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Magnetic Nanoparticles: Synthesis and Potential Biological Applications

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Abstract

Nanoparticles have a potential impact on numerous biomedical applications. Various synthesis roots and a wide range of applications in the area of bioimaging, drug delivery biosensing, nanomedicine and Magnetic Fluid Hyperthermia (MFH) makes magnetic nanoparticles as an attractive material for bioresearch. Magnetic nanoparticles are a group of nanoparticles that can be influenced using a magnetic field. In recent time these group of particles has been the focus of more research since they have remarkable properties. In nanoscale phenomena of finite size and surface, effects start to dominate the magnetic behaviour of individual nanoparticles. Because of the widespread applications of magnetic nanoparticles [MNPs], in this context, we discuss methods of magnetic nanoparticle synthesis in the first part followed by the role of magnetic nanoparticles in different biomedical applications.

INTRODUCTION

Nowadays nanotechnology is very important for the advancement of science since it makes use of the manipulation of matter on a scale in which materials show different characteristics than those displayed in the micro and macro scale [1]. These properties changes are attributed to the large increase in surface area in relation to the volume. The outstanding characteristics of nanomaterials, when compared with their bulk counterparts, offer a very promising future for their use wide range of application. Magnetic nanoparticles possess significant novel phenomena like superparamagnetism, high field irreversibility, high saturation field, extra anisotropy contributions or shifted loops after field cooling. These phenomena are due to the finite size and surface effects that control the magnetic behaviour of individual nanoparticles. So these groups of nanoparticles have been used in the field of biotechnology, biomedicine,material science, engineering and environmental areas [2-4]. In this context, magnetic nanomaterials, such as iron oxide, magnetite (Fe_3O_4) have been applied to various fields such as drug carriers and contrast agents in magnetic resonance imaging [5,6].

For this application, certain parameters must be controlled during the synthesis, such as the size and shape of the nanoparticles [5]. The control of the size, as well as size distribution, is necessary because allows the control of the material's properties such as superparamagnetism and hyperthermia [6]. Depending on its size, iron oxides particles present different behaviours when an external magnetic field is applied. It is known that abrupt changes in magnetic properties occur when the particle size is reduced from micrometre scale to the nanometer. In nanoscale phenomena of finite size and surface, effects start to dominate the magnetic behaviour of individual nanoparticles [7]. Frenkel & Dorfman [5], were the first to suggest that particles of ferromagnetic material below a critical particle size (less than 15 nm for common materials) would consist of magnetic monodomains, presenting a uniform magnetization state at any field. The magnetic behaviour of these particles above a certain temperature, the blocking temperature (TB), is the same of the paramagnetic particles, except that a large magnetic moment and consequently, susceptibility are presented. For biomedical applications, nanoparticles that exhibit superparamagnetic behaviour at body temperature (TB under the human's body temperature) are the most studied because of the absence of magnetic resonance and present a fast change in the magnetic state in the presence of an external magnetic field [8].

Concerning the particle shape, ellipsoid-shaped nanoparticles (elongated) are more cytotoxic than those with a spherical shape. The human monocytes produce a number of inflammatory cytokines in the presence of ellipsoid nanoparticles inside the body. So for the transport and delivery of drugsinto the specific target sites spherical form of nanoparticles are more suitable than other forms, such as hexagonal and cubic [9-11].

Industrial applications of magnetic nanoparticles include the use of magnetic recording media, separation in the petroleum industry, biomedical applications such as magnetic resonance contrast media and therapeutic agents in cancer treatment, etc, [12,13]. Each potential application of the magnetic nanoparticles requires having different properties. For example, in data storage applications, the particles need to have a stable, switchable magnetic state to represent bits of information that are not affected by temperature fluctuations. For biomedical uses, the application of particles that present superparamagnetic behaviour at room temperature is preferred [14-16]. Furthermore, applications in therapy and biology and medical diagnosis require the magnetic particles to be stable in water at pH 7 and in a physiological environment. The colloidal stability of this fluid will depend on the charge and surface chemistry, which give rise to both steric and coulombic repulsions and also depend on the dimensions of the particles,which should be sufficiently small so that precipitation due to gravitation forces can be avoided [17]. Additional restrictions on the possible particles could be used for biomedical applications (*in vivo* or *in vitro* applications). For *in vivo* applications, the magnetic nanoparticles must be encapsulated with a biocompatible polymer during or after the preparation process to prevent changes from the original structure, the formation of large aggregates, and biodegradation when exposed to the biological system. The nanoparticle coated with polymer will also allow binding of drugs by entrapment on the particles, adsorption, or covalent attachment [18-20]. The major factors, which determine toxicity and the biocompatibility of these materials, are the nature of the magnetically responsive components, such as magnetite, iron, nickel, and cobalt, and the final size of the particles, their core, and the coatings. Iron oxide nanoparticles such as magnetite (Fe_3O_4) or its oxidized form magnetite (g-Fe_2O_3) are by far the most commonly employed nanoparticles for biomedical applications. Highly magnetic materials such as cobalt and nickel are susceptible to oxidation and are toxic; hence, they are of little interest [21-23].

