. Pascal, J. L. Pascal, F. Favier, M. L. Elidrissi Moubtassim, C. Payen, "Electrochemical synthesis for the control of γ-Fe_2O_3 nanoparticle size. Morphology, microstructure, and magnetic behavior", ***Chem. Mater.,*** 1999, 11 (1), 141-147.

140- X. C. Sun, N. Nava, "Microstructure and magnetic properties of Fe (C) and Fe (O) nanoparticles", ***Nano. Lett.,*** 2002, 2 (7), 765-769.

141- S. Brice-Profeta, M. A. Arrio, E. Tronc, N. Menguy, I. Letard, C. Cartier dit Moulin, M. Nogues, C. Chaneac, J. P. Jolivet, Ph. Saintctavit, "Magnetic order in γ-Fe_2O_3 Nanoparticles: A XMCD study", ***J. Magn. and Magn. Mater.,*** 2005, 288, 354-365.

142- M. P. Morales, S. Veintemillas-Verdaguer, M. I. Montero, C. J. Serna, A. Roig, Ll. Casas, B. Martínez, F. Sandiumenge, "Surface and internal spin canting in γ-Fe_2O_3 nanoparticles", ***Chem. Mater.,*** 1999, 11 (11), 3058-3064.

143- P. J. Goodhew, J. Humphreys, R. Beanland, "Electron Microscopy and Analysis", (3rd Edn.) Taylor & Francis, CRC Press, 2000.

144- D. V. S. Rao, K. Muraleedharan, C. Humphreys, "Microscopy: Science, Technology, Applications and Education", In: A. Méndez-Vilas, J. Díaz (Eds.), TEM Specimen Preparation Techniques, FORMATEX Research Center, Extremadura Es, 2010, pp. 1232-1244.

