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An Overview on Synthesis and Applications of Iron Oxide Nanoparticles

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Abstract: Iron oxide nanoparticles especially magnetite and maghemite find various applications in the biomedical as well as engineering field due to its biocompatibility and non toxic nature. There are various applications especially in the field of biomedicine. Due to the wide applications of iron oxide nanoparticles its demand in various fields is increasing considerably. In this review, we have made an attempt to present an overview of the synthesis methods and applications of iron oxide nanoparticles. They are used in the biomedical field as contrast agents in MRI, for targeted drug delivery, hyperthermia etc.Magnetic nanoparticles are of great importance due to its unique magnetic property in the nanoregime. They exhibit superparamagnetic behavior that is they are magnetic only in the presence of magnetic field, which makes it a suitable candidate for research now and then. Also among all magnetic nanoparticles, magnetite and maghemite gain special attention because of its biocompatibility and non-toxic nature. Hence here a discussion is focusedabout the properties to be satisfied by iron oxide nanoparticles to be used for various applications.

Keywords: Iron Oxide, Superparamagnetism, Biomedical Applications, Nanostructures.

1. Introduction

Core-shell nanoparticles are the most important type of multicomponent nanoparticles which is studied extensively by researchers. The properties of either the core or the shell or both are used for various applications. Core-shell particles are said to exhibit improved physical and chemical properties over their single-component counterparts, and hence are potentially useful in a broad range of applications[1]. Of all core-shell nanoparticles, that with magnetic core is the most important in various fields ranging from engineering to biomedical applications[2]. The attraction towards the magnetic core is due to the ease of functionalization, which can impart new properties to the nanoparticles. The molecules which are normally used for surface functionalization include drug molecules, fluorescent molecules, polymers and organic molecules which can be hydrophobic or hydrophilic. The most commonly used core materials are magnetite (Fe_3O_4) and maghemite (Fe_2O_3), which have unique magnetic properties, when brought down to nanoscale. Core-shell nanoparticles with superparamagnetic nanoparticles are promising materials, where, the coating or the shell can stabilize magnetic nanoparticles, leading to better dispersion and biocompatibility. The surface shell can be further modified with functional molecules to tune the properties of core-shell system for various applications.

Of all iron oxides, γ- Fe_2O_3 and Fe_3O_4 exhibits superparamgnetic nature at nanoregime, whereas they are ferrimagnetic in its bulk form. They are classified as inverse spinel structure, where the cations occupy the tetrahedral and octahedral site resulting from the cubic close packed array of O^{2-} anions. Magnetite has Fe^{2+} as well as Fe^{3+} and maghemite having Fe^{3+} alone. In magnetite, half of Fe^{3+} is placed in the Td-site and half in Oh-site, apart from Fe^{2+} occupying the Oh-site[3].

Of all the magnetic materials, magnetite is the best biocompatible material. The biocompatibility and cytotoxicity of iron oxide nanoparticles are well studied. Iron present in SPIONs can be metabolized, stored and transported inside the body by proteins, which include ferritin, transferring, hemosiderin, such that the metabolized iron can be incorporated into the iron pool[4]. In a rodent model, no adverse effect was observed up to 100 mg Fe per kg, and even an injection of 600 mg Fe per kg was found to be not fatal[5]. *In vivo* studies also prove that SPION are non-toxic. Mice treated with magnetic nanoparticles for four weeks proved that the nanoparticles were equally distributed among organs in a time-dependent manner[6]. Also nanoparticles of size less than 50 nm were capable of crossing the blood brain barrier (BBB) and reach the brain, without inducing any toxicity[7].Uncoated nanoparticles induce greater toxicity compared to the coated ones. A study by Mahmoudi*et al*[8] showed that the uncoated nanoparticles induce greater toxicity than the biocompatible polyvinyl alcohol (PVA) coated nanoparticles. SPIONs are considered to be benign to the body because iron oxide is dissolved under acidic conditions, and the resulting iron ions can be fed into the natural iron storage which is 3-5 g iron for an adult human[9].

The properties like size, surface charge, hydrophilicity*etc.* are important in determining the *in vitro* and *in vivo* fate of magnetic nanoparticles[10]. Once the particles are injected into the blood stream, they are rapidly coated with plasma proteins and the process is called opsonization. This results in the removal of nanoparticles from the body. Negatively charged and neutral particle surfaces provide the maximum blood circulation time[11].

