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A review: Development of magnetic nano vectors for biomedical applications

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Abstract

The study of magnetic nanoparticles (MNPs) is an emergent field of science in this era due to their widespread utilization in the various fields of biomedical science. Developing concerns of magnetic nanoparticles in the researcher's field led to design a huge number of MNPs including individual or binary metallic particles, oxides, (ferrites), biopolymer coated composites, metallic carbides and graphene mediated nanoparticles. Numerous synthetic routes are defined in literature to attain the desired size, crystal structure, morphology and magnetic properties. To build up biocompatibility, MNPs subjected to surface treatments by coating with some suitable organic or inorganic biomaterials which not only improves its physical characteristics but also elevate its chemical stability. These biomaterials coat either isolatly or in a combined state to enhance the colloidal stability, magnetic properties as well as prevent it cytotoxicity and surface corrosion in the biological media. These properties are essential for the particles and empowering their effectiveness in various biomedical science i.e., drug delivery Magnetic resonance imaging (MRI), hyperthermia, biosensors and gene therapy etc. Current review recapitulates the verdicts of previous research on the subject of magnetic nanoparticles. It will also explain the recent advancements of biomaterials that execute a dynamic role in various medical treatments. Our main focus is to report the particle types, design and properties as well as discussing various synthetic routes including sol gel, co-precipitation, microemulsion, green synthesis, sonochemical method and polyol synthesis etc. These methods produced particles of excellent yield with unique magnetic properties, coercivity and crystallinity and enhanced biocompatibility as compared to traditional methods used to develop MNPs.

Keywords: Biomaterials; Magnetic nanoparticles (MNPs); Biomedical Applications of MNPs; Magnetic resonance imaging (MRI); Drug carriers; Hyperthermia

1. Introduction

Magnetic nanoparticles (MNPs) have countless attention owing to their magnetic properties and biocompatibility, and many canvassers have tried to formulate MNPs with great functionality. This field is extensively appealing for inventors, for the reason that of the auspicious consequences that can modernize the zone of biomedicine and bring forth better, enhanced, inexpensive diagnostics and curing treatments, along with superfluous benefit of limited aftermath. MNPs have been fabricated as a significant policy to transport orthodox medicines, vaccines and nucleotides. MNPs can attach to biological materials for instance drugs, proteins, enzymes, antibodies, or nucleotides and can be concentrating to the targeted place that can be an organ, tissue, or tumor by means of an exterior continuous and discontinuous magnetic field [1,2]. MNPs are safe to use in biological entities due to their small size external handling. Once they collected at tumor site, they can easily manipulate to transfer the heat and destroy the targeted cells without affecting the whole organs. Hence, they are the best replacement of the radiotherapy and chemotherapy. [3-8].

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These are the metallic particles shows excellent magnetic properties. Most of these particles are either used isolated or in combined state with some other materials forming oxides, alloys, complexes with transition metals i.e., Cobalt, nickel, manganese and gadolinium etc. Variety of polymer coated materials also reported. Transition metals are usually preferred due to their excellent magnetic behavior like paramagnetic, ferromagnetism, and even superparamagnetic nature. Their properties i.e., coercivity, low Curie temperature, paramagnetism, and magnetic susceptibility generally counts on the route of their fabrication. Application of MNPs cannot be explain in a single paragraph. There are countless areas which cover the applications of MNPs in mineralogy, catalysis, in data storage devices, in environmental application and a giant class of biomedical science. [8-12]. This review presents the types, various methods for the synthesis of magnetic nanoparticles, their biocompatibility and different methods used for the synthesis of magnetic nanoparticles.

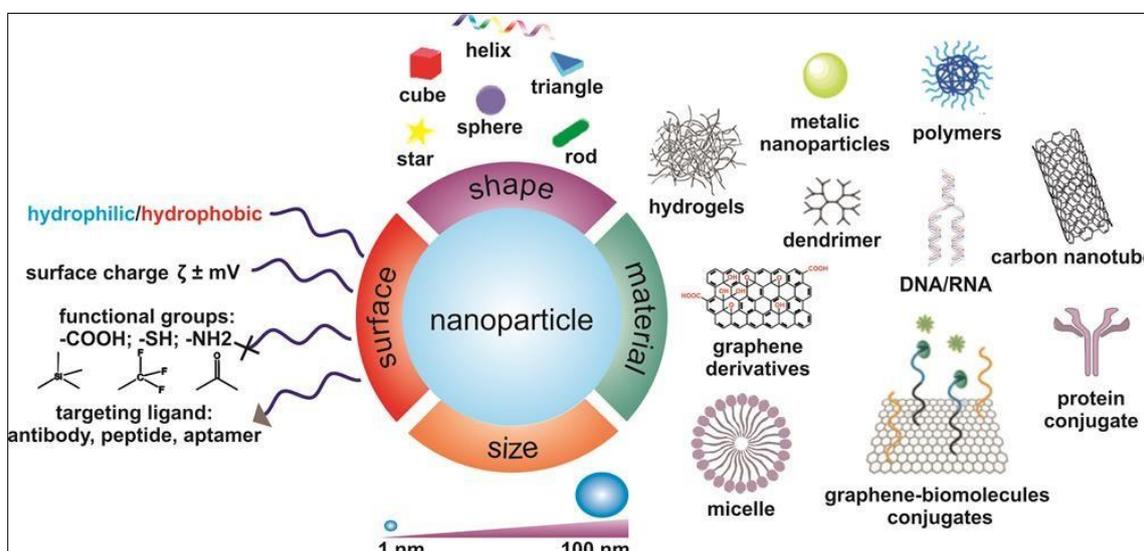


Figure 1 Classification and applications of different forms of magnetic nanoparticles [13]

2. Metallic magnetic nanoparticles

Metals show several unique properties in which some of them directly depends on the electron distribution in outer most orbits. Magnetic behavior is also one of them. Number of transition metals exhibit magnetic performance in several biomedical fields. Transition metals i.e., Fe, Ni, Co, Mn, etc are the most common and widely discussed representatives of their class. Mostly Fe utilized in the form of its compounds i.e., as oxides, carbonyls, or in the form of complexes a very few reported them as isolate because iron is very delicate and sensitive towards surface oxidation. Keeping this point in consideration Hou and his coworkers develop nanoparticles having cubic body centered crystalline structure with 65 nm particle size (Figure 2 A) by using PVP for surface treatment. The next image (B) in the figure illustrates nickel nanoparticles fabricate by using organic phase method at elevated temperature. In this method nickel acetyl acetonate reduced to the nickel nanoparticles in the presence of surfactant act as a mediator to control the size of resultant particles as the result 3.7 nm sizes with mono-dispersity of the resultant product successfully attained. Similarly, they design a comparative synthetic route by using massive organo phosphines and observed that these materials encourage the reduce particles size >6nm while their absence promote the large particle size up to 11nm (figure 2 C and D). [20,41]

2.1. Metallic Oxide and Ferrites

Iron oxide is a renowned material shows excellent magnetic properties. It has many potential applications in biomedical science due to its unique magnetic properties. It can either design as isolated particle or combined form with some other materials to get useful magnetic properties with high magnetization. Although, it gains popularity in biomedical applications due to its economical, biocompatible, and outstanding chemical stability but their efficiency cannot be ignored in some special areas of biomedical science including magnetic separations, drug carrier magnetic hyperthermia treatment, and biosensing etc. [13-17]. Wu et al. and many other scientists reported several routes comprehensively for the synthesis of iron oxide including chemical methods and physical approaches. [19-21] Many researchers reported variety of chemical methods especially the most common one is solution-based methods while the least common method was laser pyrolysis or chemical vapor deposition [15,22,23].

