CHAPTER – 1

Introduction

1.0 Introduction

Magnetic nanoparticles (MNPs) are the most important class of materials for several bioapplications such as magnetic resonance imaging, magnetic hyperthermia, drug delivery, tissue engineering, and cell separation [1–4]. For these applications, high saturation magnetization (M_S) valued MNPs (transition metals, e.g. Fe, Co, Ni or metal oxides e.g. Fe_3O_4, γ-Fe_2O_3) could be the best choice [5]. But, the high toxic nature and sensitivity towards oxidation, limit the usage for practical applications of metallic materials[2]. Thus, appropriate surface treatments for such metallic nanoparticles are necessary. In contrast, iron oxides (Fe_3O_4 and γ-Fe_2O_3) are less sensitive to oxidation and have high biocompatibility[4,6].Further, they are easy to get functionalize[7]. Hence, these oxides are very promising candidates for a wide range of bioapplications. Amongst the two, magnetite (Fe_3O_4) or its substituted counterpart, have shown better efficiency in aforesaid biomedical uses because of their relatively higher M_S values[8].

The magnetic hyperthermia using magnetite nanoparticles provides localized heating at the targeted tumoural tissue due to the influence of external alternative current (AC) magnetic field[9]. This localized heating under strictly controlled conditions becomes feasible for treating the cancer cells. It also preserves the healthy cells from heating during treatment which reduces the possible side effects by hyperthermia with magnetite nanoparticles. For the practical applications, the temperature required during magnetic hyperthermia (MHT) should be in the range of 42 - 46 °C. As the Curie temperature (T_C) of undoped magnetite nanoparticles is ~580 °C thus the continuous rise in the temperature during MHT limit their usage[10]. On the other hand, the MNPs with T_C near 50 °C have been developed but their poor biocompatibility and low M_S values disqualified them for such applications.

The present thesis discusses about achieving the stabilization of temperature (T_S) in the range of 42-46 °C using tetravalent (Zr or Hf), trivalent (Al), divalent (Zn) or monovalent (Li) substituted magnetite nanoparticles during magnetic hyperthermia.

1.1 Crystal structure of Magnetite

Magnetite (Fe_3O_4) has an inverse spinel crystal structure with face centered cubic unit cell [11]. The oxygen ions are located regularly in cubic close packed positions along the [111] axis. The oxygen ion array contains holes partially filled with ferric (Fe^{3+}) and ferrous (Fe^{2+}) ions. The unit cell is comprised of 56 ions having 32 O^{2-} anions, 16 Fe^{3+} and 8 Fe^{2+} cations. The chemical formula of magnetite (Fe_3O_4) could be given as $FeO \cdot Fe_2O_3$. The half of the Fe^{3+} ions are tetrahedrally coordinated and the remaining half of Fe^{3+} and all the Fe^{2+} are octahedrally coordinated in this inverse spinel structure (Fig.1.1). Thus, Fe_3O_4 could be written as $(Fe^{3+})_A(Fe^{2+}Fe^{3+})_BO_4$ where A represents tetrahedral site and B represents octahedral site.