Moreover, the major advantage of using particles of sizes smaller than 100nm is their higher effective surface areas, lower sedimentation rates, and improved tissular diffusion [24-26]. Another advantage of using nanoparticles is that the magnetic dipole-dipole interactions are significantly reduced because they scale as r6 [27]. Therefore, for *in vivo* biomedical applications, magnetic nanoparticles must be made of a non-toxic and non-immunogenic material, with particle sizes small enough to remain in the circulation after injection and to pass through the capillary systems of organs and tissues, avoiding vessel embolism. They must also have a high magnetization so that their movement in the blood can be controlled with a magnetic field and so that they can be immobilized close to the targeted pathologic tissue [28-30]. For *in vitro* applications, composites consisting of superparamagnetic nanocrystals dispersed in submicron diamagnetic particles with long sedimentation times in the absence of a magnetic field can be used because the size restrictions are not as severe as *in vivo* applications. The major advantage of using diamagnetic matrixes is that the superparamagnetic composites can be easily prepared with functionality [30].

SYNTHESIS ROOTS OF MAGNETIC NANOPARTICLES

Magnetic nanoparticles (MNPs) have wide applications, in the field of biomedical, biotechnology, engineering, material science and environmental areas therefore much attention has been paid to the preparation of different kinds of MNPs [31-33]. MNPs have been synthesized with a number of different compositions and phases, including pure metals Fe, Co and Ni, metal oxides, such as Fe_3O_4 and γFe_2O_3, ferrites, such as MFe_2O_4 (M = Cu, Ni, Mn, Mg, etc.) and metal alloys, such as FePt, CoPt. Popular methods including co-precipitation, microemulsion, thermal decomposition, solvothermal, sonochemical, microwave assisted, chemical vapour deposition, combustion synthesis, carbon arc, laser pyrolysis synthesis have been reported for the synthesis of MNPs [34,35].

Classical synthesis by Co-precipitation

The co-precipitation technique is probably the simplest and most effective chemical method for the preparation of magnetic particles. Iron oxides like Fe_3O_4, γFe_2O_3 are usually prepared by an ageing stoichiometric mixture of ferrous and ferric salts in an aqueous medium. The chemical reaction of Fe_3O_4 formation can be written as,

$$Fe^{2+}+2Fe^{3+}+8OH^- \rightarrow Fe_3O_4+4H_2O \quad (1)$$

According to the thermodynamics of this reaction, complete precipitation of Fe_3O_4 must be expected at a pH between 8 and 14, with a stoichiometric ratio of 2:1 (Fe^{3+}/Fe^{2+}) in a non-oxidizing oxygen environment [36]. However, magnetite (Fe_3O_4) is not very stable and is sensitive to oxidation. Magnetite is transformed into maghemite (γFe_2O_3) in the presence of oxygen.

$$Fe_3O_4+2H^+ \rightarrow \gamma Fe_2O_3+Fe^{2+}+H_2O \quad (2)$$

Oxidation in the air is not the only method to transform magnetite (Fe_3O_4) into maghemite (γFe_2O_3). According to equation 2 various electron or ion transfers depending upon the pH of the suspension are involved. Surface Fe^{2+} ions are desorbed under acidic and anaerobic conditions to form hexa-aqua complexes in solution. While under the basic conditions, the oxidation of magnetite consists of the oxidation-reduction in the surface of magnetite. The oxidation of ferrous ions is always correlated with the migration of cations through the lattice frame work, creating cationic vacancies to maintain the charge balance, which explains the structure of maghemite [37]. In maghemite, iron ions are distributed in the octahedral (Oh), and tetrahedral (Td) sites of the spinal structure, but maghemite differs from magnetite by the presence of cationic vacancies within the octahedral site. The main advantage of the co-precipitation process is that a largenumber of nanoparticles can be synthesized. However, the control of particle size distribution is limited, because only kinetic factors are controlling the growth of the crystal. In the co-precipitation process, two stages are involved [38]. When the concentration of the species reaches critical supersaturation, a short burst of nucleation happens, and after that, there is a slow growth of the nuclei by diffusion of the solutes to the surface of the crystal. To produce monodisperse iron oxide nanoparticles, these two stages should be separated; i.e., nucleation should be avoided during the period of growth [39]. Figure 1 illustrates the different synthesis methods of Magnetic NPs.

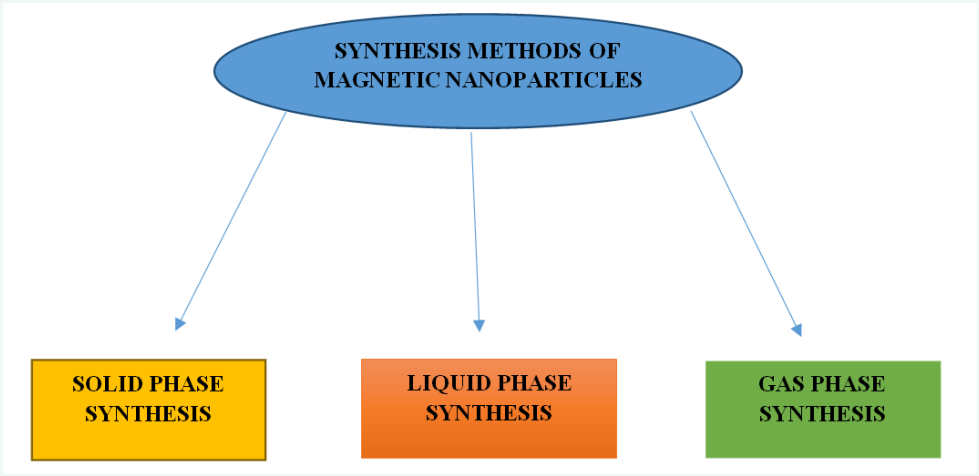

Figure 1 Different synthesis methods of Magnetic NPs.