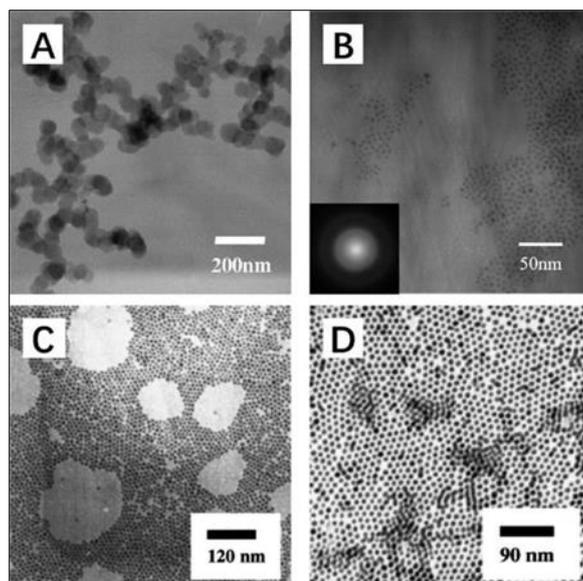


Figure 2 TEM images of Fe (A) Ni (B) and Co (C and D) [20,41]

In the synthesis of iron oxide scientists majorly focused on surface treatment and to enhance iron oxide's colloidal stability with some suitable coating materials which shows high affinity towards these particles [14,18]. Coating materials should be carefully selected depends on their function discussed by McCarthy and Weissleder [24]. Mornet et al. reported an efficient synthesis method of maghemite in detail with significant properties including high control of core size, uniform particle distribution, and carefully controlled particle diameter.[25] Another one step method involves co-precipitation of Fe^{+2} to Fe^{+3} based on chemical bonding of dextran macromolecules through amino propyl silane in basic solution of hydrophilic molecules. The process can competently use to prepare maghemite with excellent cubic crystalline structure along with good dispersion. This can be achieved by little modification in said method by using ultrasonic chemical coprecipitation or by using microwaves [26,27]. Iron oxide coated with biocompatible polymer raises its chemical stability reduces its surface oxidation and diminishes its toxic attitude in biological entities. Surface functionalized iron oxide can easily coat with polymer by using mixture of ethyl alcohol, hexane and water which act as solvent. By heating this mixture with FeCl_3 and sodium oleate to produce a complex of iron-oleate, waxy solid appearance indicted the preparation of this complex. This complex and oleic acid is heated sensibly with the non-polar solvent named as 1-octadecane to produce magnetic iron oxide nano crystals [28]. Superparamagnetic iron oxide (SPIOIN) coated with PLG prepared by distillation at 260°C in the presence of inert media by reacting Tris (acetylacetonate) iron (III) as a precursor of iron with oleic acid and oleyl-amine which has potential application in magnetic resonance imaging MRI [29]. Another iron oxide magnetic fluid which shows great affinity towards DNA phosphate framework is iron oxide coated particles with a copolymer of polyethylene glycol and polyetherimide prepared by co-precipitation method [30]. NiO overlaid with ethylene diamine tetra acetate (EDTA) prepared from dichloro nickel hexahydrate $\text{Cl}_2\text{H}_{12}\text{NiO}_6$ either in EDTA solution or a strong alkaline solution (NaOH) by co-precipitation method. In addition to this Gosh et al. reported superparamagnetic nickel and manganese oxides by hydrothermal method.[69].

Ferrites are the dark color either black or dark gray with high strength or brittle materials. The main constituent of these materials is iron oxide having ferrimagnetic properties with a variety of transition metal dopants. These metallic dopants are usually cations represented as M^{2+} (e.g. Zinc (Zn), manganese (Mn), cobalt (Co), nickel (Ni), iron (Fe), platinum (Pt) and palladium (Pd) etc.). Magnetic properties can be improved for molecular imaging by this technique a divalent cations having general formula MFe_2O_4 can be synthesized by several methods. It has been reported that Mn based ferrites shows less toxic effects as compared to Co and Ni [31,32]. Suitable stabilizing agent is very essential because it influence on particle size of crystal reported in the case of Co-ferrite synthesis [33]. For the fabrication of Co-nano ferrites ($\eta^5\text{-C}_5\text{H}_5$) $\text{CoFe}_2(\text{CO})_9$ was used as starting material and noticed that particle size reduced by using hexadecyl-amine and oleic acid moderate by using different concentrations of precursor and stabilizing agent and switch to large monodisperse crystalline structures by using mixture of two organic acids oleic and lauric acid. These particles have promising applications against tumor cells [34,35]. In biomedical applications iron is more common than cobalt as it has low toxicity. [36] Polymer polyhydroxy, polyamine and polyethylene glycol (PEG) functionalized carbon coated Co-nanoparticles were fabricated for drug delivery; this work was theoretical biomedical applications without discussion of any biocompatible tests [37]. Stevenson et al. stated Co- composite materials proved to be an auspicious

material for retinal imparities. The composite comprised on Co nanoparticles dispersed in a block copolymer as a starting material of biocompatible poly dimethyl siloxane and $\text{Co}_2(\text{CO})_8$ [37]. Crystalline Co-nanoparticles with polyol are also significant member in biomedicines [38]. Co-silica based materials also shows potential applications for healing of detached retinas in cataract surgery [39,40]. Similarly, solution phase reduction of cobalt chloride at high temperature and a suitable stabilizing agent were used to develop biocompatible mono dispersed Co-nano crystals [41]. Some other metallic ferrites reported with excellent magnetic flux and biocompatibility is based on Zn, Mn, and Ni based ferrites. Zn based ferrites cannot be used independently in biomedical applications especially in hyperthermia treatment due to its surface oxidation. Its magnetic behavior towards external magnetic field can be improved by mixing it with some other metals exhibit good magnetic properties. This can be done by changing concentration of zinc in the mixture of metal ferrites as shown in (figure 3,4). It modifies the magnetic flux of the resultant material. Moreover, Zn ferrites are highly temperature sensitive and decrease the Curie temperature by reducing the distance between magnetic spots. This is advantageous to use Zn in most of the ferrites formulation for getting desired properties. It can induce magnetization for self-control hyperthermia by mixing nonmagnetic divalent Zn cation with different concentrations of other magnetic particles i.e. Co, Mn and Ni because it increases the orbital angular momentum etc. [42-44]. Apart from this, in Co-Zn and Mn-Zn ferrites, Zn ion concentration effects on particle size destructively i.e., increase concentration of Zn cation decrease particle size and vice versa [45-47].

Mn based ferrites MnFe_2O_4 show outstanding characteristics in comparison with other metallic ferrites with High degree of magnetization, initial permeability, and resistivity. Coercively Mn ferrites are superior to other magnetic ferrites based on cobalt nickel or iron [48-50]. Mfe and his coworkers reported Mn ferrites as a unique magnetic resonance imaging (MRI) agent with some exceptional properties useful for hyperthermia treatments and drug delivery [51,52]. Nickel based ferrites also show promising applications in biomedical science due to their low cost and excellent chemical stability in biological moieties. Nickel based ferrites especially Ni-Zn is proved to be nominal heating smart materials for hyperthermia treatments due to their special characteristics of magnetism. Usually, they loss some magnetic properties when they subjected to high frequency [53].

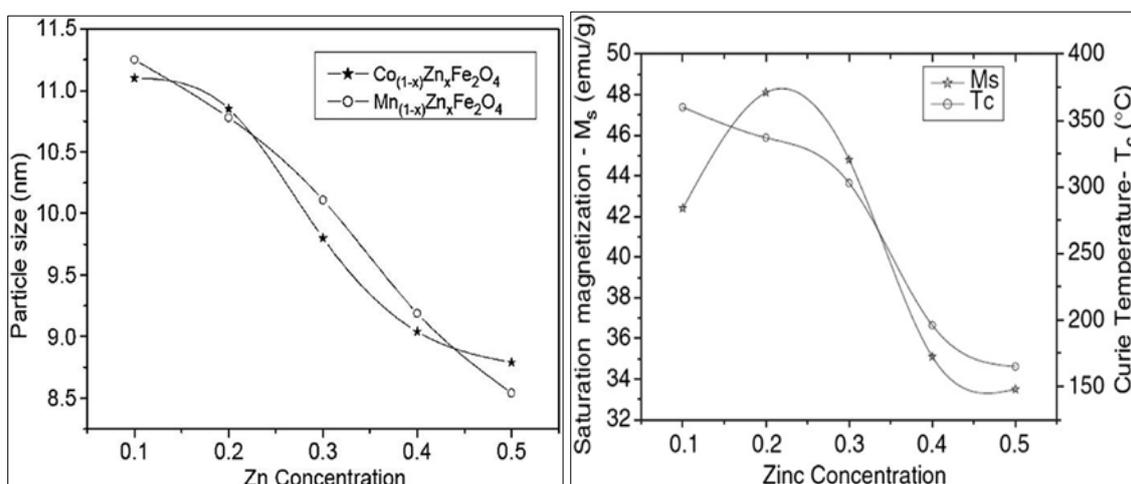


Figure 3 and 4 Reduction of Particle size by incorporation of Zn particles at room temperature and Effect of Zn doping on specific magnetization and Curie temperature [42]

In ferrofluids nickel-based ferrites appeared as a spin glassy layer on the surface of the material [54,55]. Calcium (Ca) is an active member of biological media due to its biocompatibility, environment friendly and can withstand high temperature range. Although it does not have potential magnetization as compare to other metallic ferrites many researchers reported several types of Ca- ferrites but only a few of them discussed their biological significance. CaFe_2O_4 has wide range of applications in the bulk form especially in pigments, in optical devices, in Lithium (Li) ion batteries, during steel manufacturing it is used as purifier to remove several types of impurities i.e., H_2S , Sulphur (S), Phosphorous (P) and unwanted oxygen in the form or oxides [56,57].