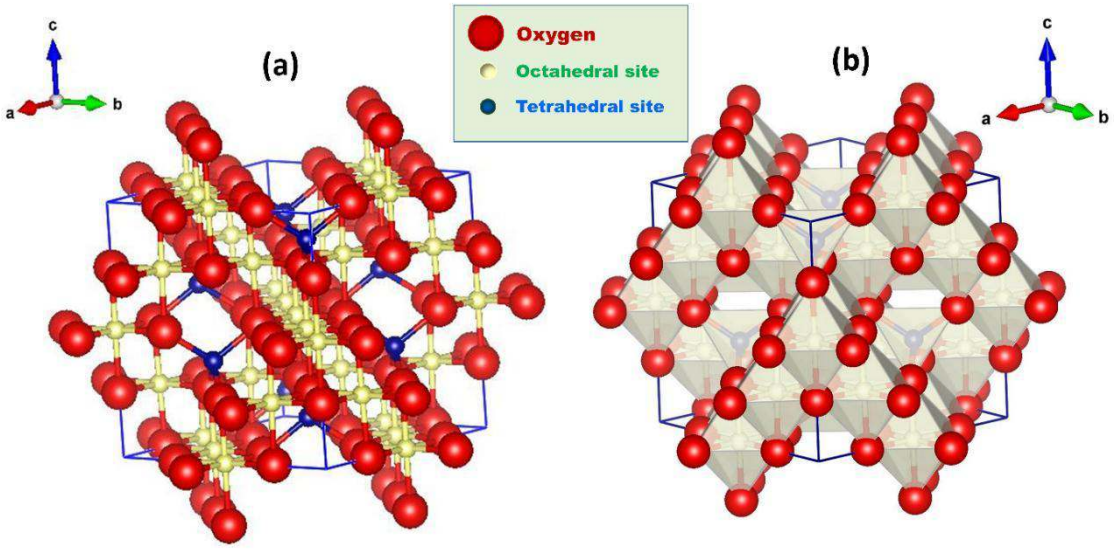

Figure 1.1: Crystal structure of Fe_3O_4 [11].

1.2 Magnetic properties of magnetite

The magnetic moments on tetrahedral site (Fe^{3+} ions) are antiferromagnetically coupled with the magnetic moments on octahedral site (Fe^{3+} and Fe^{2+} ions). The spins of the tetrahedral sites and the spins of octahedral sites are antiparallel as well as unequal in magnitude. Therefore, these interpenetrating sublattices aligned antiparallel with unequal moments give rise to the observed ferrimagnetism[12].

It has been widely reported that the magnetic properties such as the coercivity (Hc) of magnetite depends upon particle size, shape and other parameters[13]. The transition from a multi to single domain structure occurs upon decreasing the size of the particles. However, the critical size for single domain MNPs depends on the crystal structure and morphology of the materials [13]. On further decrease in particles size, it provides another critical size which is due to the transition from single domain (ferrimagnetic/ferromagnetic) to superparamagnetic. The variation of critical size for single domain and superparamagnetic nature for different MNPs is shown in Fig. 1.2.

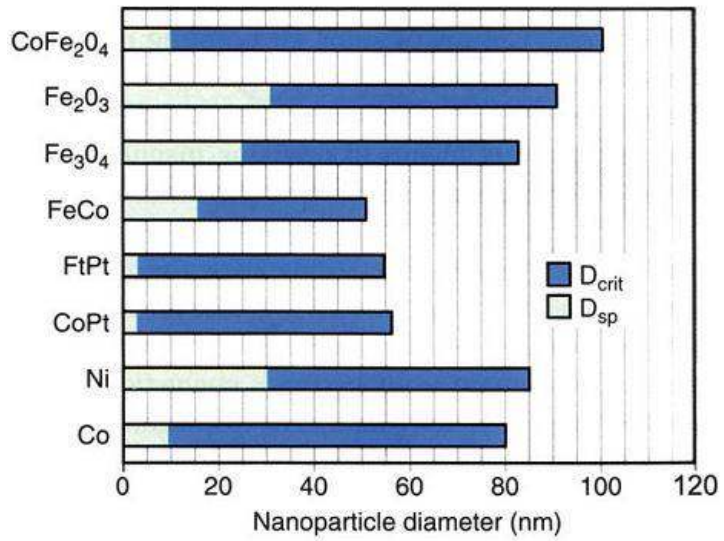

Figure 1.2: The single domain size (D_{crit}) and superparamagnetic limit (D_{sp}) for various ferro- or ferrimagnetic materials at room temperature. (After Krishnan et al. [14])

For superparamagnetic nanoparticles, the thermal energy may be sufficient to change magnetization spontaneously i.e. the magnetic moment of each nanoparticle could rotate randomly due to thermal agitation. Therefore, in the absence of external magnetic field the net magnetic moment could be zero. But, in the presence of external magnetic field, the net statistical alignment of magnetic moments towards magnetic field direction occurs. Further, the lack of remanent magnetization after removal of external magnetic field improves the colloidal stability of these nanoparticles.

The superparamagnetism is achieved if the size of the Fe_3O_4 nanoparticles is well below 20 nm [13]. Theoretically, the estimated critical size for forming a multi-domain structure is 128 nm for spherical one and 76 nm for cubic shaped magnetite nanoparticles[15]. In contrast, the experimentally determined critical size for cubic type magnetite nanoparticle is found to be at greater than 160 nm[16]. Some of the literatures also suggest that the critical size for cubic magnetite nanoparticles lies between 30 – 46 nm[17].

