Chapter 4

Suitability of Ferrites for Biomedical Applications

Meenakshi Dhiman^{1,*} and Shikha Rana²

¹Chitkara University Institute of Engineering and Technology, Chitkara University, Punjab, India

²Department of Physics, Himachal Pradesh University, Shimla, India

meenakshi.dhiman@chitkara.edu.in

Abstract

This chapter aims at the latest amelioration in the biomedical application of spinel ferrites. Magnetic hyperthermia treatment of tumour cells and contrast resonance imaging of human body parts, are a few applications of spinel ferrites that have gained substantial interest nowadays. The thermo-therapeutic and radiology based diagnosis treatment has many benefits over traditional methods used for disease diagnosis and imaging treatment of chronic carcinogenic origin diseases. The various types of doped and undoped spinel ferrite nanoparticles are investigated and optimised for different biomedical applications. Through this chapter, an attempt is made to provide readers the knowledge about various required characteristics and latest used strategies for the successful implementations of spinel ferrite in biomedical applications at commercial levels.

Keywords

Spinel Ferrite, Magnetic, Functionalization, Hyperthermia, Drug Delivery, Magnetic Resonance Imaging

Contents

Suitability of Ferrites for Biomedical Applications.....	162
1. Introduction.....	163
2. Ferrites.....	165
3. Biomedical application	166
3.1 Hyperthermia	166

3.2	Target specific drug delivery	172
3.3	Magnetic resonance imaging	175
Conclusion.....		177
References		178

1. Introduction

Spinel ferrite nano ranged magnetic particles (SFNMs) are ferrimagnets with exemplary magnetic characteristics, that are highly dependent on particle size and shape anisotropy [1]. SFNMs are generally divalent ion doped spinel metal oxides structures which have plenty of applications in storage [2] , electromagnetic devices [3], catalysis [4] sensing [5], targeted drug delivery [6], diagnosis and imaging [7], thermotherapeutic cancer treatment [8] and waste water contamination removal [9]. The doped cations are randomly arranged on two crystallographic sites in spinel structure and their arrangement determines the optical, magnetic and electrical characteristics of the SFNMs [10,11,12,13]. The doped cations have particular site preference according to sizes of dopant ion and of interstitial site, preparation method and type of reaction conditions or environment [14,15,16].The positioning of dopant ion within the crystallographic structure i.e. cation distribution has great impact on the magnetic behaviour of the SFNMs. The electron spin depends on the lattice sites and it determines the overall magnetic moment of the lattice [17,18,19]. On the bases of cation distribution, the SFNMs are divided into three main types; spinel, inverse spinel and mixed spinel configurations [20]. Extensive studies of each type of SFNMs are still undergoing and much has been investigated in various in-vitro, ex-vitro and in-vivo biomedical applications [21,22,23]. The main required characteristics of SFNMs in biomedical area are super paramagnetic nature at 300 ° K. They also have small magnetic and eddy losses, large resistivity and permeability, high chemical, mechanical and thermal stability and compatibility [24,25,26]. These features of SFNMs entice the researchers' attention for their diversified biomedical uses.

The biomedical field areas include techniques which are engineered and designed with biological entities. The resulting hybrid systems are employed in conventional methods to form multifunctional and targeted diagnosis, imaging, and delivery treatments [27]. Despite a lot of experimentation in biomedical areas, fast diagnosis, easy contrast imaging, site specific drug delivery and many other like needs of the medical science is still unfilled. Metal/Metal oxides, polymers, hydrogels, Lipids, liposomes, ceramics like many material groups are employed in medical areas either by natural way or chemical

way [28,29]. From last few decades, the advancements in bioengineering techniques are focused on nanodevices, nanodrug carrying systems and nanomagnetic imaging techniques, formed by incorporating properties of nanomaterials with hybrid systems [30]. These nano hybrid systems have shown efficacious delivery with enhanced precision and sensitivity. The interest in biomedical applications of SFNMs increases with the fact that they have retained good magnetic properties even after use of various functionalization techniques on the bare SFNMs. This chapter includes discussions on the various possible functionalization, synthesis techniques and properties of SFNMs which are utilized in biomedical fields.