In the development of inorganic nanomaterials which applicable in biological devices has been acknowledged owing to their remarkable applications. The toxic behavior of these nanomaterials towards the infected cells would generate a new benchmark of their pharmaceutical applications [58-61]. Several metallic oxides reported in literature revealing them as peers of active oxide forming species exhibit substantial antimicrobial and antibacterial applications [62,63]. Even though Magnesium oxide and magnesium-based ferrites are active mediators in the field of medicines but their

toxicology towards the diseased cells is not considerably demonstrated in literature henceforth, to investigate the toxicology of MgFe_2O_4 is a hot topic in the field of cancer treatment. Most of the researchers reported the cell toxicology in endothelial cells of different human organs i.e., in umbilical cord veins, cardiac macro vascular cells, astrocytoma cell, breast tumor cells and their efficiency in the cryosurgery of tumor infected cells at nano level [64-66].

3. Binary metallic alloys

Another category of magnetic nanoparticles are binary metallic alloys. In few cases binary metallic alloys were coated with other materials to enhance their magnetic properties along with their chemical stability in biological media. Iron palatinate (FePt) nanoparticles are an example of such materials. These particles were coated with gold (Au) to improve their biocompatibility. On the other hand, hydrophilicity can be enhanced by tuning their surface chemistry with help of surfactants having carboxyl (COOH -) or amine (NH_2 -) groups. Cubic face centered crystalline structure was 1st reported at elevated temperature by solution phase reduction and decomposition of Pt (II) acetylacetonate and iron Penta carbonyl respectively in the presence of a non-polar solvent like octyl-ether [67]. Hou and his coworkers reported monodisperse FePd nanoparticles via thermal decomposition method in the presence of phosphines and adamantanoic acid as stabilizers. They reported that monodisperse character of the particles can be achieved by maintaining suitable molar ratio of surfactants in the reaction mixture as shown in the figure 5. They also worked on rare earth binary components with transition metal and reported SmCo_5 alloy with improved magnetic anisotropy [59]. There is a new class of bimetallic nano alloys with promising magnetic functionality is iron-cobalt nano ferrites. These particles with different ratios can be synthesized by vapor deposition process and usually during synthesis chances of surface oxidations increased which can be prevented by the coating of Ag , Au , or with graphite [68,70]. Gadolinium based ferrites reported by using spray pyrolysis and mechanical crushing of a dried product followed with pyrolysis [71].

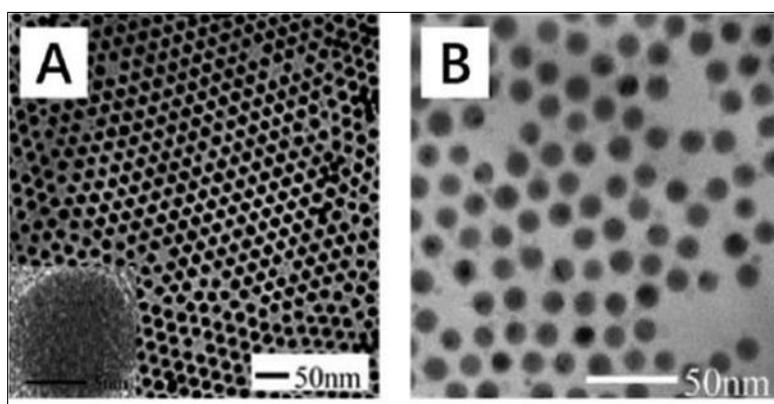


Figure 5 TEM images of Fe-Pd alloy (A and B) with particle size 11 and 16 nm respectively. [68]

3.1. Magnetic Ferrofluids

As the name indicates these are the solutions of homogeneously dispersed magnetic nanoparticles in a liquid with good colloidal stability. The dispersing solvents are either water or organic liquids show the affinity towards magnetic nanoparticles. Magnetic ferrofluids have lots of prospective uses in multiple research areas. These are unambiguous subsets of smart materials whose physical characterization alters by external magnetization. Magnetic ferrofluids can be classified into two categories: Magneto rheological fluids (15 to 40 nm) and Ferrofluids (less than 15 nm). Magneto rheological fluids comprise colloidal suspensions with particle range (5-10 nm) of magnetic nanoparticles uniformly dispersed in liquid matrix which can be polar or non-polar for example different types of oils including kerosene, mineral oil, silicone synthetic or semi-synthetic oil etc. These oils can be used either alone or with the combination of various other liquids [72-75]. The magnetic phase particles are pure metals, metallic oxides or ferrites having oxides of different divalent metals i.e. Zn, Mn, and Ni etc. with the formulation of MO. Fe_2O_3 . Sometime surface treatment is mandatory to prevent attraction between dispersed nanoparticles with the help of surfactants. For this purpose, variety of dispersant and stabilizers employed during the synthesis of these smart molecules. It is necessary to select the dispersant very carefully by keeping in view its properties should match with carrier liquids for example silica, Chitosan, ethylene glycol (EG) polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Poly acrylic acid (PAA), and gelatin [76]. These stabilizers decrease the toxic effect prevent the surface oxidation increased the biocompatibility, bio-adhesion colloidal stability and give rise to the uniformly dispersed particles [77-80]. These types or ingredients are essential for the ferrofluid synthesized by either water-based media or organic based media.

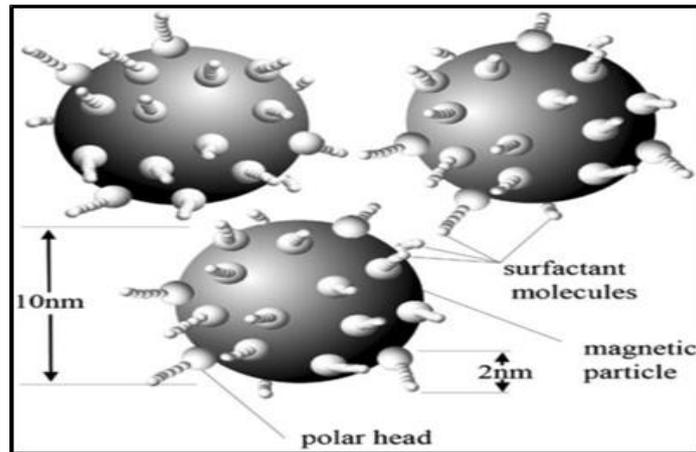


Figure 6 Surface functionalization of MNPs in ferrofluids. [73]

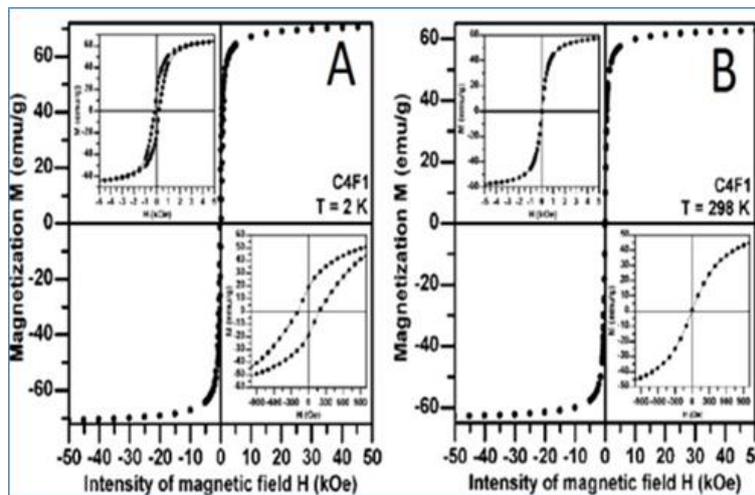


Figure 7 A and B Magnetic properties of chitosan-coated magnetite at 2K and 298 K respectively [77]