Bulk-like properties, such as saturation magnetization, coercive field, and Verwey transition are observed for magnetite particles of size 150 nm [12]. Magnetite crystals with a particles size of 5 nm are observed to display superparamagneticbehaviour at room temperature, with transition to a blocked state at $T_B$of about 45 K, which depends on the applied field [13]. The finite size has various effects on the structural and magnetic ordering of nanoparticles. The most studied phenomena of finite size effect in magnetic nanoparticles are single domain limit and superparamagnetism.Larger magnetic particles possess multi-domain structure wherein the areas of uniform magnetization are separated by domain walls. When the sample size is reduced, there is a critical volume below which the formation of domain wall ceases. As the size decreases, the magnetic material changes from a multi-domain structure to a single domain structure. The obvious change that happens when moving from bulk to nanomaterials is the reduction of coordination. When the size of a particle with magnetic atoms is small enough, the energy necessary to divide itself into magnetic domains is higher than the energy needed to remain as a single domain. The energy barrier to be overcome to change from spin-up to spin down state is proportional to magnetic anisotropy constant K and volume of the magnetic particle V. In bulk materials, the magnetic anisotropy energy is much larger than the thermal energy k_BT, whereas in nanoparticles, the thermal energy is sufficient to overcome the anisotropic energy barrier. This rapid magnetic fluctuation in the nanoparticles lead to zero net magnetic moment, and this behavior is called superparamagnetism[14]. The magnetic properties like coercivity and saturation magnetization change as a material goes from bulk to nanoscale. The effect of size on saturation magnetization is explained on the basis of the presence of disordered surface spin. In bulk cases, since the disordered surface layer is minimal compared with the total volume of the magnet, the surface spin canting effects are negligible. Upon reduction of the size of magnetic materials to nanoscale regime, the surface canting effects are pronounced and the value of saturation magnetization of a particle, (m_s)

$$m_s = M_s(1 - \frac{6t}{d})$$

where d is the diameter of a particle, $M_S$is the saturation magnetization of bulk materials, and t is the thickness of the disordered surface layer [15]. For particles of size less than 5 nm, the change in $m_s$value becomes more noticeable because the internal spins of the nanoparticle also start to be canted along with surface spins due to increased interactions between the surface and internal spins.

General methods of synthesis of core-shell structure

Uncoated iron oxide nanoparticles have very low dispersibility in different solvents and also aggregate faster. Biomedical applications demands particles dispersed in aqueous media. Derjaguin-Landau-Verwey-Overbeek

(DLVO) theory predicts theoretical stability of nanoparticle dispersions [16]. According to this theory, the total interaction energy is determined by the sum of van der Waal's attractive (V_A) and electric double layer repulsive (V_R) forces that exist between particles as they undergo Brownian motion. Stability of magnetic nanoparticles can be achieved by two types of repulsive forces: steric and electrostatic. In the case of steric stabilization, layers of large molecules are adsorbed on the surface of the nanoparticles to prevent the attraction. Electrostatic stabilization originates from the repulsive electrostatic force, which nanoparticles experience, when they are surrounded by a double layer of electric charges. The magnetic nanoparticles have to be coated with a suitable surfactant to prevent their aggregation both in the biological media as well as in the presence of a magnetic field. Nanoparticles with large surface area to volume ratio tend to agglomerate to reduce their surface energy by van der Waal's attraction between the particles. In the case of magnetic systems, dipole-dipole interaction also promotes the aggregation, resulting in larger particles with non-uniform size distribution. Thus, it is essential to cap the surface of magnetite nanoparticles to avoid the aggregation of the nanoparticles.