1.3 Synthesis methods

Several techniques are utilized for the synthesis of magnetic iron oxide based nanoparticles of various sizes, surfaces and spatial confinements such co-precipitation[18], polyol[19], hydrothermal[20], decomposition[21], microemulsion/ miniemulsion[22], microwave refluxing[23] and sol-gel[24]. Amongst, the nanoparticle synthesis methods for getting single phase one uses glycol or a polyglycol/glycol mixture as solvent. This also provides a procedure of monodisperse size particles. In addition, these polyglycol(s) gets adsorbed on the surface of the nanoparticles which enhance their colloidal stability.

1.3.1 Co-precipitation

The co-precipitation process involves the precipitation and subsequent reduction of iron(III) oxyhydroxide (FeO·OH) and iron(II)hydroxide [$Fe(OH)_2$] into magnetite. It is similar to the hydrothermal decomposition process but the fundamental difference is the pH value at which the two synthesis methods operate. A basic environment is necessary to produce crystalline magnetite nanoparticles by co-precipitation process whereas hydrothermal decomposition process could complete without establishment of a basic environment.

Initially, Fe in the (2+) or (3+) valence states spontaneously forms iron oxyhydroxide under basic conditions. These oxyhydroxides further transformed into magnetite nanoparticles through Fe^{3+}reduction:

$$2Fe^{3+} + Fe^{3+} + e^- \rightarrow Fe^{2+} + 2Fe^{3+}$$

$$OH^- \rightarrow \frac{1}{4}O_2 + \frac{1}{2}H_2O + e^-$$

$$2Fe(OH)_3 + Fe(OH)_3 \rightarrow \frac{1}{4}O_2 + \frac{1}{2}H_2O + FeOFe_2O_3 + 4H_2O$$

However, the co-precipitation of $Fe^{3+}/Fe^{2+}$is highly dependent on both pH value of the reaction medium and the stoichiometric ratio of Fe^{3+}/Fe^{2+} ions. The preferred pH is near 11 and Fe^{3+}/Fe^{2+} ratio is 2:1.

$$Fe^{3+} + Fe^{2+} + 5OH^- \rightarrow Fe(OH)_3 + Fe(OH)_2$$

$$2Fe(OH)_3 + Fe(OH)_2 \rightarrow FeOFe_2O_3 + 4H_2O$$

1.3.2 Micro/miniemulsion

Emulsion method involves the utilization of immiscible solvents. Depending on the solubility of precursors, high or low dielectric solvent are generally employed in this process. The emulsion systems are established through addition of a dispersant with a significantly different dielectric constant than that of the solvent. For establishing a water-in-oil system (W/O), water or a similar solvent and solubilizing the carrier molecules are used. The presence of the two immiscible fluids forms micro/nanobeads. These beads are dispersed in a low dielectric solvent such as N,N-dimethylformamide, acrylonitrile, and acetone which is called the 'oil' phase. In contrast, an oil-in-water (O/W) system is also established by comparative to the W/O system albeit the micro/nano beads are suspended in the 'oil' phase and dispersed in the 'water' phase. Initially the salts transformed into respective hydroxides and get captured inside the micro/nano beads. Subsequently, the hydroxides get converted into oxides and yields to nanoparticles of oxides e.g. Fe_3O_4.

1.3.3 Decomposition

It is a convenient method for the production of nanoparticles from iron and other metal precursors. In this process, reaction vessels may be heated at an elevated temperature for an extended period of time which provides the thermal induction for precursor decomposition. The utilization of high temperature solvents such as ethylene glycol also provides multiple functionalities for precursor decomposition. In addition, ethylene glycol provides chemical species for surface adsorption which could improve the colloidal stability. The solution of mixture of $FeCl_3$ with sodium acetate in ethylene glycol kept in a polytetrafluoroethylene (PTFE) lined autoclave vessel. The autoclave is then heated to 200 °C for 8 h which allow the formation of $FeO{\cdot}OH$ and $Fe(OH)_2$compounds. The thermal energy provides the driving force to induce decomposition of oxyhydroxides to crystalline magnetite.