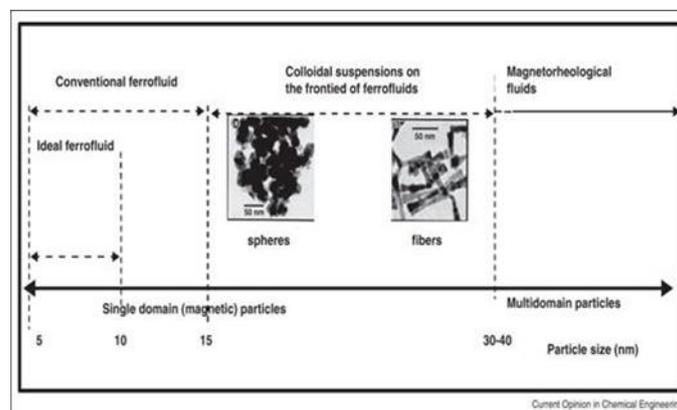


Figure 8 Classification of magnetic ferrofluids [74]

Following Fig 6 illustrates the surface coating on a particle. 10 nm size particles are coated with the 2nm thickness of this surfactant layer which is the main reason to create repulsion and prevent aggregates formations. Surfactant coating

consist of long chain hydrophilic and hydrophobic ends this will restrict the Vander Waals forces of attractions [73]. Belessi et al. reported a chitosan coated magnetite hybrid nanoparticles and explore their excellent coating and efficiency of magnetization at elevated temperatures. They predicted this foretells hybrid as a superparamagnetic hybrid at room temperature as shown in the fig 7. Chitosan coating also prevent it from agglomeration. [77] Lopez and coworkers reported the development of ferrofluids different from traditional ferrofluids on the basis of particle shape and size [74]. They fabricate big size spherical particles having diameter approximately 24 nm whereas the other one is fibrous form of ferrofluids as shown in Figure 8.

4. Metallic carbides

In comparison to oxides metal carbides (iron carbide and nickel carbide etc.) also show promising applications in biomedical science as they possess high degree of magnetization in comparison to oxides. But due to their in height challenging fabrication particularly difficult to attain controlled size and morphology makes them very less common in researcher's considerations. In recent times Hou et al. worked on the fabrication of iron carbide Fe_5C_2 nanoparticles they decompose iron penta carbonyl $\text{Fe}(\text{CO})_5$ in the presence or organic solvent named as octadecylamine and carbonize crystalline iron nanoparticles [80]. This is quite remarkable that the entire process of synthesis is still a mystery as they use bromide which proves critical for these nanoparticles as they use it to tune up the surface of iron carbide. Particle size of the final amorphous material is about 20nm. In addition to this they also suggested another route for the fabrication of some other types of iron carbides i.e. Fe_2C , Fe_3C and Fe_5C_2 with different crystalline shapes such as hexagonal, monoclinic, and orthorhombic respectively. This method basically a wet chemical method in which they use iron at iron oxide in the presence of halide ion that helps to develop bonding between iron and carbon atom [81]. Figure 9 shows that iron carbides reveals weak ferromagnetic behavior.

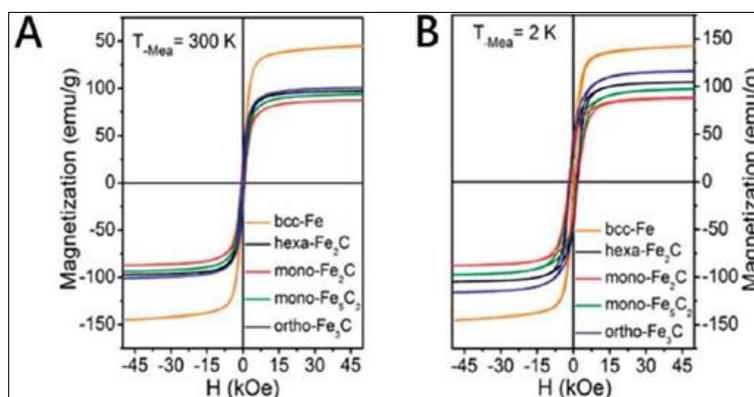


Figure 9 Ferromagnetic behavior of iron carbide at different temperatures A 300K and B 2K [81]

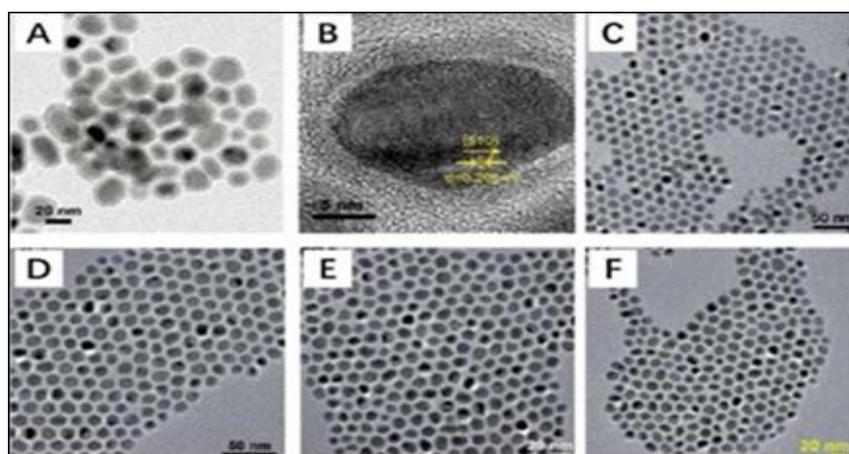


Figure 10 (A and B) TEM AND HRTEM images of iron carbide and crystalline morphology of iron carbide in (C,D,E,F) as hexagonal and monoclinic Fe_2C , monoclinic Fe_5C_2 and orthorhombic Fe_3C respectively [80,81]

Use of halide ion is also advantageous as it provides the selective absorption and hence, it controls the carbon bond formation, contents and its saturation in the resulting nanoparticles, which results in the formation of variety of crystalline shapes. As shown in the figure 10. Zhothu W, and his co-workers reported Ni@Ni₃C core shell nano materials. They use organo phosphine oxide (trioctyle phosphine oxide) at low temperature surface modification of the by coating carbon on the Ni particles to produce foresaid nanoparticles. These particles exhibit high coercivity reduced magnetization at single dimension [82].

5. Graphene based magnetic nanoparticles

Graphene is a single honey comb like sheet of sp² hybridized densely packed carbon atoms arrangement grabs our immediate attention of scientists due to their unique properties. This network of carbon atoms is hydrophobic in nature. Delocalized - electrons can effectively consume to make it drug carrier. The basic principles for drug loading are stacks of electrons and hydrophobic interactions. Surface functionalization is essential to make it biocompatible and a number of oxygen containing groups like Carbonyl (C=O) Carboxyl (-COOH) and hydroxyl groups (-OH) etc. introduced on the surface of graphene converted into its derivative called Graphene Oxide which is compatible for biopolymers [83]. Introducing these oxygen containing groups increase the hydrophilic character and polarity makes it water soluble. These functionalities provide a link between the biopolymer and graphene oxide to make it applicable in various biomedical fields [84]. For example, it has potential applications in stem cell engineering drug delivery, biosensors, bioimaging, and marine anti fouling dye degradation and as antimicrobial agent as shown below in figure 11. Enormous literature is available which reveals that these materials can be a potential applicant to substitute the present resources castoff in several biological applications [86-92]. Number of biopolymers can be linked on the surface of graphene to decrease its toxic effects. Gelatin and chitosan are the most common biopolymers used for this purpose and reported as excellent tools for drug carriers [88,89]. Graphene decorated nanomaterials with appropriate metallic provisions holding paramagnetic properties including Co, Fe, Zn, Au, Ag, Fe₂O₃ and ferrites of different metals which aid to improve productivity of graphene nano composites and their efficiency in biomedical science [85].