Also the surface of magnetite nanoparticles has Fe^{2+}, it is necessary to coat magnetite nanoparticles with inert materials to protect them against oxidation. Thus, coating the surface of the nanoparticles has multiple advantages: reduce the leaching of the core nanoparticles and stabilize the nanoparticles at physiological pH. Nanoparticles can be surface functionalized by polymeric molecules, inorganic materials or monomeric stabilizers [17]. Coating nanoparticle with drug molecules, which have characteristic biological activities, is of importance[18]. The bioactive molecules can be effectively conjugated to the surface of the nanoparticles by covalent bonding. Also stabilization of nanoparticles with different materials, especially drug molecules enables them to be used as multifunctional platform. So far most of the reports in the literature, discusses about the coating of SPIONs using surfactants, polymers and inorganic materialsIron oxide nanoparticle can be synthesized by various methods ranging from physical methods such as mechanical grinding and biomineralization processes to wet chemical methods such as co-precipitation[19], microemulsion[20], hydrothermal[21], sol-gel[22], electrochemical[23], sonochemical[24], polyol method[25], thermal decomposition [26], *etc*. Wet chemical methods offer great advantages of controlling the particles size, particle size distribution, degree of crystallinity, and phase purity. Wet chemical methods are solution based and are classified into two categories: hydrolytic and non-hydrolytic routes. Hydrolytic synthesis relies on the hydrolysis of ferrous-ferric precursors, whereas non-hydrolytic route follows the pyrolysis of iron-organic compounds. Water molecules have very high affinity towards the ferric and ferrous ions. The presence of water in the hydrolytic routes results in very complicated surface binding situations involving water and hydroxyl ions, which not only affect the surface coating by stabilizing agents, but also vary the particle surface charge density and surface chemical composition. The high affinity of water to iron ions can be explained on the basis of Hard-Soft acid-base (HSAB) concept [27]. The iron atom on the magnetic iron oxide surface is a hard Lewis acid, while compounds containing O or N atoms, such as water, alcohols, ethers, ketones, ammonia, amines, imines, *etc*, are hard Lewis bases. Therefore, based on the HSAB theory, hard acids react faster and form stronger bonds with hard bases and vice versa[28]. In iron oxide nanoparticles, the surface iron atoms behave as Lewis acids and bind with species that donate a pair of electrons. In aqueous solution, iron atoms coordinate with water, which dissociates readily leaving the surface of magnetite nanoparticles functionalized with hydroxyl group. Hydroxyl groups being amphoteric, reacts with both acids and bases. Thus, by tuning the pH of the solution medium, the surface charge of magnetite nanoparticles can be varied [29]

. Co-precipitation of Fe^{3+} and Fe^{2+} salts in the presence of a base is the classical method to prepare magnetite nanoparticles. Iron oxide nanoparticles can be prepared on a large scale by this method. The equation for the formation of magnetite can be written as

$$2Fe^{3+} + Fe^{2+} + 8OH^- \longrightarrow FeO.Fe_2O_3 + 4H_2O$$

The method can yield large amount of nanoparticles, depending on the volume and concentration of the reagents. The size and shape of the produced nanoparticles can be tailored by adjusting the pH, ionic strength, temperature, nature of the salts and initial precursor concentration. Addition of a surfactant (such as citric,

gluconic or oleic acid, dextran, starch, *etc*) during the formation of magnetite can control the size and size distribution. Two stages are involved in the co-precipitation process: an initial short burst of nucleation when the concentration of precursor reaches critical supersaturation and a slow growth of nuclei by diffusion of the solutes to the surface of the crystal. Co-precipitation method can be done by two ways: the normal co-precipitation and the reverse co-precipitation methods[30]. In the first case, an alkaline aqueous solution is added to the mixediron salt solution. This results in a rapid change in the pH, locally, which controlsthe size, thereby affecting the size distribution. The reaction finally ends with apolydisperse size distribution. Reverse co-precipitation can overcome the drawbacksof the normal co-precipitation method, wherein an acidic solution of themetal salts is added to the alkaline solution to get the metal oxide nanoparticles.The rate of addition of the salt solution, the pH and the reaction temperature canbe varied to vary the size and size distribution. Magnetite nanoparticles can be functionalized by two ways: *in situ* co-precipitation and post-synthesis functionalization.

In *in situ* co-precipitation technique, a mixed metal-ions precursor is added to the base solution containing the capping agent. The molecule to be attached to the surface of the nanoparticle is dissolved in the base and the metal precursor solution is added to the base. The nanoparticles are formed in the presence of the capping agent (bioactive molecule/drug) and hence a higher uniformity in size and smaller particle size is expected by this method of synthesis. In post synthesis functionalization method, the magnetite nanoparticles in their naked form are first synthesized using the reverse co-precipitation technique. The pH of the nanoparticle dispersion is then adjusted before adding the capping agent, and the resultant dispersion is stirred for specific time for the bond formation between the surface of the nanoparticles and the capping agent.