Solid phase synthesis

Solid-phase approaches can be used for the synthesis of carbon-encapsulated magnetic nanoparticles (CEMNPs). Solid phase synthesis methods include, those based on high-temperature annealing of materials such as Fe_2O_3 plus C powders [40], elementary Fe plus C powders and Co NPs plus copolymers, However, the size and thus the magnetic properties of the final particles could hardly be controlled, and superparamagnetic particles could not be obtained as the starting particle size was usually much larger than 10 nm [41,42].

Combustion synthesis

This method has been employed in the preparation of carbon-encapsulated magnetic nanoparticles CEMNPs [43]. Martirosyan et al., produced cobalt ferrite, $CoFe_2O_4$, crystalline NPs (50-100 nm) by using the carbon combustion synthesis of oxides (CCSO) During the combustion synthesis process, a thermal reaction wave that produced by the exothermic oxidation of carbons, propagates through the solid reactants mixture of CoO and Fe_2O_3 converting it to cobalt ferrite. They found that the extensive emission of CO_2 increased the porosity and friability of the product. Also, a complete conversion to ferrite $CoFe_2O_4$ structure was attained only for carbon concentrations exceeding 12% wt. Solid state interactions between CoO and FeO with the growth of the crystalline cobalt ferrite particles started in the early period of the combustion and continued into the post-combustion zone. As expected, the average particle size increased with increasing combustion temperatures [44].

Annealing

To overcome the problems of relatively low productivity, the existence of complex phases and the difficulty in separating carbon-encapsulated superparamagnetic nanoparticles (CESNs) from impurities in the gas phase synthesis approach recently proposed a synthesis of a Fe/C solid solution CEMNPs with high controllability of chemical composition and particle size [45]. The unique feature of this approach is that CESNs can be prepared to have different sizes and thus different magnetic properties just by annealing a Fe-C solid solution at different temperatures. Also, have advantages like low temperatures heat treatment at 600˚C, and the majority of the NPs have a size of about 8 nm, and also they are embedded in an amorphous carbon matrix. The materials that have such fine ferrous NPs show a superparamagnetic behaviour at room temperatures. However, after heat treatment at high temperatures such as 800˚C, most of the NPs have a size of about 30 nm and are encapsulated into graphitic carbon shells. The materials having such large ferrous NPs show a permanent magnetic behaviour at room temperatures. Jianghong, et al., by applying the annealing technique synthesized iron NPs with boron nitride (BN) and carbon (C) nanocoatings [46]. Mixtures of Fe_2O_3 and boron or carbon powders were employed as the starting materials they were annealed at temperatures above 1273 K in a nitrogen atmosphere. The advantages of the solid-phase approach include good controllability of the particle sizes, thus good controllability of superparamagnetism; it generates of few impurities and is suitable for large-scale production.

Liquid phase synthesis

Liquid-phase methods of synthesis have numerous benefits than a gasphase and solid-phase synthesis methods. It is the most common synthesis methods for preparing nanoparticles (NPs) and nanostructured materials, size and shape control can beattained at low temperature within a short time and low-cost compared to solid-phase synthesis methods. This methodincludes the co-precipitation of metal oxides and ferrites, from aqueous salt solutions, microemulsion synthesis for uniformly sized nanoparticles, solvothermal method, thermal decomposition etc.

Co-precipitation

Co-precipitation is a facile and convenient way to synthesize MNPs like metal oxides and ferrites, from aqueous salt solutions. This can be achieved by the addition of a base under an inert atmosphere at room temperatures or at elevated temperature. Iron oxide nanoparticles (either Fe_2O_4 or γ -Fe_2O_3) and ferrites are usually prepared in an aqueous medium for which chemical reaction of the formation may be written as Equation (3).

$$M^{2+} + 2Fe^{3+} + 8OH^- \rightarrow MFe_2O_4 + 4H_2O \quad (3)$$

Where, M can be Fe^{2+}, Mn^{2+}, Co^{2+}, Cu^{2+}, Mg^{2+}, $Zn^{2+,}$ and Ni^{2+}. Iida et al., synthesized Fe_3O_4 nanoparticles by hydrolysis in an aqueous solution containing ferrous and ferric salts at various ratios with a 1,6-hexanediamine as the base [47]. They found that when the ratio of ferrous to ferric ions was increased, the formation of large hydroxide particles as a precursor of Fe_3O_4 was promoted, which resulted in an increase in the size of Fe_3O_4 nanoparticles. As a result, the mean diameter of Fe_3O_4 nanoparticles increased from ~9 to ~37 nm as the molar percentage of ferrous ions with respect to the total iron ions was increased from 33 to 100%. Also, it was demonstrated that magnetic properties of Fe_3O_4 nanoparticles could be controlled by adjusting the molar ratio of ferrous to ferric ions as well as the particle diameter. Another most important factor influencing the synthesis is the iron concentration which generally the optimum values are between 39 and 78 mM [48]. In the synthesis of Fe_3O_4, precipitation at temperatures below 60°C typically produces an amorphous hydrated oxyhydroxide that can be easily converted to Fe_2O_3, while higher reaction temperatures (>80°C) favour the formation of Fe_3O_4 [49]. The suitable pH for the rapid formation of Fe_3O_4 is attained by the addition of excess amounts of the base. In terms of simplicity of the synthesis method, co-precipitation is the preferred route. In this method, the reaction temperature and time are lower than other methods such as thermal decomposition and hydrothermal. Also, the solvent is environmental friendly (water) besides the reaction yield is high and scalable. But, the size distribution is relatively narrow and the shape control is not good.