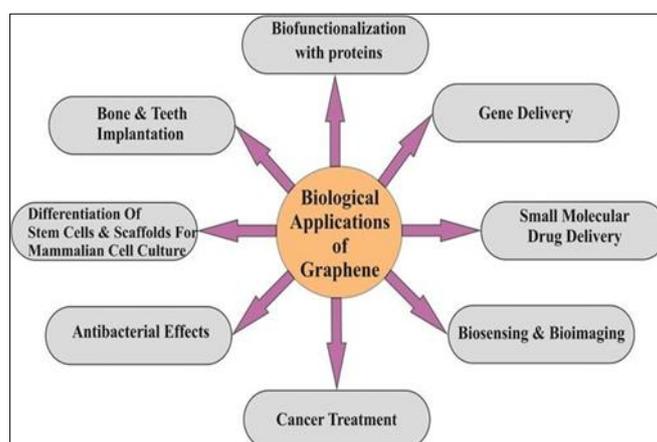


Figure 11 Flow chart for biological applications of graphene [85]

Al-ani and his coworkers reported this graphene-Au composite useful in drug delivery and different types of treatments including photo, chemo and combination therapy [93]. Graphene incorporated with silver nanoparticles shows extensive applications due to their large surface area porosity and elasticity it is used as a biosensor for attacking and killing various microorganisms' detection of hydrogen sulfide (H₂S) and as water disinfectant. Moreover, reduced graphene oxide festooned with silver nanoparticles illustrates high cytotoxic behavior towards the tumor cells in human lungs as compare to simple graphene oxide doped with silver nanoparticles [94,95]. Aforesaid in ferrites, zinc has some interesting properties that demonstrate excellent outcome in several medical treatment applications mostly it is used in combined form either in the form of oxide or ferrites. Nasker and his colleagues reported a highly biocompatible and sustainable graphene based nano composite ornamented with ZnO and Au halted with bovine serum albumin towards tumor cells in human ovarian cells [96]. Low et al. demonstrated this graphene decorated with zinc oxide or Zn composites as gene biosensors for DNA and RNA sequences respectively [97]. Similarly, graphene draped with Zn based zeolites named as Zinc clinoptilolite are potential slow drug discharge drug carriers. [98] Furthermore graphene SnO₂, lead (Pb) and Ni reported as biosensors, for degradation of several dyes as well as to remove radioactive materials such as Thorium (Th) and Uranium (U) at elevated temperature of the system [99- 101].

A number of Fe and Fe₂O₃ composites are known to date due to their unique properties. They exhibit far much better biological stability low level of toxicity and high degree of magnetization.[103] These special features make it popular in the field of magnetic resonance imaging (MRI), targeted drug delivery and in biological separations. Chen's group discovered a pH sensitive drug carrier composite based on graphene iron oxide exhibit super paramagnetic properties and also develop a preparation method to use aforesaid composite as MRI contrast agent [104-107]. A few researchers also report this material a therapeutic agent especially in photo thermal therapy [106]. Number of polymers used to make graphene-based biomaterials and for this purpose different types of natural biopolymers i.e. cellulose, chitosan and gelatin are most common coating materials

Reduced graphene oxide coated with cellulose nanocrystals, carboxymethyl cellulose and bacterial cellulose reported as outstanding materials in various fields like medicines, environmental applications, antibacterial agent, drug carrier and tissue and scaffold engineering respectively. [108-111,116] Nandgaonkar et al. reported a material show major outcomes in the field to provoke nervous system in different muscles and cardiac tissues by using bacterial cellulose coated with reduced graphene within single pot in situ biosynthesis mechanism [112]. Luo et al. discussed graphene biomaterials as an active member for drug delivery. They fabricate a drug loaded hydrogel comprises on Bacterial cellulose and graphene oxide. The results of these hybrid materials foretell that they are pH responsive in nature and actively release drug especially in neutral and acidic medium [113]. Another fluorescent property of graphene based biomaterials is in the form of Quantum dots which has the ability to retain their physical properties with reduced horizontal dimensions about 10nm rich in carboxyl (-COOH) groups on the surface [114].

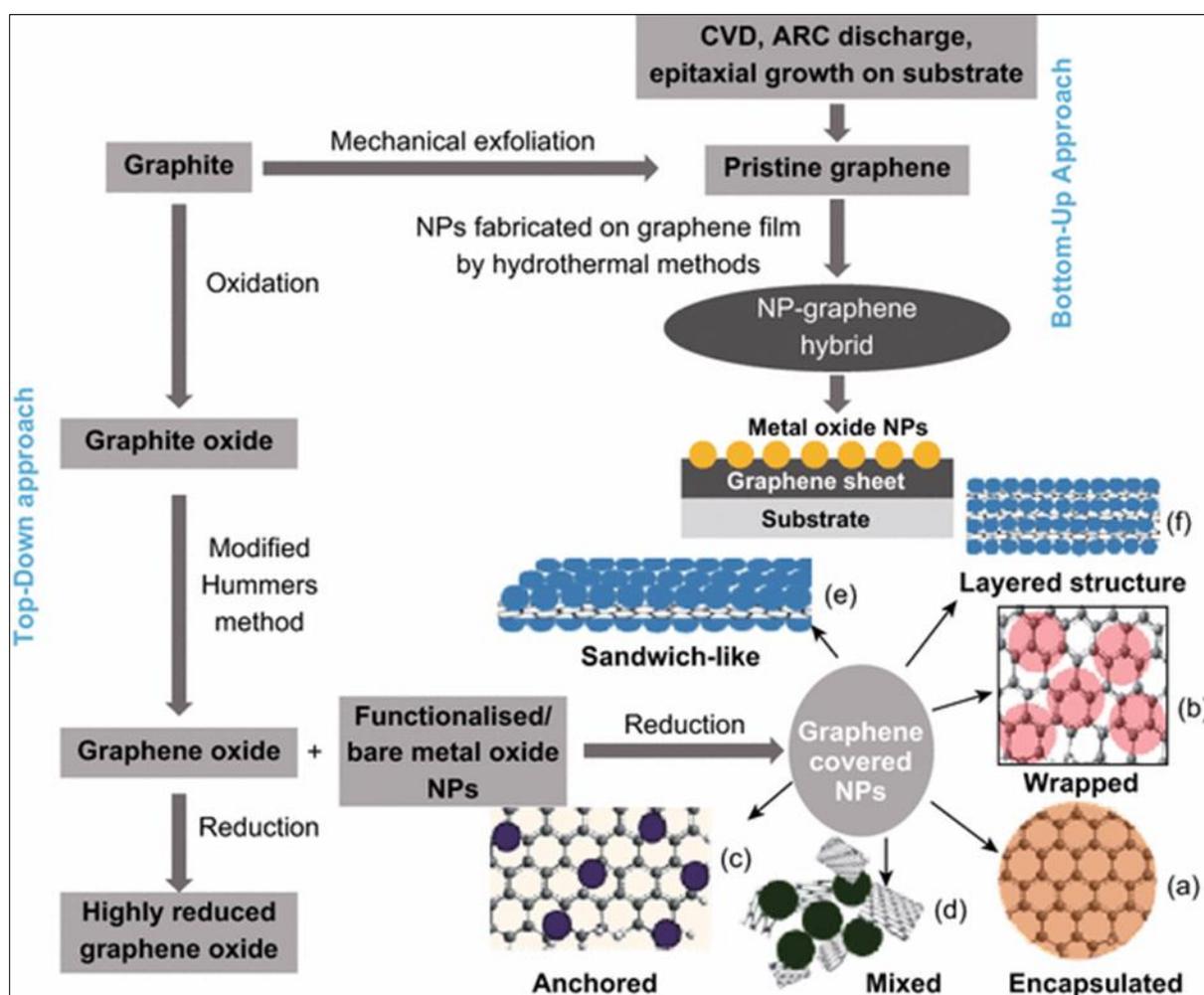


Figure 12 Flow chart with graphene synthetic routes for graphene and different types of graphene nano hybrids [90]

Graphene quantum dots foretells outstanding properties including chemical stability, low toxicity, and biocompatibility which boost their ability of drug delivery and anticancer behavior, deprived of using any traditional material used for Pre modification of drug carrier intended for screening the drug uptake within the cell. For example, in many cases drug delivery agents cannot envisioned without the assistance of organic fluorescence materials or dyes informed about the

cellular uptake and movement of drug within the cell. [114,115]. Using polymer hydrogels overtone with GQDs outspread the drug delivery application. JavanBakht and his coworkers reposted one of such examples is based on hydrogels prepared through carboxymethyl cellulose (CMC) as polymer matrix to form flexible films and GQDs act as fillers via casting method by loading an anticancer drug doxorubicin (DOX). These hybrids composite predict the importance of GDQs in these hydrogels by making them pH sensitive and elongated DOX release time [116,117].