Eventhough co-precipitation is an economic method to synthesis magnetite nanoparticles on large scale, the method yields nanoparticles which are polydisperse. High temperature decomposition of organometallic iron precursors yields particles of monodisperse size with hydrophobic surface. The method uses high boiling solvent and the iron precursor is decomposed at high temperature. The size of the nanoparticle is tailored by changing the concentration of the precursor and surfactant. Oleylamine and oleic acid are the most commonly used surfactants for thermal decomposition. Sun *et al.* reports the synthesis of magnetite nanoparticles using iron(III) oleate as precursor , which is heated at 300^{o}C in the presence of oleylamine, oleic acid, 1,2-hexadecanediol and benzyl ether. The size of magnetite nanoparticles obtained through this process is 4-8 nm[31]. Metal precursors which are zero valent give metal nanoparticles, which can be further, converted to metal oxide. Hyeon*et al* reports the synthesis of maghmeitenanoparticle from iron carbonyl in the presence of oleic acid and octyl ether[32]. But the synthesis reported yields water insoluble iron oxide nanoparticles. To synthesize magnetite nanoparticles with hydrophilic surface Li *et al.* refluxed ferric chloride in 2-pyrrolidone at 245^{o}C [33]. Monodisperse water soluble magnetite nanoparticles can also be prepared by refluxing iron acetylacetonate in triethylene glycol at elevated temperatures [34].

Hydrothermal or solvothermal reactions are performed in autoclave where the pressures can be higher than 2000 psi and temperature higher than 200^{o}C. Magnetite nanoparticles with controllable size and monodisperse size distribution can be achieved by simple one-pot hydrothermal synthesis [35,36]. The fate of the resulting nanoparticles is decided by time, temperature and solvent[37].

Classification of iron oxide core-shell structures

The core-shell structure of magnetic nanoparticles can have shell or coating which can be organic molecule, inorganic moiety or metal nanoparticles. The major role of the shell in the case of magnetite nanoparticle is to prevent oxidation of iron on the surface, to interact with the physiological environment and to form stable dispersion in suitable solvent.The organic molecules can be polymers, polymers, and small molecules. Literature reports the synthesis of magnetite nanoparticles coated with dextran[38], chitosan[39,40], polyethylene glycol (PEG)[41, 42], citric acid[43]*etc*.The bond formation between nanoparticle surface and these molecules are usually pH dependent. The point of zero charge for magnetite is observed at pH 6.8 [44]. Below this pH, protonation of the particle surface occurs, leading to the formation of ≡Fe-OH_2^+ moiety, and above this pH deprotonation of the particle surface occurs, forming ≡Fe-O^-[45].

PEG coated nanoparticles have been directly attached to the nanoparticle via *insitu* co-precipitation[46]or *via* ligand such as silane[47]. The PEG attaches to the nanoparticle surface by its functional groups and it has free groups on its surface which can readily interact with the bioentity or drug molecules to act as drug carrier [48-50]. Dextran which is a polysaccharide is coated on to the SPIONs and most of them are clinically approved[51, 52]. Moldaye*t al.* in 1982 first prepared dextarn coated SPIONs following *in situ* technique[53]. Chitosan is a cationic, hydrophilic polymer, which is non-toxic, biocompatible molecule, largely used in coating SPIONs[54]. They can be conjugated to nanoparticle surface both directly as well as by linker[55-57]. Chitosan is best suited for gene delivery, due to the cationic nature, which allows it to interact with the genetic material.

The iron oxide-fluorescent core-shell nanoparticles also are of importance. There are various approaches to attach fluorescent molecules to magnetite nanoparticles. The fluorescent molecules can be incorporated in magnetite-silica core-shell nanoparticles. Silica shell acts as an effective barrier against the interaction of magnetic core and fluorescent molecule, which will in effect prevent the quenching. Also the silica shell will reduce the toxicity of bare nanoparticles. Silica shell can also be easily functionalized or it is easy to incorporate fluorescent dyes or quantum dots[58]. The organic dyes are incorporated during coating process thereby forming dye incorporated silica shell on the magnetic core[59, 60].

Apart from these, metal such as gold has also been used to prepare magnetic core-shell structures. Gold coated magnetic nanoparticles are stable under acidic and neutral pH conditions, but a gold shell will considerably reduce the magnetic property of magnetite core[61, 62]. Apart from inorganic metals, inorganic oxides like silica shell are also used to design magnetic core-shell particles with improved physical and chemical properties. Silica shell of various thicknesses can be constructed on magnetite nanoparticles, thereby tuning the interaction between the magnetite core[63]. The silica coated magnetite nanoparticles ranges from 1-2 nm to 150 nm depending on the method of synthesis [64, 65].