145- Image J, https://imagej.nih.gov/ij/. [Online].
146- B. H. Kim, J. Yang, D. Lee, B. K. Choi, T. Hyeon, J. Park, "Liquid-phase transmission electron microscopy for studying colloidal inorganic nanoparticles", ***Adv. Mater.,*** 2018, 30 (4), 1703316.
147- S. Mourdikoudis, R. M. Pallares, N. T. K. Thanh, "Characterization techniques for nanoparticles: Comparison and complementarity upon studying nanoparticle properties", ***Nanoscale,*** 2018, 10 (27), 12871-12934.
148- B. D. Hall, D. Zanchet, D. Ugarte, "Estimating nanoparticle size from diffraction measurements", ***J. Appl. Crystallogr.,*** 2000, 33, 1335-1341.
149- T. Tatarchuk, M. Bououdina, W. Macyk, O. Shyichuk, N. Paliychuk, I. Yaremiy, B. Al-Najar, M. Pacia, "Structural, optical, and magnetic properties of Zn-doped $CoFe_2O_4$ nanoparticles", ***Nanoscale Res. Lett.,*** 2017, 12, 1-11.
150- R. Hufschmid, H. Arami, R. M. Ferguson, M. Gonzales, E. Teeman, L. N. Brush, N. D. Browning, K. M. Krishnan, "Synthesis of phase-pure and monodisperse iron oxide nanoparticles by thermal decomposition", ***Nanoscale,*** 2015, 7 (25), 11142-11154.
151- T. Li, A. J. Senesi, B. Lee, "Small angle X-ray scattering for nanoparticle research", ***Chem. Rev.,*** 2016, 116 (18), 11128-11180.
152- W. Wang, X. Chen, Q. Cai, "*In-situ* SAXS study on size changes of platinum nanoparticles with temperature", ***Eur. Phys. J. B,*** 2008, 65, 57-64.
153- M. Singh, I. Sinha, A. K. Singh, R. K. Mandal, "LSPR and SAXS studies of starch stabilized Ag–Cu alloy nanoparticles", ***Colloids Surf. A***, 2011, 384 (1), 668-674.
154- L. T. Lu, "Water-Dispersible Magnetic NPs for Biomedical Applications: Synthesis and Characterisation", 2011, Ph.D. Thesis, University of Liverpool.
155- D. D. Sarma, P. K. Santra, S. Mukherjee, A. Nag, "X-ray photoelectron spectroscopy: A unique tool to determine the internal heterostructure of nanoparticles", ***J. Mater. Chem.,*** 2013, 25 (8),1222-1232.
156- C. Blanco-Andujar, "Sodium Carbonate Mediated Synthesis of Iron Oxide NPs to Improve Magnetic Hyperthermia Efficiency and Induce Apoptosis", 2014, Ph.D. Thesis, University College London.
157- S. Sabale, V. Jadhav, V. Khot, X. Zhu, M. Xin, H. Chen, "Superparamagnetic MFe_2O_4 (M= Ni, Co, Zn, Mn) nanoparticles: Synthesis, characterization, induction heating and cell viability studies for cancer hyperthermia applications", ***J. Mater. Sci.: Mater. Med.,*** 2015, 26 (3), 127.
158- K. Gharbi, F. Salles, P. Mathieu, C. Amiens, V. Colliere, Y. Coppel, K. Philippot, L. Fontaine, V. Montembault, L. Samia Smiri, D. Ciuculescu-Pradines, "Alkyl phosphonic acid-based ligands as tools for converting hydrophobic iron nanoparticles into water soluble iron–iron oxide core–shell nanoparticles", ***New J. Chem.,*** 2017, 41 (20), 11898-11905.
159- D. Marion, "An introduction to biological NMR spectroscopy", ***Mol. Cell. Proteomics,*** 2013, 12 (11), 3006-3025.
160- D. Scheid, D. Stock, T. Winter, T. Gutmann, C. Dietz, M. Gallei, "The pivotal step of nanoparticle functionalization for the preparation of functional and magnetic hybrid opal films", ***J. Mater. Chem. C,*** 2016, 4, 2187-2196.
161- S. Vowinkel, S. Paul, T. Gutmann, M. Gallei, "Free-standing and self-crosslinkable hybrid films by core–shell particle design and processing", ***Nanomaterials,*** 2017, 7 (11), 390.
162- H. Kato, "Processing and Characterization with Lasers", In: "Size Determination of NPs by Dynamic Light Scattering, in Nanomaterials", H. Zeng, C. Guo and W. Cai S. C. Singh (Eds.), Wiley-VCH, 2012, Ch. 8.
163- J. Lim, S. P. Yeap, H. X. Che, S. C. Low, "Characterization of magnetic nanoparticle by dynamic light scattering", ***Nanoscale Res. Lett.,*** 2013, 8 (1), 381.
164- M. Wolfgang, "Powerpoint Presentation: Nanoparticle Size Analysis: A Survey and Review, in Nanomedicines Alliance", October 2015.