1.4 Applications

There are several applications reported for magnetite nanoparticles because of their unique magnetic properties as well as appropriate biocompatibility. In addition, the dispersibility and functionalization ability of these materials enhance the suitability for bioapplications. These bioapplications can be categorized into two typical groups such as "*in-vitro*" and "*in-vivo*" applications [25]. The activities that are performed in laboratory environment and outside of living organisms are termed as *in-vitro* applications. For instance, the magnetic detection and separation of cells, proteins, DNA using superparamagnetic magnetite nanoparticles are the examples for *in-vitro* studies [25]. On the other hand, *in-vivo* (refers to living animals) applications are related to the disease diagnosis techniques like MRI, and the therapies methods such as magnetic hyperthermia and gene/drug delivery systems.

1.4.1 Magnetic Resonance Imaging (MRI)

MRI is utilized to detect the soft tissues like muscles, blood flow in vessels and the density of each tissue inside the body. The mechanism of MRI is based on the alignment of unpaired magnetic spins of tissues towards applied magnetic field direction. In general, many of the tissues of body contain more than 70% of water (with different densities in various tissues) and the hydrogen nuclei of water molecules act as tiny magnets. These are aligned randomly but respond to the applied field. Aligned spins towards the applied field direction may further get diverted during exposure to radio frequency (RF) signal in the MRI devices. Based on time contrast upon returning the spins to its original position, the MR images could be formed. These relaxations are divided into two modes such as T_1 and T_2 relaxations [26]. T_1 relaxation is correlated to the longitudinal relaxation of spins (spin-lattice coupling) and T_2 is related to the transverse relaxation(spin-spin coupling) [26]. In the last decades, superparamagnetic magnetite nanoparticles are utilized as

contrast agents for MRI. These nanoparticles could modify the number of reacted spins in the tissues which alter the relaxation times and enhances the contrast of the image[26].

1.4.2 Targeted drug delivery

The MNPs could be utilized for the distribution of drug in specific location of body. It has been reported that the MNPs could couple with different multifunctional materials and drugs or gene. The size of the magnetic particles is one of the key parameter for their usage in targeted drug delivery systems[27]. The smaller size of the particles can move freely in vessels and their retention time in blood can be enhanced. In addition, the particles size is suitably well so that they exhibit superparamagnetic behavior which enhances the performance because of smaller M_r and H_C values. Further, their higher M_S value and their biocompatibility are considerably helpful for *in-vivo* applications.

1.4.3 Magnetic hyperthermia

Hyperthermia is a thermal therapy which could be used for the treatment of cancer cells. This word is derived from two Greek words. The “hyper” means “rise” and “therme” means “heat”. It is reported that the growth of the cancer cells can be terminated at temperatures ranging from 41 to 46 °C if applied for 20 to 60 min[28]. However, it has also been reported that the hyperthermia may also cause undesirable effects such as burns, blisters etc. to even healthy cells. This happens if the temperature of the surrounding tissues rises beyond 50 °C. Therefore, to increase the treatment efficiency, the hyperthermia technique is used locally instead of whole body exposure. The local heating of the targeted cell or tissue can be performed by different external sources [29]. Further, hyperthermia can be divided into three different types based on their heat source such as electrical, optical and magnetic hyperthermia. The performance of hyperthermia strongly

depends on the intensity of generated heat and its delivery to the affected region [29]. Relatively, the magnetic hyperthermia found to exhibit better performance.

In magnetic hyperthermia process, the MNPs are injected into the body and then brought into the blood circulation. These particles are then transferred to the location of the tumors site using an external direct current (DC) magnetic field. After that, the heat is being generated near the tissues through an external AC magnetic field. The characteristics of magnetic hyperthermia are (i) local therapy i.e. only the region containing MNPs will be affected and (ii) controlled temperature (41–46 °C) which depends on MNP and the magnetic field. Due to these characteristics, the magnetic hyperthermia is expected to provide a safe, easy and effective approach for the treatment of cancer. Gilchrist et al. [30] were first to explore the effect of magnetic hyperthermia. In their study, they treated metastases in lymphatic nodes of dogs using maghemite nanoparticles in the presence of external magnetic field of frequency 1.2 MHz. Now, there is a well-established procedure for application of MNPs in hyperthermia treatment. Up till now, this technique has been explored for clinical phase trials against prostatic and esophagus cancers. The researchers are actively engaged in the search for the possibility to cure cancers of other types by this technique[31]. Therefore, in comparison with conventional therapies such as surgery, chemotherapy, and radiotherapy the MHT has been considered as a novel alternative therapy with few side effects.