Applications of magnetic core-shell structures

A. Contrast agents in MRI

MRI scanners have become indispensable diagnostic tools in almost all the major research and medical institutions in the world, following the Nobel winning discovery of this new non-invasive technique by Prof P. Lauterbur in 1972, which is an image formation technique by reconstruction from a number of NMR measurements [66]. The technique relies upon the relaxation of water protons, which depends upon the magnetic field, pulse sequence and on the heterogenous distribution of water in an organism [67, 68]. Even though MRI is known to be an efficient imaging technique, it is always difficult to differentiate between the diseased and normal cells in the same tissue because of the identical environment experienced by the relaxing protons. To increase the sensitivity of imaging, contrast enhancement agents can be used and they efficiently vary the relaxivity of water protons. Based on the relaxation mechanism, they are classified as positive (T_1) and negative (T_2) contrast agents [69]. Inorganic paramagnetic complexes based on Gd^{3+} and Mn^{2+} are used as T_1 contrast agents[70] and superparamagnetic iron oxide nanoparticles act as T_2 contrast agents [71]. The r_2/r_1 value decides whether a material can be used as T_1 or T_2 contrast agent. The superparamagnetic iron oxide nanoparticles (SPION) show higher ratio and is classified as T_2 contrast agents, whereas ultra-small superparamagnetic iron oxide nanoparticles (USPION) and gadolinium chelates show lower ratio (<2 at 0.5 Tesla) and are classified as T_1 contrast agents [67]. Magnetic nanoparticles in a tissue environment, when subjected to a magnetic field, produce a heterogeneous field gradient allowing the water protons to diffuse. The dipolar coupling between the magnetic moments of water protons and that of the particles leads to spin dephasing and T_2 relaxation, resulting in reduced signal intensity, and hence termed as negative contrast enhancement [72]. Iron oxide nanoparticles with core diameter less than 10 nm (USPION) produces positive contrast enhancement in T_1 weighted images[73]. Magnetite nanoparticles are already marketed as MRI contrast agents in different names such as ferridex, ferrumoxtran, resovist*etc*[74, 13].

To be used as MRI contrast agents, the nanoparticles should have colloidal stability at physiological pH of 7.4 and ionic strength of 0.17 M [45]. Apart from pH conditions, the stability of nanoparticles against the wide variety

of proteins under physiological conditions also need to be considered. To minimize the aggregation of nanoparticles by binding with proteins *in vivo* is done by coating the nanoparticles with anti-biofouling polymers. PEG is known to the best anti-biofouling protein. PEG coated magnetite nanoparticles synthesized from iron acetyl acetonate was found to have long blood circulation duration [75].

Size is a major factor which decides the blood circulation time of SPIONs, hence iron oxide based contrast agents are classified as ultra-small SPIONs (USPION) and SPIONs. Particles of size approximately less than 40nm are classified as USPIONs[74].

B. Targeted drug delivery

Magnetic drug targeting and delivery using magnetic core is a promising field to avoid the drawbacks of conventional chemotherapy. In magnetically targeted drug carrier system, the magnetic nanoparticles carrying the anti-cancer drug is injected into the patient's body. An external magnetic field is used to localize the drug carrier at the tumour site (figure 1). The drug is then released from the carrier, either by enzymatic activity or changes in physiological conditions such as pH or temperature[76, 77].

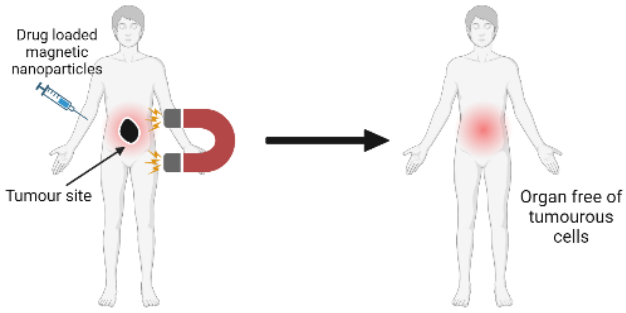

Figure 1: Release of drug using magnetic nanoparticles at the tumour site. The drug loaded SPIONs are directed to the tumour site using an external magnetic field.