6. General parameters for designing MNPs

It is not easy to execute the design of MNPs according to application so, to plan the basic strategies regarding the synthesis, type and design of magnetic nanoparticles according to the application is very significant. A number of factors that can affect on particle design during fabrication which will become the major reason to bring a vivid change in the predicted consequences, so they should be optimized at initial stages. Especially in biomedical field MNPs are extensively used as they exhibit good magnetic properties drug loading capacity, biomarkers, act as target drug carrier, in number of therapeutic treatments due to their biocompatibility, non- toxicity, particle size and surface area. Hence their physical and chemical properties equally contribute to determine their functionality in biomedical science. [118-129]. For instance, physical parameters include magnetic behavior, particle size and optimized relationship between the substrate and reacting medium are very essential. Magnetic properties and be utilized in many ways it help in dragging the particles inside the body by applying external magnetic field to accumulate them at the targeted site and either release drug or increase the temperature to kill the cancer cells (common in hyperthermia) or as MRI contrast agent [130-131]. For this purpose, size is very important feature with specific surface area. Several articles available in literature to describe the size-controlled fabrication of MNPs depend upon the method and application for which the employed ranges from few nm to μm in size. [132-135]. Biocompatibility of MNPs is one of the key features for using them in biological media and to attain this colloidal stability is mandatory. This target can be achieved by surface functionalization either by coating it with suitable biomaterials (proteins, enzymes, micelles and liposomes etc.) or inorganic coatings i.e. biologically inert metals Au, Ag, and Pt etc.[136,137] surface functionalization can aid to inhibit cluster formation, corrosion and redox reaction with the biological media. [138-142].

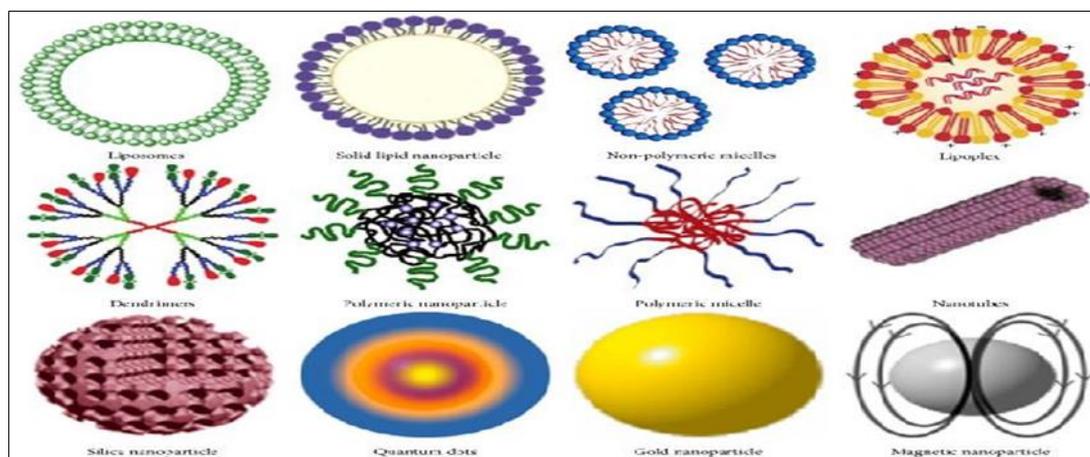


Figure 13 Different form of surface functionalized magnetic nanoparticles used in various applications [146]

Surface treatment of MNPs introduce some functional groups on their surface that act as a linker for external coatings via chemical bond. Many scientists reported that particles which are covalently bonded with the coating exhibit good properties in the biological medium as their bond are stimuli responsive. For example, if the particle loaded with a specific drug covalently it will defuse its bond at the targeted site either in the response of ideal temperature, pH or by the activity of certain enzyme. Number of successful drug carriers reported which having either hydrophilic, or electrostatic interfaces, or different coordinate complexes. Therefore, bonding strengths should also be carefully monitored during fabrication process [143-146].

7. Synthesis of magnetic nanoparticles

These are the methods involves the breaking of huge particles to smaller size up to nano level. Usually, all the starting materials in this type of approach are in solid state but these processes are not useful for acquiring the desirable shape, size, fix lattice structure that causes abnormalities in the magnetic properties of the particles [147-149]. This category

only employed for starting materials usually either liquids or gases to concentrate nanoparticles. Both physical and chemical methods can be used for these materials. In Physical techniques for such materials are Condensation, Evaporation, Sputtering, Plasma Arcing and Laser Ablation. Laser evaporation is very common technique in literature to fabricate these nanoparticles. The starting material of this category usually powdered granules. Particle size of these granules is ranges in micrometer which is reduced by mean of laser evaporation to 20-50 nm size. Temperature, laser power and chamber's atmosphere plays a vital role in the synthesis of these MNPs in the above-mentioned process [150-155]. A number of chemical techniques involve in the synthesis of MNPs Herein, we report the most efficient and effective techniques for the synthesis of MNPs.

7.1. Co-Precipitation method

The utmost suitable and extensively cast-off method for the production of MNPs with quite well ordered, fine size, and excellent magnetic characteristics can be designed by this method. Another reason for the diversity of this method it is very convenient to develop MNPs by using safe and less harmful materials and procedures [156,157] This method involves the water-soluble salts of desired MNPs dispersed in an alkaline solution either at elevated temperature or in an intermediate at room temperature. [158-160]. A simple reaction is given below:



Types of salts (chlorides, nitrates, and sulphates etc.) reaction parameters i.e. pH value, or and Fe^{2+} and Fe^{3+} ionic concentration, temperature, medium of synthesis either inert or not and rate of agitation etc. are the main factors that effects the particle size, shape and its surface chemistry. For example, to get the small particle size one should make sure that pH and ionic strength should be high. Similarly, to avoid agglomeration and superficial oxidation the reaction should be carried out in the presence of inert gas i.e., N_2 gas medium. [198,161,158,163-164] Temperature is another reason that influence the particle type for instance to synthesize magnetite Fe_3O_4 temperature of the reaction mixture should be maintained less than 80°C while further decrease in temperature below 60°C will encourage the fabrication of hematite Fe_2O_3 . Even though particle aggregation still is a major risk due to high pH value during this method. For the reason that the resultant particle size is extremely small with highly charge surface area tends to for aggregates. Hence, the desired range of particle size is difficult to obtain.[164].

8. Thermal Treatment Method

Variety of transition magnetic metal oxides and metallic magnetic nanoparticles can be fabricated by this method. This method involves the thermal decomposition of chemical bonds of organometallic materials at high temperature.

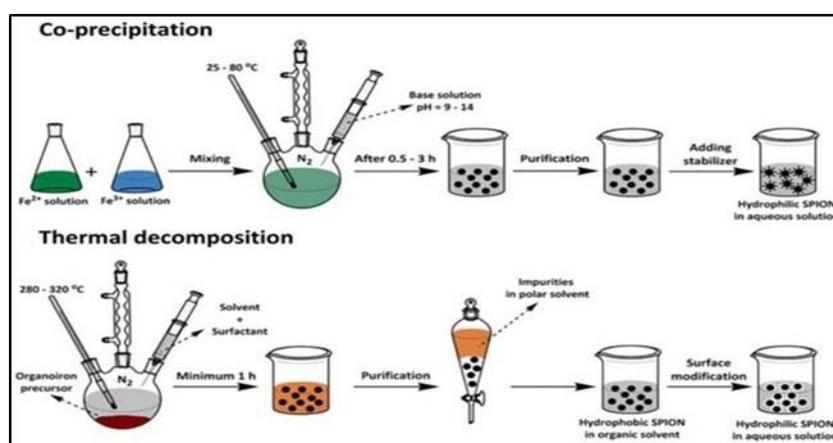


Figure 14 Synthesis of iron oxide by co-precipitation and thermal decomposition method [168]

These organometallic i.e. metal acetylacetonate $\text{M}^{\text{X}+}(\text{acac})$ ($\text{M} = \text{Ni, Mn, Zn, Fe}$ and Y and $\text{X} =$ oxidation state 1,2,3,4,etc) compounds heated in the presence of nonmagnetic organic surfactants and solvents. Usually, the most common surfactants i.e. fatty acids, cetyl trimethyl ammonium bromide (CATB), Oleic acid, and Oeylamine, etc. and organic

solvents ethylenediamin (ED) number of carbonyls i.e. $\text{Fe}(\text{CO})_5$ and benzyl ether MY+ (Cup) (cup= nitroso phenyl hydroxyl amine) in literature are reported yet. [158].