Figure 1: Figure including basic characteristics, synthesis methods and applications of SFNMs.

2. Ferrites

The doped cubic SFNMs are widely studied ferromagnetic materials with settable magnetic properties. The various types of synthesis methods as mentioned in figure 1 are employed for preparation of SFNMs, which provides possibility to get engineered desired range SFNMs [31]. The SFNMs are generally of nano size and have large magnetic interactions which cause them to agglomerate easily. Since 1949, when Louis Néel explained magnetic interactions first time many theories and optimization techniques are used to control and explain intrinsic and extrinsic magnetic behaviour of the magnetic materials [32]. Krishnan et al. [33] have reviewed the magnetic characteristics dependence on the particle size of SFNMs. The synthesis, annealing and calcination temperature determines the particle size, phase formation and morphology of the prepared samples. SFNMs have been used in various Diagnostics and Therapeutic application as shown in figure 2. This common problem of agglomeration and bio stability of SFNMs is avoided by combining these magnetic entities with biopolymers, carbon based materials, silica, bioactive ingredients etc. [31]. Polyethylene glycol, Folic acid, Dextran and liposomes like ingredients are commonly employed nowadays for hybrid formations, which are applied in various biomedical applications of SFNMs [34,35]. Silica functionalized magnetic nanoparticles are assimilated with alkoxysilane surface active groups which expedite their multiple applications [35,4]. In any biomedical use, the desired features like controlled drug delivery, enhanced diagnostic behaviour and the interaction between the cell and hybrid system depends on the nature, size, morphology of the hybrid system, type of surface coating and charge. The toxic behaviour of SFNMs in clinical trials and medical diagnosis is highly determined by their surface chemistry, solution stability, size, dose and procedure used, internal structure, chemical composition, adsorption and opsonization rates [36].

Figure 2: Figure showing various therapeutic and diagnostic applications of SFNMs.

3. Biomedical application

3.1 Hyperthermia

Magnetic hyperthermia refers to the elimination of cancer cells without significant damage to healthy cells, particularly overheating. The use of direct high temperature exposure for treatment of various body problems is known as ‘Hyperthermia’. Hyperthermia means atypical rise in body temperature from external source, not similar to general body temperature rise situations like fever or heatstroke. Hyperthermia is a thermotherapeutic treatment which could be employed for removal of cyst, for control over infection and pain in the body. Also, the local or whole body hyperthermia treatment is chosen according to the level of cancer spreading in the patient body too, as cancer cells are less active at high temperature (>315 K) [37]. The various advancements in this thermotherapeutic treatment are differentiated by their power deposition method and the gross targeted body area. The Cancer treatment by a non-invasive thermotherapeutic method helps to regulate temperature of the tumour site with external governance through

magnetic forces as shown in figure 3. Hyperthermia processes are generally done by using mobile heating carriers either externally or internally and water bath like heating source. Every used method has some advantages and disadvantages and used according to the level of cancer spread in the human body. Source heating is more effective and less invasive, whereas water bath heating is more pertinent for metastasis cancers. The chief limitations of hyperthermia treatment are local inhomogeneous thermal heating of affected region and abysmal heating of deeply located effected regions [8]. Hence, to deal with these limitations nanotechnology based treatment practices are widely studied nowadays. Nano-ranged materials are influencing every aspect of human life cycle by their exemplary characteristics. Every scientific field has some requirements in terms of desired shape, size, characteristics etc. and fortunately nowadays, excessive research on the properties and characteristics of nano-ranged materials through optimization leads to designing of desired materials. The various advancements in this thermotherapeutic treatment are differentiated by their power deposition method and the gross targeted body area [38].

Figure 3 Illustration of Practical set up required for study of therapeutic nature of magnetic nanoparticles [41].