Drug delivery can be done by various materials like organic, polymeric, magnetic nanoparticles, *etc*. Of these, organic systems which include polymeric nanoparticles, liposomes and miscelles have limited chemical and mechanical stability, susceptible to microbiological attack and suffer from inadequate control over drug release rate[78]. Due to these demerits, inorganic nanovectors are of intense research. Magnetic nanoparticles (MNPs) are of interest in drug delivery because (i) they can be visualized as they are used as contrast agents in MRI, (ii) they can be controlled with an external magnetic field, and (iii) can be heated in an external magnetic field for triggered drug release and to produce hyperthermia/ablation of tissues. For effective delivery of drug to tumour tissues, nanoparticles must have the ability to remain in blood for a considerable time without being eliminated. The optimal size of magnetic nanoparticles used in drug delivery ranges between 10-100 nm [79]. Large objects are rapidly cleared and highly charged nanoparticles have a tendency to attract the immune system and thereby getting cleared from the body[78]. For magnetic drug targeting, a drug is bound to a magnetic compound, introduced in the body and then concentrated in the target area by means of a magnetic field, which can be generated by an internally placed permanent magnetic field or an external applied field. Targeted delivery would minimize toxicity due to the direct administration at the regions of interest in 10-100ppm level [80,81].

Most of the literature reports the delivery of anticancer drugs by coating a polymer on the magnetite nanoparticles which can carry the drug to the target site. The model drugs studied are doxorubicin (DOX) and curcumin (CUR). Ramanujan*et al.* reports polyvinyl alcohol (PVA) coated magnetite nanoparticles as drug carriers of doxorubicin. The study showed that ~45 % DOX was released in 80 hours and the coated nanoparticle was found to be a promising candidate for targeted drug delivery[82].

Hollow magnetite nanoparticles were prepared by Wang *et al.*to deliver hydrophobic drugs. Compared to mesoporous silica, hollow structured nanoshells have larger fraction of volumes in their inner space, thereby

showing higher loading capacity. DOX and CUR has been used as a model drug. pH dependent drug release was observed for both the drugs [83].

Literature reports the use of SPIONs wherein a triple-responsive (pH, magnetic field and redox) nanogel has been fabricated to effectively deliver the anticancer drug (DOX) to the cancerous cell. The nanogel has been fabricated by esterification reaction between the '-COOH' group of the pre-synthesized amphiphilic tetra-armed block copolymer, pentaerythritol-poly(ε-caprolactone)-b-polyacrylic (Pe-PCL-b-PAA) and '-OH' group of the redox-responsive crosslinker, 2-hydroxyethyl disulfide. These nanogels are further ornamented with aminosilane coated magnetic nanoparticles to impart the magnetic field responsive characteristic[84-86].

Chattopadhyay*et al*, reports the synthesis of a novel magnetically active polymeric micelle (MAPM) for magnetically targeted controlled drug delivery. The anticancer drug (DOX) was encapsulated into the MAPM and the magnetic field triggers the cell uptake of MAPM micelles preferentially toward targeted cells compare to untargeted ones[87].

C. Magnetic hyperthermia

Heating of certain organs or tissues to a temperature of 41-46^{o}C for cancer therapyis calledhyperthermia, which is considered as a supplementary treatmentto chemotherapy, radiotherapy and surgery in cancer treatment[88]. Experimentalinvestigations of the application of magnetic materials for hyperthermiawas done by Gilchrist in 1957, by heating various tissue samples with 20-100nm size particles of γ-Fe_2O_3 exposed to a 1.2 MHz magnetic field[89]. Whenmagnetic nanoparticles are exposed to a varying magnetic field (AC field), heatis generated by three ways namely hysteresis loss, Brown relaxation and Neel'srelaxation[90]. This heat generated can destroy the tumour cells as these aremore sensitive than normal tissues. Large magneticmaterials with multi-domainstructure respond to an alternating magnetic field by hysteresis power loss.Whereas, superparamagnetic nanoparticles generate heat by relaxation processesnamely Neel's and Brownian relaxation[91]. When a ferrofluid is removed from amagnetic field, its magnetisation relaxes back to zero due to the thermal energy of the environment. The relaxation can take place either by rotation of the moment within each particle called the Neel's relaxation or by the rotation of the particles known as the Brownian relaxation[92]. The relaxation time $\tau_B$for Brownian relaxation depends on the hydrodynamic properties of the fluid whereas τ_N, the Neel's relaxation time, is determined by the magnetic anisotropy energy of the superparamgnetic nanoparticles. The Neel's relaxation time (τ_N) is given by the equation