Microemulsion

The water-in-oil (W/O) microemulsion, has been widely used to synthesize uniform sized MNPs [31,50]. This is anisotropic and thermodynamically stable single-phase system that consists of three components: water, oil and an amphiphilic molecule, called surfactant. The surfactant molecule lowers the interfacial tension between water and oil resulting in the formation of a transparent solution. The water nanodroplets are containing reagents, as a nanoreactor, undergo rapid coalescence allowing for mixing, precipitation reaction and aggregation processes for the synthesis of MNPs. The shape of the water pool is spherical, and the surfactant molecules surround the nanodroplet wall. These walls act like cages for the growing particles and thereby reduce the average size of the particles during the collision and aggregation process. Thus, the size of the spherical nanoparticles can be controlled and tuned by changing the size of the water pool (*W*0 value, the water-to-surfactant molar ratio).

Santra, et al., reported a robust methodology for the synthesis of both uncoated and silica-coated MNPs of ultra-small andvery uniform size distribution by water-in-oil microemulsion [51]. They used three different non-ionic surfactants for the preparation of microemulsions and also used NH_4OH and NaOH as a base source. By mixing two identical water-in-oil microemulsions which one of them containing metal salts and the other containing the base source, microdroplets will continuously collide, coalesce, and break again and finally precipitate forms in the micelles. By the addition of solvents, such as acetone or ethanol, to the microemulsions, the precipitate can be extracted by filtering or centrifuging the mixture. They found that depending on the chemical structure of the surfactant molecules the extent of surfactant molecule adsorption onto the surface of the NPs varies. A more ordered fashion in particle aggregation is observed in the case of Brij 97 when compared to the other surfactants, because of a strong hydrophobic-hydrophobic interaction between oleyl groups attached to adjacent nanoparticles.

Vidal-Vidal, et al., reported the synthesis of monodisperse magnetite NPs with the use of one point microemulsion method [52]. The spherically shaped particles, capped with a monolayer coating of oleylamine (or oleic acid), show a narrow size distribution of 3.5 ± 0.6 nm, are well crystallized and have high saturation magnetization values. Microemulsions can be used to synthesize monodispersed nanoparticles with various morphologies. However, this method requires a large amount of solvent and also the yield of production of this method is low.

Thermal decomposition

Nanoparticles with a high level of monodispersity and size control can be obtained by high-temperature decomposition of organometallic precursors, such as $[M^{n+}(acac)_n]$, (M = Fe, Mn, Co, Ni, Cr; n = 2 or 3, acac = acetylacetonate), $M^x(cup)_x$ (cup = N-nitrophenylhydroxylamine) or carboys (such as $Fe(CO)_5$) using organic solvents and surfactants such as fatty acids, oleic acid, and hexadecylamine. Thermal decomposition of organometallic precursors which metal is the zero valent in their composition initially leads to the formation of metal NPs but if followed by oxidation can lead to a high in quality monodispersed metal oxides. On the other hand, decomposition of precursors with cationic metal canters leads directly to metal oxides NPs. Principally the ratios of the starting reagents including organometallic compounds, surfactants, and solvents are the critical parameters for controlling the size and morphology of MNPs. The reaction temperature and time, as well as the ageingperiod, may also be crucial for the precise control of size and morphology [53]. Chen, et al., prepared nickel NPs from the thermal decomposition of nickel (II) acetylacetonate in alkylamines [54]. They found that by choosing an appropriate reaction temperature and solvent, nickel NPs that have the fcc or the hcp phase can be obtained. Monodisperse nickel NPs were also obtained by introducing surfactants. Also, the results of magnetic characterization showed that the magnetic properties of the hcp nickel NPs are quite different from those of the fcc nickel NPs. Metal oxide MNPs can also be synthesized by the thermal decomposition method. Up to date, two different approaches have been used for this purpose. First, thermal decomposition of metal carbonyl precursors followed by an oxidation step using air [55] or oxidation by using an oxidant at elevated temperatures [56]. The second is decomposition of precursors with a cationic metal centre in the absence of reducing agents [57]. The presences of reducing agents lead to metal NPs even by the use of cationic precursors. Thermal decomposition seems to be the best method developed to date for size and morphology control of NPs. Also, the yield of production is high and scalable. However, one of the major disadvantages of this method is the production of organic soluble NPs which limit the extent of application uses of them in biological fields besides surface treatment is needed after synthesis; also thermal decomposition methods usually lead to complicated processes or require relatively high temperatures.