165- N. A. Belsey, A. G. Shard, C. Minelli, "Poster Presentation: Shell Thickness Determination of Core-Shell NPs", in Euramet.
166- P. Hole, K. Sillence, C. Hannell, "Interlaboratory comparison of size measurements on nanoparticles using nanoparticle tracking analysis (NTA)", ***J. Nanopart. Res.,*** 2013, 15 (12), 2101-2108.
167- V. Filipe, A. Hawe, W. Jiskoot, "Critical evaluation of nanoparticle tracking analysis (NTA) by NanoSight for the measurement of nanoparticles and protein aggregates", ***Pharm. Res.,*** 2010, 27 (5), 796-810.
168- J. A. Gallego-Urrea, J. Tuoriniemi, M. Hassellov, "Applications of particle-tracking analysis to the determination of size distributions and concentrations of nanoparticles in environmental, biological and food samples", ***Trends Anal. Chem.,*** 2011, 30 (3), 473-483.
169- A. R. Montoro Bustos, J. Ruiz Encinar, A. Sanz-Medel, "Mass spectrometry for the characterisation of nanoparticles", ***Anal. Bioanal. Chem.,*** 2013, 405 (17), 5637-5643.
170- F. Baldassarre, M. Cacciola, G. Ciccarella, "A predictive model of iron oxide nanoparticles flocculation tuning Z-potential in aqueous environment for biological application", ***J. Nanopart. Res.,*** 2015, 17 (9), 377.
171- F. Branda, B. Silvestri, A. Costantini, G. Luciani, "Effect of exposure to growth media on size and surface charge of silica based Stöber nanoparticles: A DLS and ζ-potential study", ***J. Sol. Gel Sci. Technol.,*** 2015, 73 (1), 54-61.
172- H. S. Nalwa, "Encyclopedia of Nanoscience and Nanotechnology", In: "Numerical Study of Quantum Transport in Carbon Nanotube Based Transistors", 1st Edn., American Scientific Publishers, 2004.
173- G. Höhne, W.F. Hemminger, H. J. Flammersheim, "Differential Scanning Calorimetry", 2nd Edn., Springer, 2003.
174- N. Tran, T. J. Webster, "Magnetic nanoparticles: Biomedical applications and challenges", ***J. Mater. Chem.,*** 2010, 20 (40), 8760-8767.
175- C. Xu, S. Sun, "New forms of superparamagnetic nanoparticles for biomedical applications", ***Adv. Drug Deliv. Rev.,*** 2013, 65 (5), 732-743.
176- C. J. Xu, S. H. Sun, "Superparamagnetic nanoparticles as targeted probes for diagnostic and therapeutic applications", 2009, 29, 5582-5591.
177- C. C. Berry, A. S. G. Curtis, "Functionalisation of magnetic nanoparticles for applications in biomedicine", ***J. Phys. D-Appl. Phys.,*** 2003, 36 (13), R198-R206.
178- A. L. Hei, J. P. Cai, "Development of a method for concentrating and purifying SARS coronavirus RNA by a magnetic bead capture system", ***DNA Cell Biol.,*** 2005, 24 (8), 479-484.
179- M. I. Anik, M. K. Hossain, "Biomedical Applications of Magnetic Nanoparticles", In: "Magnetic Nanoparticle-Based Hybrid Materials", Woodhead Publishing, Elsevier, 2021, Chapter 18.
180- I. Safarik, M. Safarikova, "Magnetic techniques for the isolation and purification of proteins and peptides", ***Biomagn. Res. Technol.,*** 2004, 2 (1), 1-17.
181- H. W. Gu, K. M. Xu, C. J. Xu, B. Xu, "Biofunctional magnetic nanoparticles for protein separation and pathogen detection", ***Chem. Commun.,*** 2006, 9, 941-949.
182- C. J. Xu, K. M. Xu, H. W. Gu, X. F. Zhong, Z. H. Guo, R. K. Zheng, X. X. Zhang, B. Xu, "Nitrilotriacetic acid-modified magnetic nanoparticles as a general agent to bind histidine-tagged proteins", ***J. Am. Chem. Soc.,*** 2004, 126 (11), 3392-3393.
183- H. W. Gu, P. L. Ho, K. W. T. Tsang, L. Wang, B. Xu, "Using biofunctional magnetic nanoparticles to capture vancomycin-resistant enterococci and other gram-positive bacteria at ultralow concentration", ***J. Am. Chem. Soc.,*** 2003, 125 (51), 15702-15703.
184- R. Firoz, M. S. Ali, M. N. U. Khan, M. K. Hossain, M. K. Islam, M. Shahinuzzaman, "Medical image enhancement using morphological transformation", ***J. Data Anal. Inf. Process,*** 2016, 4 (1), 1-12.