$$\tau_N = \tau_0 exp \frac{KV_M}{k_B T}$$

nd the Brownian relaxation time (τ_B) is given by

$$\tau_B = \frac{3\eta V_H}{k_B T}$$

and the effective relaxation time (τ) is given by

$$\tau = \frac{\tau_B \tau_N}{\tau_B + \tau_N}$$

where $\tau_0 = 10^{-9}$ sec, K is the anisotropy constant, $V_M$is the particle volume, $k_B$is the Boltzmann constant, T is the temperature, η is the viscosity and $V_H$is the hydrodynamic volume of the particle. The specific adsorption rate (SAR) determines the efficiency of heating of a tissue which is defined as the rate at which electromagnetic energy is absorbed by a unit mass of a biological material expressed in Watt per kilogram. The SAR is proportional to the rate of temperature increase given by the equation [93]

$$SAR = C_e \frac{dT}{dt}$$

where$C_e$is the specific heat capacity of the sample.

D. Cell separation

The *in vitro* applications include separation and detection. In magnetic cell separation, the desired cells are tagged or labeled with a magnetic marker. The magnetically marked cells are separated from the unmarked cells by a magnetic field. Finally, the cells are quantified by measuring their magnetic properties [94]. Tagging is done by chemical modification of the surface of magnetic nanoparticles with biocompatible molecules like dextran, polyvinyl alcohol, *etc*[95]. The surface coating provides a link between the magnetic entity and the target site on a cell and also they provide stability to the magnetic fluids. The magnetically labeled material is separated from the solution by immobilizing the labeled part by a magnetic field. Magnetic separation is a highly sensitive technique for the selection of rare tumour cells from blood. It is proven that malarial parasites in blood samples can be efficiently detected either by utilizing the magnetic property of parasite or by labeling the red blood cells by a specific magnetic fluid[96].

Fluorescent labeled protein avidin has been separated in vitro by biotin coated charged magnetite nanoparticles[97].

E. Multifunctional applications

The biomedical applications of magnetite core-shell structure are of importance as discussed above. Magnetite nanoparticles with appropriate surface coatings find its application in various fields. But simultaneous use of these nanomaterials in various applications is still under intense research. SPIONs coated with suitable surfactants are marketed as contrast agents in MRI. The nanoparticles can also be used as a carrier of the drug to the target site.

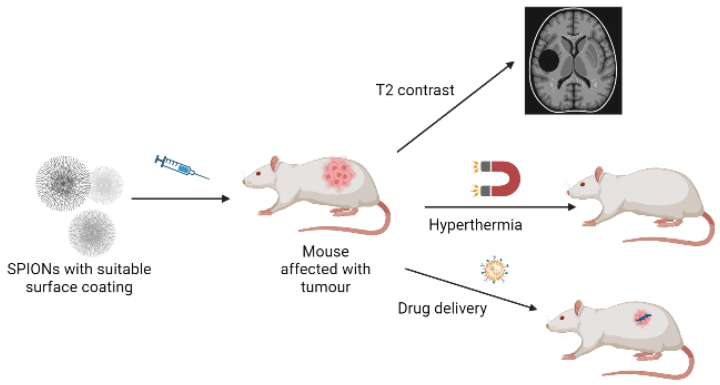

Figure 2: Drug loaded SPIONs injected to the tumour site can be used for multifunctional applications.

The same nanoparticles core can induce heat at the diseased site, thereby killing the tumour cells, which is hyperthermia. Hence careful design of magnetite core with suitable shell can be simultaneously used as contrast agent, drug delivery and hyperthermia (Figure 2).

Vinod*et al.* reports the synthesis of magnetite nanoparticles coated with pluronic F-127 polymer via oleic acid, which have dual functional property. The aqueous dispersion of coated nanoparticle acts as carrier of anticancer drug DOX and paclitaxel, by retaining the MRI property. The nanoparticle shows prolonged blood circulation time in mice[98].