Properties of the final product are directly influenced by the composition of the reacting medium. Many researchers report controlled size shape and magnetic properties of particles fabricated by this method. Coworkers of Alivisatos and Peng et al. reported the synthesis of metal oxides with narrow particle size distribution ranges between $>5\text{nm}$ and $<50\text{nm}$ [165-166]. Iron acetyl acetonate $\text{Fe}(\text{acac})_3$ decomposes in the presence of benzyl ether, oleic acid and amine at 260°C . Monodisperse particles less than 20nm designed with this method [167]. Particle shape alters by increasing reaction time period for instance Nogues et al. produced spherical particles at the time period of 2-4hrs while they turned to cubic shape if the time period increased up to 10 hours [168].

9. Micro emulsion method

Micro emulsion method also named as reverse micelles method. Thermally stable oil in water emulsion resulting to form a transparent and clear solution in the presence of suitable surfactant which generate extremely low interfacial tension. Surfactant is the main source to generate a monolayer at interface. This monolayer comprises on hydrophilic ends facing towards water and hydrophobic ends towards oil. This intramicellar place will act as small factories for the growth of nanoparticles. Entire shape size and properties are directly influenced by the choice of surfactant [169,170]. Microemulsion is an economically simple method has several advantages involve small size with narrow particles size distribution, highly crystalline materials with large surface area, attainable temperature, pressure and particles with high magnetic properties [171,172]. On the other side this method also has some defects usually unreacted surfactants left behind after completion of the reaction which affects the particle properties. Process for the fabrication of nanoparticles via microemulsion method is given below:

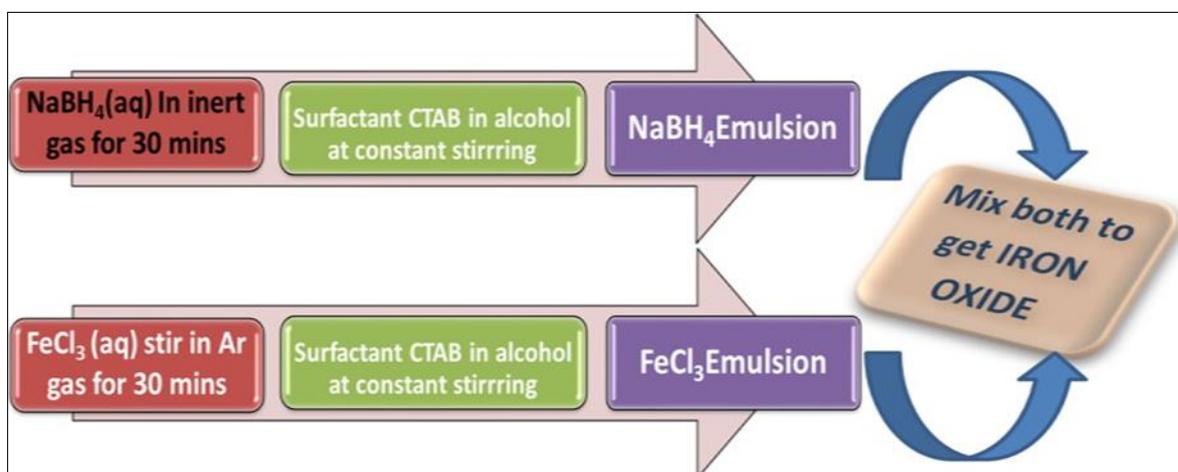


Figure 15 Mechanism for the formation of iron oxide nanoparticles by micro-emulsion method [170]

10. Hydrothermal method

As the name indicates hydrothermal or solvothermal method it is a wet chemical technique employed crystallization of an aqueous solution at high temperature and pressure about 130°C to 250°C and $0.3 - 4$ mega Pascal (MPa) respectively. This method mostly used to fabricate mono disperses narrow particle size distribution, and for desired shape. In comparison of the conventional methods with high temperature range requirements to design MNPs with good quality this method produce specks of uniform size, shape and with the prospects of further modification in size from $10 - 800\text{nm}$. [173-175]. Hydrothermal method is a solid liquid solution technique organometallic (Solid) i.e. metallic salt of linoleic acid along with an organic precursor in liquid phase i.e ethanol and water dispersed linoleic acid placed at high temperature and pressure and completed in 72 hrs. [176,177]. The temperature of the autoclave is monitored by Teflon coated stainless steel body containing cooler end equipped with the solute having final crystalline product.

Particle properties size, shape, coercivity all are directly affected by the reaction temperature, time, and precursor concentration [178,179]. Yu and his coworkers reported octahedral Zn ferrites (ZnFe_2O_4) synthesis by hydrothermal method. For this purpose, they use sheets of Zn metal in the reacting media of alkaline FeCl_2 at 180°C . The particle size obtained is 300nm [180]. Main disadvantages of this method are we cannot achieve the particle size of MNPs less than

10 nm. Monodisperse particles can persist only for short time during synthesis and the rate of reaction at any temperature is slow which only can be enhanced by the exposure of microwaves.

11. Sol gel Method

Sol gel method is another effective method for the synthesis of magnetic nanoparticles and water is act as a solvent. [181]. The molecular precursor in this method either undergoes hydroxylation or condensation to prepare a colloidal solution named as sol. This colloidal solution then dried to remove solvent and form a gel. This colloidal solution can be used either for the formation of fibers, powders, dense coating of nano material thin films/discs. Complete drying of this gel gives rise xerogel because it increases its crystalline nature and decreases the porosity of the final product which grind to give rise nano powder while on contrary incomplete drying leads to increase the porosity and the final product still is in amorphous form which is named as aerogel as shown in the figure (16) [183-185].

Main factors that affect the reaction parameters including rate of reaction, growth of material etc. are types of solvent, catalysts and precursors, reaction operating pH, temperature, types of additives and rate of stirring. Pure amorphous phase with monodispersity, theoretically programmed structures depend upon the reaction conditions along with the controlled particle size. Although its homogeneity and reaction parameters are controlled by still some post product treatments are needed to remove the impurities from final product. This method only confined to the 3D networks of the oxides. [184].

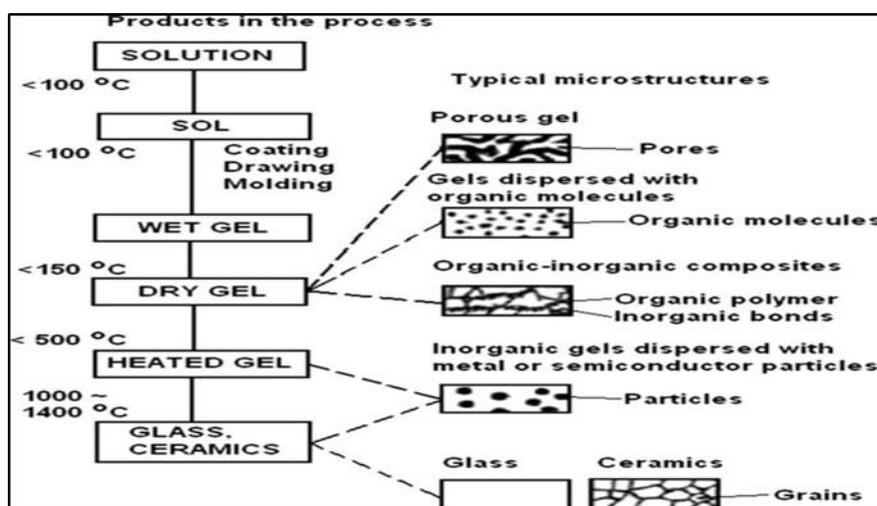


Figure 16 Flow diagram for the development of different types of nanoparticles [185]

12. Sonochemical method

This method is generally used for the synthesis of the material with rare stuffs [186]. Acoustic waves are employed to generate bubbles in the liquid which is the basis of implosive collapse of the bubbles and create acoustic cavitation. This implosive collapse results to increase the temperature and pressure of the given reacting mixture temporarily. Continuous water circulation at the interval of 5 min helps to maintain the temperature. [158,187,188]. Particle yield can be monitored by the choice of solvent and precursor, usually solvents used for this purpose having low vapor pressure and precursors are volatile in nature. An ultrasound probe usually titanium-based horn is used for the production of acoustic radiations of 20 kHz. Aggregates of amorphous powders prepared with low magnetization at room temperature. Following figure and flowchart illustrate the process of sonochemical method for the preparation of titania-based strontium ferrites. Serban and his coworkers prepare this ferrite by sonicating mixture of strontium and iron nitrate in an alkaline solution titania powder. After 2 hours sonication ferrite powder separated out from the reaction mixture.