Solvothermal roots

Hydrothermal is also called solvothermal, is a synthesis method for preparation of MNPs and ultrafine powders in the literature [58]. These reactions are performed in an aqueous media in reactors or autoclaves where the pressure can be higher than 2000 psi and temperatures higher than 200°C. Hydrothermal processing is one of the successful ways to grow crystals of many different materials. This technique has also been used to grow dislocation-free single crystal particles,and grains formed in this process could have a better crystallinity than those from other processes. Wang, et al., used a hydrothermal method to synthesize Fe_3O_4 powder [59]. They found that the nanoscale Fe_3O_4 powder (40 nm) can be obtained at 140°C for 6 h possessed a saturation magnetization of 85.8 emu g-1, this is a little lower than that of the correspondent bulk Fe_3O_4. It is suggested that the well crystallized Fe_3O_4 grains formed under appropriate hydrothermal conditions should be responsible for the increased saturation magnetization in nanosized Fe_3O_4. The well-crystallized particles have a thinner surface layer, narrower cationic distribution and less superparamagnetic relaxation, which can be used to explain the increase of saturation magnetization in hydrothermal derived particles, and to interpret magnetic property variation from different conditions in the hydrothermal process, because they would lead to the different crystallinity of particles. The hydrothermal technique is very versatile; one of the main drawbacks of the conventional hydrothermal method is the slow reaction kinetics at any given temperature. Microwave heating can be used during the hydrothermal synthesis, and this has been found to increase the kinetics of crystallization [60]. Such combination is termed as the microwave-hydrothermal method. The main advantage of the introduction of microwaves into a reaction system is the extremely rapid kinetics needed for synthesis. A dramatic increase in the reaction kinetics, up to two orders of magnitude, can be achieved by the microwave heating under hydrothermal conditions, due to the localized superheating of the solution.

Chemical reduction

Among the various solution-phase chemistry routes developed for the preparation of metal NPs, the reduction of metal salts is the most common and reducing agents such as $NaBH_4$ have been commonly employed in the reactions [61]. Nanoscale zero-valent iron (nZVI) which have been extensively used in the environmental remediation field, have commonly been prepared by mixing equal volumes of $NaBH_4$ and $FeCl_3$. A key advantage of this method is its simplicity. It can be safely done in most chemistry labs with simple chemical reagents. Also, this reaction can be done under room temperature conditions.

Sonochemical reactions

As a competitive alternative to other time-consuming preparation techniques, the sonochemical method has been extensively used to generate novel materials with unusual properties. The physiochemical effects of ultrasound arise from acoustic cavitation, which comes from the formation, growth, and implosive collapsing of bubbles in the liquid. The implosive collapsing of the bubbles generates a localized hotspot through adiabatic compression or shock wave formation within the gas phase of the collapsing bubble. The extreme conditions formed in the hotspots were beneficial to forming the new phase and had a sheer effect for agglomeration, which is necessary to prepare the high monodispersive nanoparticles [62]. Chia, et al., synthesized Fe_3O_4 NPs through sonochemical and co-precipitation methods [63]. The crystallinity and magnetic properties of the obtained products by the use of the two methods were compared and obtained results showed that those of Fe_3O_4 NPs from the sonochemical method had a higher crystallinity and saturation magnetization than those obtained from the co-precipitation method.

Microwave method

The microwave-assisted solution method has become widely used due to its advantages such as its rapid volumetric heating, higher reaction rate, reducing reaction time and increasing the yield of products compared to conventional heating methods [64]. Wang, et al., reported that the synthesis of the spinel structured $MIIFe_2O_4$ (M = Co, Mn) nanoparticles with diameters less than 10 nm by a fast and simple microwave-assisted polyol process [65]. The small particle sizes are probably the results of the fast and homogeneous reactions occurring during the microwave synthesis. They found that the reaction temperature and crystal quality could be controlled by adjusting the volume ratio of distilled water to EG under microwave heating. Wang and co-workers also reported the application of the simple microwave heating method for preparation of magnetite and hematite using $FeCl_3$, polyethylene glycol and $N_2H_4.H_2O$ [66]. They reported that the heating method plays an important role in the shape of nanocrystals. Ellipsoidal α-Fe_2O_3 nanoparticles were prepared by microwave heating. While a mixture of irregular α-Fe_2O_3 NPs and rods were prepared by an oil bath. The main advantage of the introduction of microwaves into the reaction system is in obtaining an extremely rapid kinetic for crystallization, which may be attributed to the localized superheating of the solutions under microwave heating. While in other techniques such as co-precipitation, thermal decomposition, etc., the procedures for the improvement of the crystallinity is needed to high reaction times, this is the reason for the high energy consummation.

GAS PHASE SYNTHESIS

Chemical vapour deposition

Gas-phase methods for preparing nanomaterials depend on thermal decomposition (pyrolysis), reduction, hydrolysis, disproportionation, oxidation, or other reactions to cause precipitation of solid products from the gas phase [67]. In the chemical vapour deposition (CVD) process, a carrier gas stream with precursors is delivered continuously by a gas delivery system to a reaction chamber maintained under a vacuum at a high temperature of >900°C [68]. The CVD reactions take place in the heated reaction chamber, and the products combine to form clusters of NPs. Growth and agglomeration of the particles are mitigated via the rapid expansion of the two-phase gas stream at the outlet of the reaction chamber. The CVD process has been employed to deposit iron oxide by the reaction of a halide, such as iron trichloride, with water at 800-1000°C [69]. The success of this method depends on the low concentrations of the precursor in the carrier gas, as well as rapid expansion and then the

quenching of the nucleated clusters or nanoparticles as they exit from the reactor [70]. Recently, catalytically assisted chemical vapour deposition (CCVD) has become increasingly important because of its potential for scalable production. However, this potential cannot be practically realized until some obstacles have been overcome, such as the relatively low productivity, the existence of complex phases, and the difficulty in separating carbon-encapsulated superparamagnetic NPs (CESNs) from the impurities [71].