SFNMs are becoming most widely studied and employed class among all the nanomaterials due to unique physiochemical, magnetic and optical characteristics with easy functionalization possibilities at subatomic levels. SFNMs have shown multiple applications due to their small dimensional metal based inorganic structures which could

be well governed by external magnetic forces [39]. Prudently, they have shown extraordinary reaction stability with desired physiochemical and magnetic nature for pharmaceutical and environmental applications. SFNMs are in medical use since last two centuries but with increase in possible research opportunity their use has become more approachable. SFNMs having high magnetic saturation values are found to have more heating capacity and hence provide required heat on the targeted cells [40]. The earliest used magnetic nanoparticles in 18th and 19th centuries for hyperthermia treatment were super paramagnetic particles of magnetite [37]. W. Busch and W. B. Coley have used heat inducing phenomena for treatment of cancer in the late 19th century [41,42]. Later on R. K. Gilchrist and his co-researchers had used inductive heating for the treatment colon and rectum carcinoma in [43,44]. From last twenty years, many studies are going on doped magnetite structure known as SFNMs to study various synthesis and functionalization processes for enhancement of their magnetic behaviour which could be used for their in vitro and in vivo biomedical applications. In this part of the chapter we have provided an informative explanation about their intrinsic magnetic behaviour and their influence on thermo therapeutic uses.

Magnetic hyperthermia is generally accomplished by four distinct treatment methods as mentioned in table 1. According to table 1, intracellular and extracellular thermotherapies are the most efficient treatments for cancer treatment. In the first method, SFNMs like magnetic heat sources are placed deep within the tumor site with the help of external magnetic field whereas in the second one required heat is provided from outside with the help of sources like water bath or microwave etc. But in the second one extra heat is required as direct heating of the cancer cell is not possible. The intracellular hyperthermia is found to have more potent heat distribution but need sufficient clinical studies before their implementation in the human body. For all the strategies mentioned in the table 1 prescribed therapeutic agent are classified in three ranges, as in millimeter, micrometer and nanometer.

Human body has been observed to exhibit dissimilar reaction to carcinoma cells in comparison to healthy cells [45]. The multiplication rate of these cells is very less at particular thermal conditions and as a result, hyperthermia is given specifically at the affected human body areas in contrary to entire body. The SFNMs are known to have various types of B-H curves and hence their magnetic behaviour is also different. This magnetic loss with respect to variation in external frequency is widely investigated characteristic of SFNMs for thermotherapeutic use [46]. Magnetic nanometer therapeutic agents in a colloidal form are capable to reach tumor site and perform the required function without disturbing normal cells. Also, these nanocarriers have low Curie temperature which provides controlled heating with easy possible autogenous control

[47,48]. Magnetic nanocarrier use eddy current loss and hysteresis loss like phenomena to generate heat which are observed due to their multidomain structure and small size. To raise blood compatibility with decrease in agglomeration and smooth bonding with solution affinity groups, facile functionalization of SFNMs is generally done with various polymers, silica, fatty acid and protein like biocompatible groups [49,50].

Table 1: Commonly employed four basic hyperthermia methods [44].

Strategy	Arterial Embolization	Direct Injection	Intracellular	Interstitial implantation
Heat generation	Intravascular	Extracellular	Intracellular	Interstitial
Treatment method	Directly injected through Arterially embolizing	Injected directly in to the tumor site.	Directly injected through Arterial embolization or intravenous injection	Implantation of Heating seeds
Size of agent	10^{-6} to 10^{-9} m	10^{-6} to 10^{-9} m	10^{-9} m	10^{-3} nm
Merits	Effective temperature distribution and controlled temperature dose.	Low risk of arterial catheterization.	Generally used in treatment of metastases cases.	Less cell burning.

Fatty acids like Oleic acid has shown marvellous anti-cancer activity and hence nowadays it is widely studied in combined hyperthermia based targeted drug delivery in cancer patients [51]. Prashant B. Kharat et al. [52] has used coprecipitation method to synthesize Oleic Acid functionalized Cobalt ferrite samples with mean particle size of 10 nm. The functionalized sample has high saturation magnetization (76.86emu/g) with small coercive field and remanence values. Both the samples were investigated for induction heating behaviour which is found to rise with the concentration of the samples. The SAR value is calculated for bare sample as 248 W/g and for functionalized one it is found to be 216 W/g with very small 1 mg/mL concentration, which makes the prepared sample a potential candidate for hyperthermia treatment. Also, Sandeep B. Somvanshi and his group [53] have synthesized a composite oleic acid and magnesium ferrite. They have also investigated physiochemical behaviour of the formed composite and found the