Jeong et al. documented a sonochemical method to develop a composite material of silica particles coated single walled carbon nano tubes (CNTs). For this purpose, they disperse silica particles by sonication at atmospheric pressure and temperature in an organic mixture of para Xylene (P-Xylene) and Ferrocene. A schematic diagram is shown below [190]. This method can also use for the development of other carbon based materials i.e. fullerenes, graphene, mutli-walled CNTs etc. at appropriate conditions. [190]

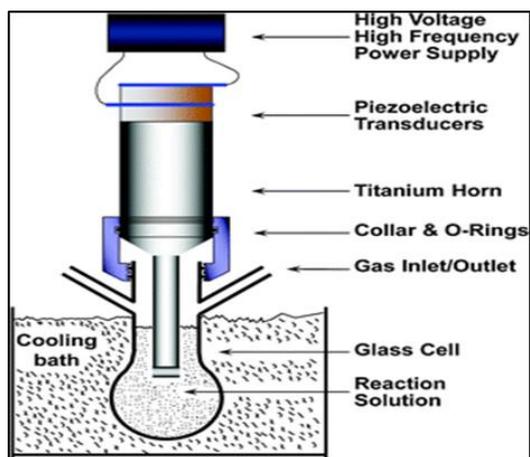


Figure 17 Process flow chart for the synthesis of strontium titania ferrites $\text{Sr Ti}_{0.6} \text{Fe}_{0.4} \text{O}_3$ by sonochemical method [189]

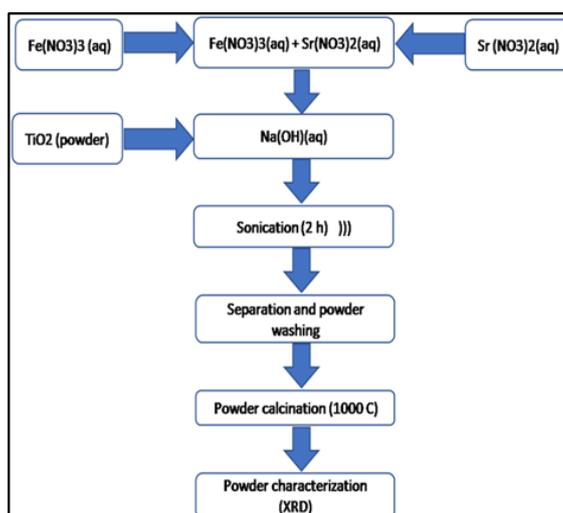


Figure 18 Apparatus used in sonochemical synthesis an ultrasonic horn of intensity 20kHz [190]

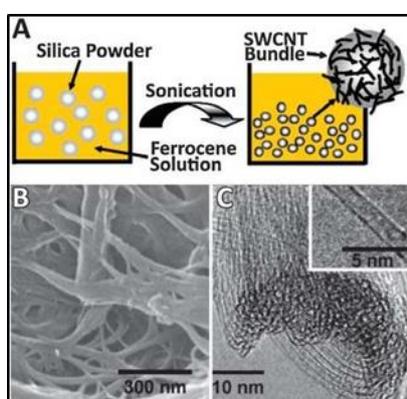


Figure 19 (A) Schematic representation of single walled carbon nanotubes coating on SiO_2 (B) SEM and (C) TEM images of the resultant particles [190]

13. Green synthesis

Green synthesis open a new door for the fabrication of magnetic nanoparticles as it is eco-friendly, safe to the environment no harmful products reinstate to the atmosphere economical and used for the fabrication nanoparticles.

Metallic particles fabricated by these methods show excellent magnetic properties by controllable particle size with narrow particle size distribution and all the reaction parameters can be monitored in a single pot. In these methods reacting material obtained from different plants (extracts, tissues, leaves and exudates etc.) microorganisms (bacteria, fungi, algae, yeast etc.) are used.[191,192] These biological materials are safe to use and prevent the external use of harmful chemicals for instance in green synthesis a number of non-toxic metal reducing agent including citric acid, ascorbic acids, flavonoids and enzymes involve reductase, dehydrogenase, oxidoreductase etc. are produced which favors the synthesis of magnetic nanoparticles. On the other hand, in case of microorganisms some species, especially some bacteria are biogenic in nature. This property helps them to sense the direction. Magnetotactic bacteria used to design protein coated iron oxide crystalline nanoparticles for biomedical application [193]. Following figure show the synthesis of silver nanoparticles from this method. [194].

14. Polyol method

This method used to fabricate fine and uniform particle size at pretty low temperature in the presence of oxygen containing compounds as precursor for example acetates, peroxides, ethers oxides and nitrates. These compounds are dissolved in polyols for instance ethylene glycol (EG) diethylene glycol or dihydroxy ethyl ether [196,197]. The procedure of this method employed to reflux the dissolved mixture of metal precursor in the presence of diol at the temperature in the range of 180 °C to 200 °C. As a result of this reaction a metal diol intermediate is formed and finally lead to the formation of metal nanoparticles by the reduction of metal nuclei. Particle size can be altered by operating this reaction even at higher temperature. This method is efficient for the fabrication of metal nanoparticles. Metallic oxide nano powders can also fabricate by simple modification of this method by adding water in the reacting mixture [198]. This method is very effective to synthesize the magnetic nanoparticles because it helps to prevent surface oxidation by developing number of hydroxyl groups on the particle surface. More over the use of organic solvent like polyol is also advantageous as it limited the problematic situation of hydrolysis faced in many cases of aqueous solvents. Following diagram is the simple illustration of polyol synthesis [199-201]. Number of functional groups plays a key role in the fabrication of nanoparticle. Oxygen containing groups especially hydroxyl group are worth mentioning amongst them fig 20 illustrates that aldehyde and hydroxyl groups from cellulose are used to design a composite based on polysaccharide coated silver nanoparticles. In this method cellulose act as template having both of these groups which are functional for reduction and stabilization of foretell particles.[19]

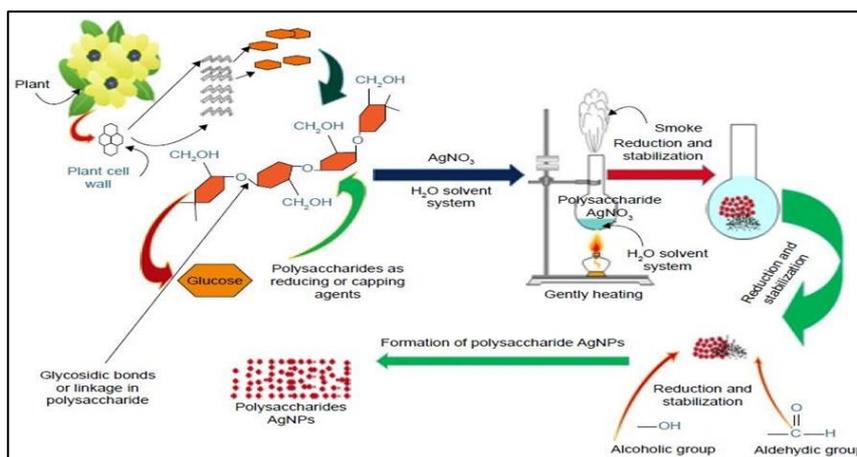


Figure 20 Schematic diagram for the development of Ag nanoparticles via green synthesis [194]

15. Conclusion

In conclusion, MNPs are versatile tools in biomedical science for various applications due to their newfangled feature in particular their effects on nano range. They demonstrate number of potential applications on the basis of these unique characteristics and aid to treat several chronic diseases i.e. cancer cells. Surface chemistry is an essential part attained by the help of surfactants and stabilizing agents, along with forecasted features including size, shape and composition as metals, metallic alloys, oxides carbides and graphene mediated composites. By interfacial coupling of these materials based on more than one component contributing several synergic features helps to promote them in future applications. Moreover, surface functionalization makes them promising applicant in various fields i.e., tissues and scaffold engineering and bone tissue engineering etc. Mostly they act as anti-thrombogenic materials, as antibacterial agents,

drug carriers and cardiac muscle actuators. Number of queries related to cytotoxicity and biocompatibility are still exist and the main obstacles for MNPs to use them in clinical applications. It is needed to explore the new doors to get the ecofriendly, operative and economical fabrication routs to design MNPs with innovative properties, so that we can acquire maximum benefit from these distinctive biomaterials to serve the humanity by improving health standards and reducing the harmful diagnostic and therapeutic effects of several uncontrollable health issues.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors of this article report no conflicts of interest throughout the work.

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