Arc discharge

Most carbon-encapsulated MNPs (CEMNPs) have been synthesized by using the arc discharge method in which metal precursors are usually packed inside a cave drilled into a graphite electrode and then subjected to arc vaporization [72]. Magnetic metal carbides can be encapsulated in the carbon using this method. Dravid and co-workers modified the arc discharge method and successfully produced nanophase Ni encapsulated in graphitic shells [73]. In this case, the product usually consisted of mixtures of different forms of carbon, including carbon nanotubes, carbon encapsulated metal particles and graphitic flakes. In addition, the metal particles had a wide size distribution. Recently, Ang, et al., synthesized carbon-encapsulated Ni particles using an electric arc discharge in de-ionized water between a solid graphite cathode and an anode consisting of Ni and C in the mass ratio of Ni:C = 7:3. The natural separation of the produced material at different depths of the water container has enabled for the examination of size-dependent magnetic properties [74]. They found that the diamagnetic contribution of the carbon capsules reduces the magnetic moment of the core, an effect that becomes more prominent as the particle sizes decrease. Unfortunately, the arc discharge method is not suitable for the coating of the large quantities of NPs needed for in the industrial production due to its low production yields. In addition, there is the difficulty in the control of particle sizes as well as the nanocoating's thickness. The product usually consisted of mixtures of different forms of carbon and separating of CEMNPs from impurities is difficult both of which makes the method cumbersome.

Laser pyrolysis

Laser light heats a gaseous mixture of iron precursor and a flowing mixture of gases and produces small, narrow sized, non-aggregated NPs. When the experimental conditions of pyrolysis are adjusted, the crystal sizes of magnetite NPs are varied, in the range from 2 to 7 nm with very narrow size distribution. Laser pyrolysis is a technique for the preparation of iron-based nanostructures are used where sensitized ironpentacarbonyl-based mixtures and ethylene, as an energy transfer agent is employed using air, as an oxidant [75]. Laser pulse has been applied in the synthesis of MNPs in the liquid phase, too [76]. Researchers developed a method to synthesize CEMNPs such as Fe-C, NiC and Co-C by irradiating nanosecond laser pulses into a metallocene-xylene solution under both room temperatures and normal atmospheric pressures [77]. In their study, the resultant Co-C MNPs with well-ordered graphitic shells have a strong resistance to environmental degradation such as oxidation with air or dissolution in acids; it also shows soft ferromagnetic properties. To synthesize NPs by this process, it has been suggested that nanosecond laser pulses at a high peak power play an important role in the formation of a proper temperature field in the solution. Due to the fact that the method is simple and can be operated under ambient conditions, it is expected that CEMNP synthesis could be scaled up relatively easily [77].

BIOMEDICAL APPLICATION OF MAGNETIC NANOPARTICLES

Biomedical applications of magnetic nanoparticles can be classified according to their application inside or outside the body (*in vivo*, *in vitro*). For *in vitro* applications, the main use is in diagnostic separation, selection, and magnetorelaxometry, while for *in vivo* applications, it could be further separated in therapeutic (hyperthermia and drug-targeting) and diagnostic applications (nuclear magnetic resonance [NMR] imaging) [78-80].

In vivo applications

Two major factors play an important role in the *in vivo* uses of these particles, which are size and surface functionality. Even without targeting surface ligands, superparamagnetic iron oxide NP [SPIOs] diameters greatly affect *in vivo* biodistribution. Particles with diameters of 10 to 40 nm including ultra-small SPIOs are important for prolonged blood circulation; they can cross capillary walls and are often phagocytised by macrophages which traffic to the lymph nodes and bone marrow [81].

Therapeutic applications

Hyperthermia, placing superparamagnetic iron oxide in altering current [AC] magnetic fields randomly flips the magnetization direction between the parallel and antiparallel orientations, allowing the transfer of magnetic energy to the particles in the form of heat, a property that can be used *in vivo* to increase the temperature of tumour tissues to destroy the pathological cells by hyperthermia. Tumour cells are more sensitive to a temperature increase than healthy ones [82,83]. In past studies, magnetite cationic liposomal nanoparticles and dextran-coated magnetite [84] have been shown to effectively increase the temperature of tumour cells for hyperthermia treatment in cell irradiation. This has been proposed to be one of the key approaches to successful cancer therapy in the future [85]. The advantage of magnetic hyperthermia is that it allows the heating to be restricted to the tumour area. Moreover, the use of subdomain magnetic particles (nanometer-sized) is preferred instead multi-domain (micron-sized) particles because nanoparticles absorb much more power at tolerable AC magnetic fields [86,87] which is strongly dependent on the particle size and shape, and thus, having well-defined synthetic routes able to produce uniform particles is essential for a rigorous control in temperature.