average crystallite size of bare and coated Magnesium ferrite particle as 18 nm and 20 nm respectively. The room temperature magnetic saturation values are 41emu/gm and 38emu/gm approximately, with very small remanence ratios for bare and coated ones respectively. With the coating of Oleic acid colloidal stability is found to increase with increase in the Specific Absorption rate (SAR) as 98 W/g in comparison to 91 W/g of bare magnesium ferrite. The maximum SAR comes with least dose of 8 mg/mL of the composite of Oleic acid with Magnesium ferrite. Cigdem E. Demirci and his research group [54] have prepared various ferrite coated oleic acid composites with probable thermotherapeutic efficacy. The prepared composites are further coated with N-(trimethoxysilylpropyl)-ethylene diamine-tri-acetate to increase their convective diffusion capacity and their heating capacity was observed in two carrier solution with different concentration. The maximum SLP was obtained as 315 W/g and 295 W/g for CoFe_2O_4 and MnFe_2O_4 or NiFe_2O_4 respectively at frequency 195 kHz and applied magnetic field 50 kA/m, which confirm the potential use of the formed composites as hopeful hyperthermia agent. Carbon nanotubes provides high surface area and could easily enter in cellular membrane [55]. In the same context, Papori Seal et al. [56] has incorporated manganese ferrite with multiwalled carbon nano tube by co-precipitation method followed by stirring. The crystallite size of the unfunctionalized and functionalized sample is found to be 4.5 and 6.9 nm. The SAR values are found to increase from 42.22 W/g to 53.14 W/g after functionalization. The heating effect of the colloidal suspension of the bare and functionalized sample is observed up to $\sim 45^\circ\text{C}$ and $\sim 46^\circ\text{C}$ in 30 minutes at 231 kHz working frequency, which also confirms their potential hyperthermic behaviour.

Table 2: Recent articles of SFNMs in hyperthermia studies.

SFNMs Particle	Preparation technique	Coating	Morphology (size)	Magnetic behaviour	Hyperthermic results	Ref
Mn-Zn Fe_2O_4	Co-Precipitation	Lauric Acid	Spherical (11nm)	SPM, $M_s = 4\text{kA/m}$, Magnetic	SAR = 456.4 kW/kg for 0.25 mg/mL with excellent cytotoxicity for HaLe cells	[57]
Mn-Ga Fe_2O_4	Sol-gel auto combustion	Oleic Acid-Pluronic F127	Near spherical (15-34 nm)	$M_s = 33.5-30.2$ emu/gm $M_r = 0.59-0.61$ emu/gm $H_c = 3.41-3.06$ Oe	Max SAR = 160.9 W/g for 3 mg/mL of the coated sample at frequency 354 kHz and magnetic field = 10.2 kA/m and non-Hemolytic nature with low toxicity	[58]