185- P. Ludewig, N. Gdaniec, J. Sedlacik, N. D. Forkert, P. Szwargulski, M. Graeser, "Magnetic particle imaging for real-time perfusion imaging in acute stroke", ACS Nano., 2017, 11 (10), 10480-10488.
186- J. Weizenecker, B. Gleich, J. Rahmer, H. Dahnke, J. Borgert, "Three-dimensional real-time *in-vivo* magnetic particle imaging", ***Phys. Med. Biol.,*** 2009, 54 (5), L1-L10.
187- Q. A. Pankhurst, J. Connolly, S. K. Jones, J. Dobson, "Applications of magnetic nanoparticles in biomedicine", ***J. Phys. D: Appl. Phys.,*** 2003, 36 (13), R167-R181.
188- K. Cheng, S. Peng, C. J. Xu, S. H. Sun, "Porous hollow Fe_3O_4 nanoparticles for targeted delivery and controlled release of cisplatin", ***J. Am. Chem. Soc.,*** 2009, 131 (30),10637-10644.
189- F. M. Hilty, A. Teleki, F. Krumeich, R. Büchel, R. F. Hurrell, S. E. Pratsinis, M. B. Zimmermann, "Development and optimization of iron- and zinc-containing nanostructured powders for nutritional applications", ***Nanotechnology,*** 2009, 20 (47), 475101.
190- I. Stelle, L. K. McDonagh, I. Hossain, A. Z. Kalea, D. I. A. Pereira, "The IHAT-GUT iron supplementation trial in rural gambia: barriers, facilitators, and benefits", ***Nutrients,*** 2021, 13 (4), 1140.
191- P. L. McCormack, "Ferumoxytol: In iron deficiency anaemia in adults with chronic kidney disease", ***Drugs,*** 2012, 72 (15), 2013-2022.
192- B. Hildebrandt, P. Wust, O. Ahlers, A. Dieing, G. Sreenivasa, T. Kerner, R. Felix, H. Riess, "The cellular and molecular basis of hyperthermia", ***Crit. Rev. Oncol. Hematol.,*** 2002, 43 (1), 33-56.
193- P. Cherukuri, E. S. Glazer, S. A. Curley, "Targeted hyperthermia using metal nanoparticles", ***Adv. Drug Deliv. Rev.,*** 2010, 62 (3), 339-345.
194- K. Maier-Hauff, R. Rothe, R. Scholz, U. Gneveckow, P. Wust, B. Thiesen, A. Feussner, A. von Deimling, N. Waldoefner, R. Felix, A. Jordan, "Intracranial thermotherapy using magnetic nanoparticles combined with external beam radiotherapy: Results of a feasibility study on patients with glioblastoma multiforme", ***J. Neurooncol.,*** 2007, 81 (1), 53-60.
195- C. Mah, T.J. Fraites, I. Zolotukhin, S. H. Song, T. R. Flotte, J. Dobson, C. Batich, B. J. Byrne, "Improved method of recombinant AAV2 delivery for systemic targeted gene therapy", ***Mol. Ther.,*** 2002, 6 (1), 106-112.
196- F. M. Kievit, O. Veiseh, N. Bhattarai, C. Fang, J. W. Gunn, D. Lee, R. G. Ellenbogen, J. M. Olson, M. Q. Zhang, "PEI-PEG-Chitosan Copolymer coated iron oxide nanoparticles for safe gene delivery: Synthesis, complexation, and transfection", ***Adv. Funct. Mater.,*** 2009, 19 (14), 2244-2251.
197- M. J. Hajipour, K. M. Fromm, A. A. Ashkarran, D. Jimenez de Aberasturi, I. R. de Larramendi, T. Rojo, V. Serpooshan, W. J. Parak, M. Mahmoudi, "Antibacterial properties of nanoparticles", ***Trends Biotechnol.,*** 2012, 30 (10), 499-511.
198- E. N. Taylor, K. M. Kummer, N. G. Durmus, K. Leuba, K. M. Tarquinio, T. J. Webster, "Superparamagnetic iron oxide nanoparticles (SPION) for the treatment of antibiotic-resistant biofilms", ***Small.,*** 2012, 8 (19), 3016-27.
199- A. Memic, H. A. Alhadrami, M. A. Hussain, M. Aldhahri, F. Al Nowaiser, F. Al-Hazmi, R. Oklu, A. Khademhosseini, "Hydrogels 2.0: Improved properties with nanomaterial composites for biomedical applications", ***Biomed. Mater.,*** 2015, 11 (1), 014104.
200- C. F. Jones, D. W. Grainger, "*In-vitro* assessments of nanomaterial toxicity", ***Adv. Drug Deliv. Rev.,*** 2009, 61 (6), 438-456.
201- M. Arruebo, R. Fernandez-Pacheco, M. R. Ibarra, J. Santamaría, "Magnetic nanoparticles for drug delivery", ***Nano Today,*** 2007, 2 (3), 22-32.
202- F. Cengelli, D. Maysinger, F. Tschudi-Monnet, X. Montet,C. Corot, A. Petri-Fink, H. Hofmann, L. Juillerat-Jeanneret, "Interactions of functionalized super-paramagnetic iron oxide nanoparticles with brain structures", ***J. Pharmacol. Exp. Ther.,*** 2006, 318 (1), 108-116.
203- K. Müller, J. N. Skepper, M. Posfai, R. Trivedi, S. Howarth, C. Corot, E.