Drug delivery

Drug targeting has emerged as one of the modern technologies for drug delivery. The possibilities for the application of iron oxide magnetic nanoparticles in drug targeting have drastically increased in recent years [88]. MNPs in combination with an external magnetic field and/or magnetizable implants allow the delivery of particles to the desired target area, fix them at the local

site while the medication is released, and act locally (magnetic drug targeting) [89]. Transportation of drugs to a specific site can eliminate side effects and also reduce the dosage required. The surfaces of these particles are generally modified with organic polymers and inorganic metals or oxides to make them biocompatible and suitable for further functionalization by the attachment of various bioactive molecules [90,91]. The process of drug localization using magnetic delivery systems is based on the competition between the forces exerted on the particles by the blood compartment and the magnetic forces generated from the magnet.

Diagnostic applications

The development of the NMR imaging technique for clinical diagnosis has prompted the need for a new class of pharmaceuticals, so-called magneto-pharmaceuticals. These drugs must be administered to a patient in order to (1) enhance the image contrast between the normal and diseased tissue and/or (2) indicate the status of organ functions or blood flow. Figure 2 represents the biomedical applications of Magnetic NPs.

Magnetic Materials are an assembly of materials which are frequently classified by their magnetic susceptibility (χ). The first type of magnetic materials is commonly known as diamagnetic. Another group of magnetic materials is ferri/ferromagnetic materials in which magnetic moments are aligned parallel to H and have a great spontaneous magnetization. H is the applied magnetic field [92]. Magnetic nanoparticles (MNPs) are an assembly of nanoparticles that can be manipulated under the influence of an external magnetic field gradient; MNPs have been the subject of research over the past years in the field of nanomedicine. MNPs consist of magnetite (Fe_3O_4) or maghemite (γ- Fe2O3) and shows unique characteristics that enable researchers to utilize them in few medical applications, for instance in magnetic resonance imaging (MRI), tissue engineering, and drug delivery and hyperthermia treatment of solid tumours [93]. Among MNPs, superparamagnetic iron oxide nanoparticles (SPIONs) had considerably been interesting in biomedicine because of their outstanding biocompatibility and stability. Each MNP is normally made from a magnetic core, to increase the stability of SPIONs in an aqueous medium and avoid nanoparticles' (NPs) agglomeration. Some groups of coating materials like macro clinic surfactant, inorganic shells, and polymers have been evaluated for modifying the surface of MNPs. For the biomedical application of MNPs, these particles must have less size with a narrow size distribution and must have a high magnetization value. Shape, size, surface chemistry, and state of dispersion are responsible for biodistribution and toxic potential of MNPs. For biomedical applications, the synthesis of SPIONs with a size less than 10 nm is highly preferred 28 because small NPs have a longer blood circulation time, thus providing a greater opportunity for specific localization [94].

MAGNETIC RESONANCE IMAGING (MRI)

MRI is one of the most influential and non-invasive imaging modalities in diagnostic medicine. However, just as other imaging techniques, MRI needs a contrast agent (CA) to overcome its low sensitivity for the discovery of various pathological processes [4]. Recently, SPIONs have been explored for new and negative CAs for image enhancement in MRI in T2 weighted images. MNPs make extremely large microscopic area gradients when they are exposed to an external magnetic field. These microscopic field gradients decrease the relaxation times of nuclear spins (T1, T2 and $T2^*$) and produce a dark or negative contrast in T2 weighted images due to the susceptibility effects of the iron core. For MRI imaging with MNPs, NPs should contain colloidal stability and less toxicity in a biological environment. To do this, NPs are covered with dextran, dextrin, and protein as CAs in MRI [95]. Molecular and cellular imagingis non-invasive imaging techniques at molecular and cellular levels, usually related to pathology or transgene expression. SPIONs are a worthy candidate for molecular and cellular imaging using MRI because they i) can decrease signal intensity, especially in $T2^*$ weighted imaging,

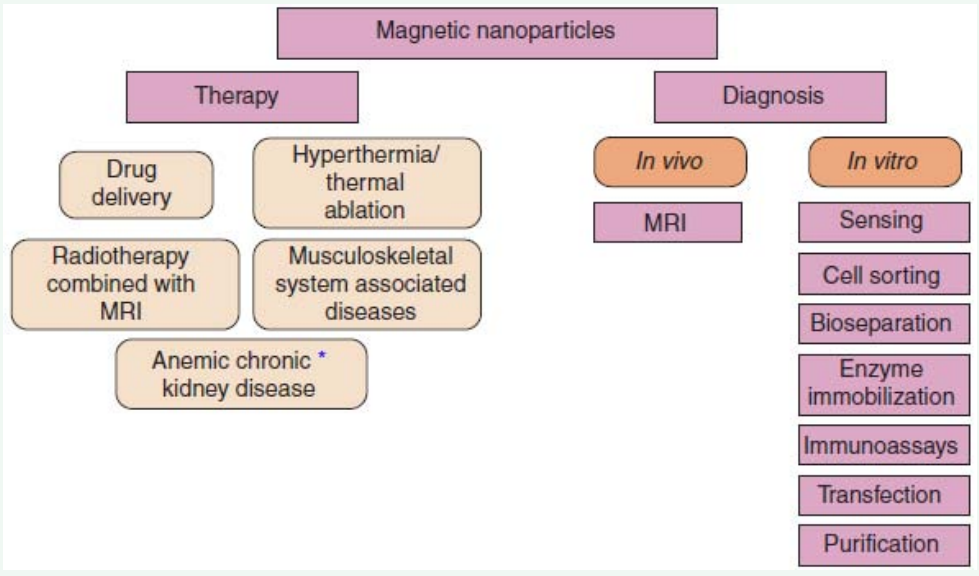

Figure 2 Biomedical applications of Magnetic NPs.