Fe ₃ O ₄ @CoFe 2O ₄ and Fe ₃ O ₄ @ZnCo Fe ₂ O ₄	Two step Co- Precipitation	-	Core shell structure(9- 12 nm)	Ms = 33.7 – 59.3 emu/gm Mr = 2.7 – 10.75 emu/gm Hc = 40.5- 225 Oe	Best SLP value = 379.2 W/g at frequency 97 kHz and magnetic field = 50 kA/m	[59]
CoxMn _{1-x} Fe ₂ O ₄	One pot oxidative hydrolysis method	Europium(III) with phen and TTA	Near spherical 25.4 nm	Ms = 58- 73 emu/gm	At frequency 335 kHz and magnetic field = 12kA/m and SAR values 201 W/gm for 0.5 mg/mL concentration.	[60]
Hematite and NiFe ₂ O ₄	Hydrothermal	----- -	Spherical and Hexagonal shapes (50 and 7 nm)	Super- paramagn etism ,Ms = 2.36 and 18.8 emu/gm Hc = 18 and 5 Oe Mr = 0.08 and 0.09 emu/gm	At Frequency 332.8 Hz and magnetic field = 1700e and SAR values 3.5 and 4.5 W/gm respectively.	[61]
Li-Zn Fe ₂ O ₄	Sol gel	RGO	Spherical (15 nm)	Ms = 62 emu/gm (bare) and 17 emu/gm (composite)	At frequency 290 kHz and magnetic field 335Oe and SAR = 502 W/gm (bare) and 334 W/gm (composite) for 1 mg/mL concentration.	[62]
Zn Fe ₂ O ₄	coprecipitation	Chitosan	Core shell structure (12 nm)	Ms = 87 emu/gm	At frequency 360 kHz and applied magnetic field = 33.3 kA/m and max SAR value = 264 W/g for 0.18mg/mL	[63]
Mn-Zn Fe ₂ O ₄	Sol gel auto combustion	PEG	Spherical (15.7 nm)	Ms = 30.1 - 44.4 emu/gm Mr = 15.6 – 5.7 emu/gm Hc = 497- 124 Oe	At applied frequency = 425 kHz and Magnetic field = 180 Oe and SAR = 8.6 – 3.5W/gm	[64]

3.2 Target specific drug delivery

From last half a century, carcinoma cells are becoming a foremost reason of human casualty and hence become utmost investigated research area in medical science. Till date, mainly chemotherapy treatment is employed for cancer treatment but extended selectivity, less solution solubility, developed drug resistance and biocompatibility and inimical effects on healthy cells like limitations of old chemotherapy are need to be addressed [65]. With capability of nanoparticles to control and change pharmacokinetics, nanoparticles have become first choice for fabrication of nanodrug systems. Nanodrugs have upgraded solution solubility, enhanced half-life and improved bio distribution results in comparison to tradition chemo drugs [66]. They also have more approaches towards cancerous tissues by entering endothelial layers in the tumor surroundings which have diameter ranging from 30 to 470 Angstroms. They show possible amassing in the interstitial tumor liquid due to enhanced permeability and retention aftermath showing low toxic behaviour. This effect was first observed, reported and investigated by Maeda et al. [67,68]. This effect offers cancer site targeted drug delivery through nanodrug carriers. The standardized drug delivery through magnetic nanoranged particles on the felicitous tumor site without any noticeable activity loss, after entering the effected region the drug reaches to the malignant cells. The magnetic nano ranged particles are transported to the tumor site mainly by two ways i.e active and passive targeting ways [69]. Active drug delivery way includes delivery of drug on specific site by functionalization of SFNMs with ligand or antibody groups for easy molecular recognition. Active drug delivery has increased the curative rate of chemo drug by enhancing the drug effectiveness. The various types of specific groups like folic acid, proteins and amide groups, RNA, gene, etc. are recently investigated for tumor specific hybrid system [70]. Passive drug delivery depends on the fact that nano ranged particles below 200 nm can comfortably leak through the micro vessels of malignant sites. Target specific drug delivery involves either ligand or antibody arbitrated methods [71,72,73].

Magnetic nanoparticles with different size and shape possess different physiochemical properties and also behave differently when used in the same systems. The various shapes and characteristics of the magnetic nanomaterials are governed by reaction media parameters like temperature, pH, precursor concentration, preparation time etc. [74]. Surface engineered and functionalized SFNMs with desired dimension and formulations are recently employed in clinical studies of drug delivery. Various multifunctional, specifically assembled core/shell hybrid magnetic ceramic groups are investigated as nanocarriers for in vivo target specific drug delivery in last three decades [75]. The type and concentration of the functional groups present on the nanocarrier surface is decided by the coating type and procedure employed [76]. This type of bonding is generally used