In magnetic hyperthermia technique, the magnetic fluids are exposed to AC magnetic field (Fig. 1.4.1). The magnetic fluids are the stable suspension of MNPs in a carrier medium such as water and hydrocarbon fluids. If an external AC magnetic field is applied, the heat is getting generated due to magnetic materials via four different heat loss mechanisms such as i) eddy current losses (observed in magnetic particles with size greater than 1 μm), ii) hysteresis losses (observed in multi-domain magnetic particles

with size greater than 1 μm), iii) susceptibility losses or relaxation losses (observed in single domain superparamagnetic nanoparticles) and iv) frictional losses or stirring losses (observed in MNPs suspended in viscous medium)[32]. It is known that the magnetic field may induce eddy current in the magnetic particles. However, the eddy current losses are insignificant for MNPs because of their low electrical conductivity. Whereas, eddy current losses relatively higher for bulk magnetic materials. Therefore, for MNPs the heat generation from eddy current is negligible as compared to other losses.

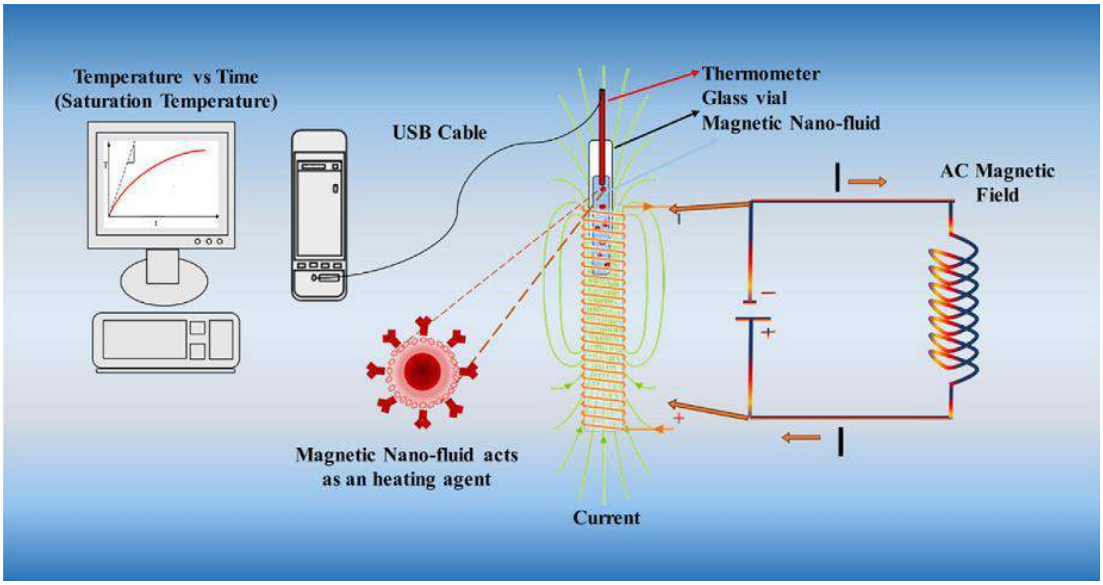

Figure 1.4.1: Schematic diagram of the experimental setup for magnetic hyperthermia application (after Ziba et al. [33]).

Below Curie temperature, the multi-domain MNPs exhibit heat generation which is due to hysteresis loss. Nevertheless, the size for these particles to have this effect should be greater than 20 nm [34]. In contrast, Vallejo-Fernandez et al. [35] suggested that the hysteresis loss could be dominant for the size in between 13 to 19 nm (Fig.1.4.2). Further, if the size of the particles is below 12 to 15 nm the thermal energy barrier for rotation of magnetic moment may also reduce. This leads to magnetic transition from

multi-domain to single domain state i.e. superparamagnetic state. For these particles, heating mechanism occurs due to susceptibility losses or relaxation losses. This loss is further classified in two types namely Néel and Brownian loss. Upon removal of magnetic field, the magnetic moments may relaxed either by motion of internal magnetic spins (Néel relaxation) or by the rotation of individual nanoparticles rotating around their own axis (Brownian relaxation).