Magnetic fluorescent nanocomposite can be simultaneously used as diagnostic and therapeutic tool. The magnetic core can be used for MRI imaging and the fluorescent shell can be used for fluorescent imaging[99, 100]. Combination of Fe_3O_4 and dyes also offers combined magnetic resonance imaging and optical imaging[101]. Iron oxide porphyrin core-shell nanoparticles are proved to be an efficient candidate for bimodal imaging [102].

Apart from fluorescent shell, core-shell nanoparticles, were core is magnetite nanoparticles and shell is either a drug carrier or the drug itself is simultaneously used in biomedical applications[103].

F. Catalysis

Metal nanoparticles are of interest in catalysis as the high surface area-to-volume ratio facilitates the use of small amount of expensive catalyst[104]. The major challenge faced in using the noble metal nanoparticles in catalyst industry is the difficulty in separating and recycling them completely from the products.

Magnetic nanoparticles forming stable fluids are of great importance in catalysis. Catalysts involved in a liquid phase reaction are recovered by time consuming tedious process like centrifugation and filtration. Magnetically separable catalyst makes it recovery easier. Thus catalyst with inner magnetic core and outer shell of the catalytic species makes the process much easier as they can be separated by an external magnetic field. The nanomagnetic system carrying the catalyst has the additional advantage of higher reactivity and high dispersibility. Magnetic nanoparticles with core-shell structure for catalytic applications is designed such that the shell is the catalyst and the core which is magnetic can act as an anchor to separate and recycle the catalyst. Ruthenium complex bound magnetite nanoparticles were synthesized for catalytic applications, which showed 100% conversion of ketones to asymmetric alcohols even after recycling it nine times[105]. Magnetite nanoparticles coated with silica has also been proved to be a support for various catalysts for organic reactions [106-108].

G. Water purification

Contamination of water with toxic heavy metal ions like Hg(II), Pb(II), Cr(III), Cr(VI), Ni(II), Co(II), Cu(II), Cd(II), Ag(I), As(V) and As(III) is becoming a severe environmental and public health problem. Use of nanoparticles for treatment of industrial waste water is another potentially useful application. Techniques like adsorption, precipitation, ion exchange, reverse osmosis, electrochemical treatments, membrane filtration, evaporation, flotation, oxidation and biosorption processes are extensively used for environmental detoxification[109]. Of all, adsorption is the most effective method for the removal of toxic metal ions and bacterial pathogens from water. The use of magnetite nanoparticles as adsorbents in water treatment provides a convenient approach for separating and removing the contaminants by applying an external magnetic field [110]. Tao *et al* developed magnetic mesoporous silica which had an ideal adsorptive and catalytic ability to remove several dyes from water under visible light irradiation[111]. Qiao*et al* developed octadecyl functionalized magnetite silica core-shell nanocomposite for the adsorption of volatile organic metabolites like hexanal, heptanal, decanal, benzaldehyde, 4-heptanone, 5-methyl-2-furfural and phenol, which are potential biomarkers of cancer from urine [112]. Tan *et al.* developed magnetite silica core-shell microspheres for efficient absorption of uranium[113]. Cyclodextrin functionalized magnetite nanoparticles are also reported to be an efficient adsorber of waste from water [114,115].

2. Conclusions

In conclusion, iron oxide nanoparticles with iron oxide as core and with a moiety as shell will act as an efficient candidate for various biomedical and engineering applications. Here, in this review an insight into the important applications of magnetite nanoparticles is being studied. The nanoparticles due to its unique magnetic properties are being used in applications such as MRI, drug delivery, cell separation etc. It is an excellent candidate due to the unique size dependent magnetic properties. The blood residence time which is an important factor for its use in biomedical application is also being discussed. The properties of iron oxide nanoparticles to be used in bio-applications need to be biocompatible, water soluble, non-toxic etc., which are being discussed in detail in the present review. Hence forth, the review presents an overall development in the synthesis and application of magnetite nanoparticles. The discussed nanoparticles are a potential candidate for biomedical and engineering applications. Eventhough SPIONs are marketed as MRI contrast agents, the clinically approved MRI contrast agents such as Feridex and Resovist have reported that these NPs are biocompatible and lack cytotoxicity. But emerging studies have begun to highlight aberrant cellular responses including DNA damage, oxidative stress,

mitochondrial membrane dysfunction and changes in gene expression as a result of SPION exposure, all in the absence of cytotoxicity. Hence biomedical field demands a detailed study of the biocompatibility of SPIONs.

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