for small size molecules. The augmentation of these magnetic nanocarriers is needed utmost to fulfil various requirements of medical science. They provide feasible formulations for regulated drug transmittance and stowing profiles [77]. Several drug loading methods are a result of either chemical bonding or physical interplay between functional group on the surface of the nano-carriers and conjoined ligand [78]. The chemical and solvent stability of SFNMs is increased by coating with various surfactants, polymers, micelles, peptides etc. The bonding through covalent bond is more firm and generally present between conjoined ligand and thiol, amine and carboxylic acid like groups present on the surface of nanocarriers [79]. They decrease the side effects of the used cyto-toxic drug by controlling their dosage and systematic delivery in the human body [80]. For last few decades, nanoengineered structures which are stable and could release drug on the correct location with controlled release mechanism are being efficiently investigated. The physical interaction involves comparatively fast bond formation due to electrostatic, hydrophobic or hydrophilic interactions [81]. The magnetic nanocarrier based targeted drug delivery was initially investigated in 1970's and further with the advancement in surface engineering dimension of drug carrier, reduced dimensions from micro to nano levels [82]. For sustained release of drug, various external (magnetic field, temperature, light) or internal (pH medium, enzyme) stimuli have been used as magnetic nanocarriers also provide opportunity for drug release in real time imaging [83,84,85].

Among different types of organic and inorganic nanohybrid systems, magneto-liposome is a promising hybrid magnetic entity which could be easily guided externally by magnetic field and could easily perform targeted isolation of tumor cells and effective drug delivery like functions [85]. Figure 4 shows illustration of target specific drug delivery governed externally with magneto-Liposome injection. The magnetic nature of this system is determined by particle size of magnetic nanoparticles. Recently, Beatriz D. Cardoso et al. [86] had synthesized a hybrid magnesium ferrite-liposome nano system. The synthesized nanoparticles have SPM nature and crystallite size around 25 nm. The curcumin loading efficiency on the composite was investigated by studying quenching effect in fluorescence emission method. The encapsulation of curcumin is found to be high (>89%). The formed nano-system has shown excellent characteristics required for drug delivery.

Figure 4: Illustration of target specific delivery of drug with magneto-Liposome injection governed with external magnetic field.

K. Sriram et al. [87] have prepared and investigated nanodrug efficiency of a hybrid system consisted of vanillin- Chitosan functionalized calcium ferrite. Taguchi method was employed to find drug encapsulation efficiency of the prepared composite. The various ratios of curcumin and vanillin-chitosan were investigated and the highest encapsulation rate was observed as 98.3%. The formed composites were also studied for in-vitro cytotoxic behaviour against MCF-7 breast cells. Their biocompatible nature was confirmed by enhanced cell viability of 1,929 fibroblast cells. Recently, J. Panda and his co-workers [88] has synthesized nano drug carrier system consisted of Cobalt ferrite functionalized with Oleic acid and Poly lactic acid and glycolic acid. The efficient loading of Docetaxel drug was found to be 8.4% with efficiency rate 81.8% on the prepared ferromagnetic sample of size 21 nm. The synthesized nanodrug carrier has good internalization efficiency and antiproliferative behaviour with very less toxicity against human RBCs.

Camp thothechin is a plant derived chemo drug usually used for the treatment of various types of cancers [89]. Isarel V.M.V. Enoch et al. [90] studied drug loading and delivery

efficiency of SPM manganese ferrite sample having size approximately 93 nm. The crystalline nature of as- prepared and modified samples was confirmed by XRD results and the saturation magnetization values were found to be 38 emu/g for as-prepared and 33 emu/g for modified sample. The drug loading efficiency on coated sample was 86% of β – cyclodextrin-PEG-Manganese ferrite and 60% of PEG-Manganese ferrite samples. The increase in drug loading confirms encapsulation of Camptothecin in β – cyclodextrin. The in- vitro drug release profile shows 54.5 %and 69.4% drug release at pH 7.4 and 6.0 respectively. The drug release profile shows slow release of drug which can be attributed to firm binding between polymer and drug. The cytotoxic effect of prepared and coated samples is studied on HCT-15 and HEK293 by using MTT assay. All the observed results confirmed the potential application of the prepared sample for efficient target specific drug delivery. The same group of researcher [91] has also studied anticancer efficacy of the composite of β – cyclodextrin with Nickel ferrite loaded with Camptothecin drug. The cytotoxic nature of the prepared composite was investigated on various cell lines. The drug loading efficacy was found to be 80% and drug release rate increase with decrease in pH value, which confirms promising use of functionalized ferrite in efficient nano drug delivery systems.