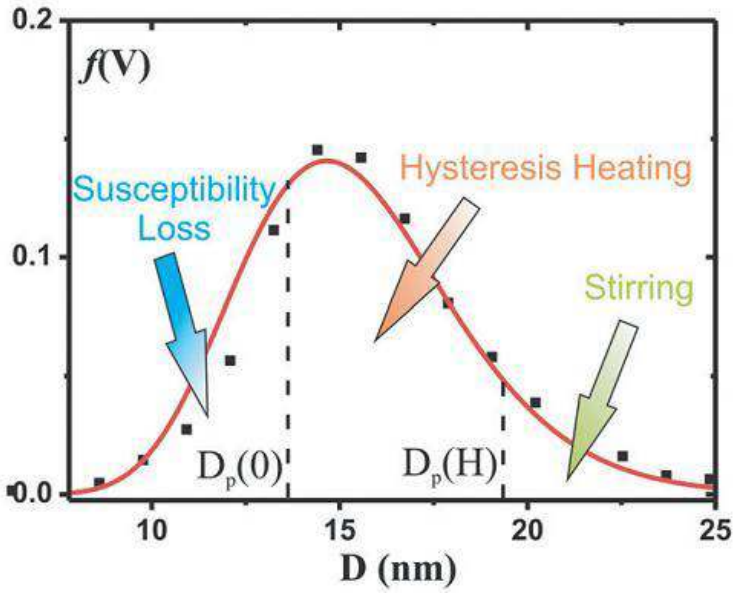

Figure1.4.2: The heat generation arising from susceptibility loss, hysteresis losses and stirring at a field of frequency 111.5 kHz and an amplitude of 250 Oe. (After Vallejo-Fernandez et al.[35])

The total energy (E) of a magnetic particle is sum of Zeeman and anisotropy terms[36]

$$E = KV\,sin^2\,\theta - \mu H_0 \sin(2\pi f.t)\,cos\emptyset$$

where K is the anisotropy constant (which arises from several contributions for e. g. magneto-crystalline energy, surface disorder, or shape anisotropy), V is the particle volume, μ is the magnetic moment, θ is the angle between μ and the anisotropy axis, ϕ the

angle between μ and the external field, t is the time and H_0 is the intensity of the alternating current magnetic field.

After the removal of the external magnetic field, the superparamagnetic particles undergo a magnetic relaxation process called Néel relaxation.

The Néel relaxation time (τ_N) is given by[37]

$$\tau_N = \tau_0 \exp(\frac{KV}{k_B T})$$

where τ_0 is the attempt time 10^{-9}–10^{-13}s and k_B is the Boltzmann constant.

The Néel relaxation is due to thermally driven continuous fluctuations of the magnetic moments. Thermal energy (k_BT) is sufficient to overcome the anisotropy energy barrier that separates orientation states (local minima) of the magnetic moments. In contrast, the multi-domain and single-domain MNPs do not show Néel relaxation because of their anisotropy energy cannot be overcome by the thermal energy. However, both blocked and superparamagnetic nanoparticles exhibit Brownian relaxation. The characteristic time for this $\tau_B$is given by [37]

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

where η is the dynamic viscosity of the medium, V_H is the hydrodynamic diameter of the suspended MNPs. The Brownian relaxation time is associated with the random hydrodynamic interaction with molecules of the liquid medium and the corresponding rotational diffusion time[37].

It is clear that $\tau_B$is not directly related to the magnetism of the superparamagnetic nanoparticle. But, it increases with increased particle diameter within the superparamagnetic range. The hydrodynamic diameter V_H cannot be measured accurately

because in colloidal dispersions the particles are coated with one or more dispersants which may form multiple layers over their surface. Also, the value of V_H includes the entrained molecules of the carrier liquid when the particle moves. In general, the hydrodynamic diameter V_H is measured by the technique such as photon correlation spectroscopy (PCS). For instance, a 10 nm diameter particle coated with oleic acid has a typical hydrodynamic size of about 25–75 nm.