ii) are biocompatible due to their biodegradable iron core, and iii) can be magnetically manipulated. Specific cell tracking is another successful application of SPIONs in MRI [96]. *In vivo* cell tracking aims to offer insight into the underlying biological processes existing in new cell-based therapies. Ideally, *in vivo* cell tracking will permit us to monitor the movement of cells between and within tissues and offers molecular information depicting cell function and viability within those tissues. The use of MRI for cell tracking of SPION-labeled dendritic cells has made its way even to the clinic to monitor the dendritic cells vaccines for immunotherapy. Moreover, MRI cell tracking can be used to follow the transplantation of pancreatic islet cells and for monitoring new stem cell-based therapies [97].

Hyperthermia

There are many methods for treatment of tumours, such as administration of anticancer drugs, surgery, radiotherapy, and hyperthermia. Hyperthermia is a method in cancer therapy, where the tempered nature is increased throughout the target tissue. The viability of cancerous cells is decreased by raising the temperature of the target tissue to 42-45°C 50 and ~30 min heat is enough to destroy the tumor tissue, in order to damage or kill cancer cells by provoking cell apoptosis, or to make cancer cells more sensitive to the effects of radiation and/or certain anti-cancer drugs [98]. Since MNPs are able to produce heat in an alternating magnetic field (AMF), they can be utilized for hyperthermia treatment to heat and kill the cancer cells. MNPs can produce heat by hysteresis loss when placed in a high-frequency ~1 MHz magnetic field, so they permit the heating to be restricted to the tumour area. The degree of heat produced depends on the magnetization properties of specific MNPs' formulations and magnetic field parameters [99]. There are numerous studies representing that hyperthermia using SPOINs could be effective for inducing complete tumour regeneration in several types of tumour model including T9 glioma in rats, MM46 mouse mammary carcinoma, and PLS10 rat prostate cancer [100].

One of the most auspicious approaches for the treatment of cancer is magnetic drug targeting (MDT). SPIONs, e.g. magnetite (Fe_3O_4), maghemite (γ-Fe_2O_4), and other ferrites are common MNPs used for MDT because they can be guided by an external magnetic field. Targeting of drugs by MNPs has been advanced to reduce drug wastage, the frequency of drug administration, and the possible side effects of drugs on healthy tissues [101]. MNPs that are used for drug delivery consists of two main parts: i) magnetic core to the magnetic accumulation of MNPs at the target, and ii) biodegradable surface for drug reservoir to be able to release the drug. Unlike traditional drugs, NPs can be designed for drug delivery because they can easily cross biological barriers. Presence of the blood-brain-barrier (BBB) is a major problem in drug delivery to the brain. Since NPs can cross the BBB, Nanocarriers (e.g., MNPs) could act as magnetic carriers to the brain. Since NPs can cross the BBB, Nanocarriers (e.g., MNPs) could act as magnetic carriers to the brain tumours [102]. Today, MNPs have been investigated for the targeted delivery of several anti-cancer agents, and studies using MNPs for MDT still continue [103]. Chun-Han Hou, et al., investigated the effect of magnetic hydroxyapatite nanoparticles injected around the tumour of mice. The mice were placed in an inductive heater with high frequency and alternating magnetic field. Laboratory results showed that the tumour volume of mice was reduced with injected magnetic hydroxyapatite nanoparticles, which demonstrated its therapeutic effect in the mice [104].

Biosensing

The functional unit of the magnetoresistive sensors based on MNPs for biosensing application consists of the sensor and MNPs binding to the sensors. The working principle of this type of magnetoresistive sensors is that the magnetic fields produced by the magnetic particles which change the magnetic fields of the sensor result in electrical current or resistance changes within the sensor [105-107]. Steven M Hira, et al., shows that the successful detection of a 35-base pathogenic DNA target by Hall-based magnetic transduction. The detection platform has low background noise, large signal amplification ratio following target binding, and can discriminate low concentration of DNA labelled by 350 nm superparamagnetic bead.

CONCLUSION

Current developments in nanotechnology have promptly advanced new therapeutic and diagnostic concepts in all aspects of medicine. Magnetic nanoparticles (MNPs) can be simultaneously functionalized and directed by a magnetic field, thus providing promising tools for numerous biomedical applications. MNPs can be designed so that they can selectively accumulate in cancer cells and providing "targeted" treatments that may not be possible with conventional techniques. To this end, MPs need to have a special surface coating, which causes these materials to be non-toxic, biocompatible and targetable. The treatment of cancer by hyperthermia method could be more effective by using MNPs-based drugs because they can manipulate under an external magnetic field and increase the efficiency of treatment due to the accumulation of these particles in tumour targets. Therefore, the development of MNPs could be effective for theragnostics application because they can facilitate the imaging and drug delivery and also could be useful in disease therapy. Here discussed the biomedical applications such as drug delivery, hyperthermia, and biosensing.

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