3.3 Magnetic resonance imaging

It is an imaging technique which produces image of body part by utilizing the nuclear magnetic resonance phenomena shown by water molecules or fat present in human body and help in differentiating between normal and pathological tissues. The various types of atoms like Hydrogen, Helium, Carbon, Oxygen etc. can be utilized for the MR imaging but the commonly used is Hydrogen [92]. The nuclear spin of hydrogen atom gets aligned according to applied magnetic field either in parallel or anti-parallel way. The intensity difference between both the possible alignments is calculated by the given formula:

$$\Delta E = \frac{\gamma h B}{2\pi} \dots\dots\dots (1)$$

Where, γ is gyromagnetic ratio, B is applied magnetic field and h is Planck's constant [93]. This difference is very small and leads to less sensitivity due to feeble detection of hydrogen molecules. On the application of external resonant alternating radio frequency, the applied electromagnetic energy is absorbed by nuclei and this leads to alignment of nuclei in anti-parallel direction. Molecules regain their original spin alignment and come to relaxation state after removal of radio frequency [94]. The recovery of longitudinal magnetization (parallel alignment) and decay of transverse magnetization (antiparallel

alignment) are two possible NMR relaxation phenomenon and time taken for these two processes T1 and T2 determine the signal intensity [95]. There is a variety of contrast agents that are used in MRI to enhance the imaging quality by improving relaxation time. The use of magnetic nanomaterials in MRI provides better control over longitudinal and transverse relaxation times due to magnetic interactions between hydrogen atom spin and electronic spin of the used magnetic nanomaterials [96]. The efficiency of the contrast agent is calculated as the slope of the graph between the equivalent ion concentration and any of the relaxation time (r_1 and r_2), which is also known as ‘relaxivity’ [97]. The efficiency of the contrast agent is determined by type, shape, size, hydrophobic nature and clustering effect like factors. The relaxivity depends on the bonding between paramagnetic ion and water molecules and dephasing of parallel aligned nuclear spins [98]. In case of bulk magnetic contrast agents the dephasing of aligned nuclear spin phenomena dominates. As we move towards nanosized contrast agents, their magnetic behaviour highly depends on the size as their multidomain structure that becomes single domain below 10 nm. The critical size of single domain can be calculated by

$$D_c = \frac{36\sqrt{AK}}{\mu_o M_s^2} \dots\dots\dots (2)$$

Where A and K are exchange and anisotropy constant, μ_o is permeability and M_s is magnetic saturation value[99]. The size of magnetic nanomaterials is found to control the r_2 values. The latest surface engineering of magnetic nanoparticles provides better control on r_1 and r_2 values by changing the surface morphology and core-shell composition [100,101]. The type of coating determines the relaxivity and protons behaviour and generally decreases with decrease in dimension of the contrast agent [102]. The SFNMs based Contrast agents have core shell structures in which core is magnetic to provide enhancement to signal and outer shell has water loving groups and bioactive targeting materials to enhance compatibility [103]. Georgia Basina et. al. [104] have prepared hydrophilic functionalized magnetite and manganese ferrite samples and confirmed their crystallinity and surface morphology by XRD and HRTEM results. The prepared samples have particle size between 10-12 nm and they are modified with organic coating of tri-block copolymer Phronic F-127. The values of transverse relaxation times T_2 were investigated and relaxivity values are observed as 324 and 453 m/M/sec for manganese ferrite and magnetite samples. The obtained results have confirmed the potential application of the prepared sample as MRI contrast agent. Yuxiang Sun and his co-workers [105] have synthesized oleic acid functionalized Manganese-zinc ferrite nanoparticles of different shapes (Sphere shaped, worm shaped and agglomerated cluster type). They have also loaded the widely used Paclitaxel drug on these samples for dual

mode in vivo MRI and drug release studies. The drug loading rate and release rate is found to vary with the shape and observed to be good for agglomerated cluster and worm shaped samples. After investigated in vivo tumor the ranostics studies, the researchers have confirmed the potential in vivo use of the prepared samples for MRI studies. L. Ansari et al. [106] has prepared a hybrid of Zinc- Cobalt ferrite functionalized with DMSA for in vivo MRI studies. The prepared samples have size between 5 - 10 nm and MR imaging study was done on rats. The T2 values of the bare and modified samples were found to increase with decrease in ferrite sample and relaxivity value increase with increase in ferrite sample concentration. The r2 values are observed as 32.85 and 168.96 mmol/L/sec for bare and modified samples. The investigated results confirmed the potential use of prepared samples as MRI contrast agent.