The existence of both relaxation times gives an effective relaxation time τ

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

As stated earlier, during magnetic hyperthermia experiment, the ferrofluids are exposed to external magnetic field. The temperature rise with respect to time (dT/dt) is measured throughout the process. After certain time, the temperature may become stable i.e. no further rise in temperature with increased duration. This temperature is termed as stable temperature (T_S). The stable temperature should be in between 42 to 46 °C for the practical applications because the temperatures beyond this are prone to affect even normal cells. Therefore, the MNPs having T_C in this range are suitable to avoid painful problems. However, there are some factors which affect T_C values and subsequently the T_S values. The second important parameter in MHT is SAR, which actually implies the power of MNPs to raise the temperature for required treatments. The MNPs with higher SAR values can generate required heat with lower dose. However, the SAR value depends upon different factors such as particle size and shape of magnetic particles, M_S values, amplitude and frequency of AC magnetic field. To check the applicability of MNPs with adequate SAR values for *in-vivo* application or even clinical trials, mainly depend on the evaluation during *in-vitro* studies. For *in-vitro* studies, the parameters of the fields and the characteristics of MNPs are optimized.

The magnetic hyperthermia also depends upon the coating over the MNPs. Several materials have been utilized as coating over MNPs for *in-vitro* or *in-vivo* evaluation[38]. These coatings can be categorized into two main groups such as organic and inorganic. The organic group consists of three materials including surfactants, polymers, and biological molecules. The inorganic group contains metals/non-metals, metal oxides/sulfides and silica. It has been reported that the Ms value of undoped nanoparticles of Fe_3O_4 was 64.35 Am^2Kg^{-1}. However, after coating with PEG, DEX, PVP, and BSA, its value decreased to 58.42, 56.59, 55.70, and 58.64 Am^2Kg^{-1} respectively. The variation in the Ms values of the coated Fe_3O_4did not alter significantly as compared with the uncoated ones. But, the presence of coating enhanced the biocompatibility of samples[38].

Gonzalez-Fernandez et al. [39] studied the effect of particle size (varied from 5 to 110 nm) on the SAR value. It was observed that the highest SAR value was 137 W/g for 24 nm and lowest SAR value was 1 W/g for 110 nm for Fe_3O_4 nanoparticles. They suggested that the higher SAR value conforms to the superparamagnetic behavior of the nanoparticles [39]. As the particle size increased, the SAR value decreased to zero by reaching the multi-domain particle (110 nm). If the dispersity of MNPs changes from mono- to poly-, the SAR values found to be decreasing. This could be due to the reduction in the distribution of homogeneous particles which effectively retard the rate of total heat generation. Therefore, the distribution of magnetic particle size plays a significant role during induction heating. The magnetic properties of $CoFe_2O_4$ nanoparticles with various shapes and sizes are reported by Joshi et al. [40]. It has been observed that the Ms and SAR values enhanced with increasing particles size having different shapes. For example, this SAR value was considerably larger for facet irregular shaped MNPs than that of spherical-shaped. The obtained temperature during MHT for

faceted MNPs was not in the range of 41 to 47 °C and could even burn the cancer cells. Similarly, the obtained temperature for spherical shaped MNPs of size around 15 nm was more than 55 °C after 4 min of exposure which could also damage the normal cells. In their study, it was observed that MNPs of size 12 nm diameter may be a promising candidate to prevent such problems.

The SAR values of nanorods of magnetite at a low (150 Oe and 210 kHz) and a high (300 Oe and 765 kHz) magnetic field are also compared [41]. At two fields, the SAR values were 10 W/g (lower field), and 759 W/g respectively. The larger SAR value at higher field was found to be appropriate MHT application. However, the temperature in the range of 42–47 °C was observed after 30 min of exposure at higher field.

It is well documented that the magnetic properties of Fe_3O_4 varies with doping of different elements. The cations used for substitution in Fe_3O_4 replace Fe-ions either from octahedral or tetrahedral or both the sites. The replacement may occur either for Fe^{2+} or Fe^{3+} or both ions. The substituent ions may or may not have magnetic moments. All these factors including the concentration of dopants affect the magnetic properties of substituted magnetite. The difference between the magnetic moments at octahedral and tetrahedral sites results into the magnetization of the material. For example, Mohapatra et al. [42] have synthesized MFe_2O_4 (M = Mn, Fe, Co, Ni and Zn) nanoparticles using solventless thermolysis technique. They observed that the saturation magnetization value decreased in an order of periodic arrangement i.e. Mn>Fe>Co>Ni> Zn. This was due to the cationic distribution based variation in the magnetic moments of the ferrites. The change in the magnetic properties of these substituted Fe_3O_4 nanoparticles also regulates the SAR values. Fantechi et al. [43] reported that the magnetic hyperthermia properties of ferrite ($M_xFe_{3-x}O_4$) nanoparticles improved by substituting Fe^{2+} ions by Co^{2+} ions. They observed SAR value of 40.4 W/g for x = 0.6 sample which decreased to 10.8 W/g for x =