Lancelot, P. W. Thompson, A. P. Brown, J. H. Gillard, "Effect of ultrasmall superparamagnetic iron oxide nanoparticles (Ferumoxtran-10) on human monocyte-macrophages *in-vitro*", ***Biomaterials.,*** 2007, 28 (9), 1629-1642.

204- A. S. Lubbe, C. Bergemann, W. Huhnt, T. Fricke, H. Riess, J. W. Brock, D. Huhn, "Preclinical experiences with magnetic drug targeting: Tolerance and efficacy", ***Cancer Research,*** 1996, 56 (20), 4694-4701.

205- M. Kettering, "Magnetic nanoparticles as bimodal tools in magnetically induced labelling and magnetic heating of tumour cells: An *in-vitro* study", ***Nanotechnology,*** 2007, 18 (17), 175101.

206- S. Goodwin, C. Peterson, C. Hoh and C. Bittner, "Targeting and retention of magnetic targeted carriers (MTCs) enhancing intra-arterial chemotherapy", ***J. Magn. Magn. Mater.,*** 1999, 194 (1-3), 132-139.

207- T. Neuberger, B. Sch€opf, H. Hofmann, M. Hofmann, B. von Rechenberg, "Superparamagnetic nanoparticles for biomedical applications: Possibilities and limitations of a new drug delivery system", ***J. Magn. Magn. Mater.,*** 2005, 293 (1), 483-496.

208- B. Shapiro, "Towards dynamic control of magnetic fields to focus magnetic carriers to targets deep inside the body", ***J. Magn. Magn. Mater.,*** 2009, 321 (10), 1594-1599.

Sphinx Journal of Pharmaceutical and Medical Sciences, Vol. 5, Issue 1, 2023, pp. 1-32.

SJPMS

Sphinx Journal of Pharmaceutical and Medical Sciences

e-mail: sjpms@sphinx.edu.eg

SPHINX UNIVERSITY

الجسيمات النانوية المغناطيسية: التصنيع والتوصيف والتطبيقات الطبية الحيوية والتحديات

محمود محمد شيحه[١،٢] – أسماء محمد مصطفي[٣] – دنيا جمال نصر[٣] – ريم يوسف شاهين[١]

[١]قسم الكيمياء الصيدليه ، كلية الصيدله ، جامعة سفنكس ، أسيوط الجديدة ١٠ ، مصر

[٢]قسم الكيمياء الطبيه الصيدليه ، كلية الصيدله ، جامعة أسيوط ، أسيوط ٧١٥٢٦ ، مصر

[٣]كلية الصيدله ، جامعة سفنكس ، أسيوط الجديدة ١٠ ، مصر

تعد تكنولوجيا النانو إحدى تخصصات البحث والتطوير ذات النمو العالمي السريع في مجالات الطاقة والإلكترونيات وتخزين البيانات والغذاء والرعاية الصحية حيث تُظهر الجسيمات النانوية المغناطيسية خصائص مختلفة عن نظيراتها نظرًا لنسبة السطح الكبيرة إلى الحجم ، مما يزيد من تفاعلها. يتم استخدام طرق مختلفة لتصنيع هذه الجزيئات ، وتشمل هذه الطرق طرقًا فيزيائية وكيميائية وبيولوجية ، يتم بعد ذلك توصيف الجسيمات المصنعه التي تم الحصول عليها باستخدام تقنيات مختلفة. يعد اندماج تكنولوجيا النانو والتطبيقات الطبية ، أو ما يسمى بالتطبيقات الطبية الحيوية لتقنية النانو ، مجالًا للتطوير ، مما يسمح بتطبيقاتها البيولوجية في العديد من المجالات مثل أنظمة توصيل الأدوية ، والعلاج الجيني ، واستخدامها كأدوية مضادة للبكتيريا ، والاستخدام في هندسة الأنسجة. تم تصنيع أنواع مختلفة من جسيمات النانو المغناطيسيه سواء كانت مكونة أحادية أو مغلفة تخدم هذه الأغراض المذكورة ، ولقد ألهمنا الاهتمام المتزايد بتلك الجسيمات لتصميم هذا المرجع مع التركيز على التصنيع والتوصيف والتطبيقات الطبية الحيوية والتحديات التي تواجه تطبيقاتها.