1 at an external field of 150.79 Oe having frequency 183 KHz. The Ms values were 98 and 87 Am^2/kg for the samples with x = 0.6 and 1 respectively. Oh et al.[44] produced $MnFe_2O_4$ cubic nanoparticles using thermal decomposition technique. The M_S value was reported to be 71 Am^2/kg and the SAR values were 50, 95, 150, 210 and 270 W/g at 307 kHz frequency and the fields of 251, 377, 503, 628 and 754 Oe respectively. It is also reported that the $CoFe_2O_4$ nanoparticles with M_S value 60.4 Am^2/kg was synthesized by co-precipitation method[10]. Iqbal et al. [45] reported that the $NiFe_2O_4$ nanoparticles with M_S value of 15 Am^2/kg have shown the stable temperature at 42 °C and 47 °C at the fields of 260 kHz & 49 Oe and 260 kHz & 69 kHz respectively. They also synthesized silica coated $MnFe_2O_4$ nanoparticles by reverse micelle method. The ferrofluids of various concentrations of these nanoparticles were prepared and their SAR values were in the range of 47 to 84 W/g. They reported that the ferrofluid concentration of 2.6 mg/mL with the SAR value of 53.45 W/g (f = 260 kHz & H = 69.11 Oe) could achieve temperature of 42 °C and hence may be considered as the suitable candidate for magnetic hyperthermia[45]. Further, the spherical nanoparticles of $Zn_{0.9}Fe_{0.1}Fe_2O_4$ having M_S value near 10 Am^2/kg could show SAR value of 36 W/g at 700 kHz frequency and 34.4 Oe field[46]. Nevertheless these MNPs had lower M_S value could raise the temperature up to 39 °C and cannot be prescribed for MHT application.

1.5 Scope of present investigation

It can be observed from the literature that the heating ability (in terms of SAR values) of MNPs depends upon several factors such as magnetic behavior, size, shape, coating material, type of doping element, concentration of dopants, frequencies and amplitudes of the AC magnetic fields. It is also clear that the frequency and amplitude of the AC magnetic field, coating material and type of doping elements are playing decisive roles in obtaining the stable temperature in therapeutic range. The M_S values for Fe_3O_4

nanoparticles were found to be varying with type and concentration of dopants as well as synthesis protocol. For practical applications with lowest side effects of MHT, it is necessary to achieve stabilization of temperature (T_S) is achieved in the therapeutic region (42-46 °C). The researchers have tried to monitor the temperature during hyperthermia using magnetic resonance imaging (MRI). However, it was found to be time consuming and expensive. The other way to control this temperature is to use MNPs that have a Curie temperature (T_C) in the therapeutic range (42–46 °C). For such materials, as soon as the temperature reaches near the T_C, they transform from the ferromagnetic/ferrimagnetic to the paramagnetic state and heating stops automatically. Such materials can act as an in vivo switch. The materials based on this principle include $ZnGd_xFe_{2-x}O_4$, $Zn_xGd_{1-x}Fe$, $Ni_{1-x}Cr_x$, Cu–Ni alloy and $La_{1-x}Sr_xMnO_3$. However, they suffer from two major drawbacks, which relate to their low M_S values and inferior biocompatibility. In a few studies, it has been concluded that a temperature below 50 °C can be achieved during MHT with a lower concentration of MNPs (0.5 to 10 mg/mL). However, for clinical applications, one may need a higher concentration of MNPs. Thus, achieving a controlled heating with either pure or substituted ferrites (Fe_3O_4 or γ-Fe_2O_3) is a major challenge for magnetic hyperthermia, theranostic or drug delivery purposes.

The present work reports about the achievement of stabilization of temperature (T_S) near 42 °C by $M_xFe_{3-x}O_4$ (M = Zr, Hf, Al, Zn or Li) nanoparticles in the presence of various magnetic fields. The thesis also deals with the systematic investigations of the structural, microstructural and magnetic behaviors of the aforesaid MNPs.