Conclusion

The interest of researchers in investigating magnetic nanostructures in arenas of biomedical and healthcare sector application is majorly due to their nontoxic behaviour, biocompatible nature and above all, the ease at which these can be maneuvered externally with the application of electrical and magnetic fields, makes them potential players. SFNMs and their composites with desired size and engineered structures and shapes are recently employed for various biomedical applications. Although Fe_3O_4 has conventionally been employed for customary clinical studies, but with easy functionalization methods and various tailored characteristics SFNMs are widely studied. The efficiency of SFNMs has clearly found to be depended on the surface chemistry and by applying biopolymers as stabilizer for core-shell their functionality can still be increased. A significant breakthrough has been made by superparamagnetic particles in achieving high efficacy in cancer treatment as heating agents in Magnetic field assisted Hyperthermia Treatment. During secured procedures, superparamagnetic Nano particles are used to enhance effectiveness through homogeneous heating of the target tissues but adequate control is required as overheating or inhomogeneous heating among healthy cells might occur. Generally the small size of SFNMs brings about many benefits, such as uniform dispersion and distribution of nanoparticles resulting in uniform heat generation, prevention of agglomeration, fine tuning of shapes and sizes, biophysical properties like hydrophilicity, hydrophobicity etc. result in increased functionality further provides several advantages like lowering dosage, effective pharmaceutical activity, improved drug stability, minimization of side effects and efficient drug accumulation, which are much desired in biomedical application systems.

Although these SFNMs are much studied and investigated for their applications in MRI, hyperthermia, targeted drug delivery etc. biomedical applications. However, there is still

a vast scope identified and suggested by the researchers for improvisation in the efficacy of nanomaterials as drug delivery systems, in advanced nano formulations for bio-applications and extension in cancer treatment agents.

References

- [1] M. Dhiman, S. Rana, M. Singh, and J. K. Sharma, "Magnetic studies of mixed Mg–Mn ferrite suitable for biomedical applications," *Integr. Ferroelectr.*, vol. 202, no. 1, pp. 29–38, 2019, <https://doi.org/10.1080/10584587.2019.1674821>
- [2] Y. Fu *et al.*, "Copper ferrite-graphene hybrid: A multifunctional heteroarchitecture for photocatalysis and energy storage," *Ind. Eng. Chem. Res.*, vol. 51, no. 36, pp. 11700–11709, 2012, <https://doi.org/10.1021/ie301347j>
- [3] P. Bhattacharya, S. Dhibar, G. Hatui, A. Mandal, T. Das, and C. K. Das, "Graphene decorated with hexagonal shaped M-type ferrite and polyaniline wrapper: A potential candidate for electromagnetic wave absorbing and energy storage device applications," *RSC Adv.*, vol. 4, no. 33, pp. 17039–17053, 2014, <https://doi.org/10.1039/c4ra00448e>
- [4] S. Rana, A. Sharma, A. Kumar, S. S. Kanwar, and M. Singh, "Utility of Silane-Modified Magnesium-Based Magnetic Nanoparticles for Efficient Immobilization of *Bacillus thermoamylovorans* Lipase," *Appl. Biochem. Biotechnol.*, vol. 192, no. 3, pp. 1029–1043, 2020, <https://doi.org/10.1007/s12010-020-03379-7>
- [5] N. S. Chen, X. J. Yang, E. S. Liu, and J. L. Huang, "Reducing gas-sensing properties of ferrite compounds MFe_2O_4 ($M = Cu, Zn, Cd$ and Mg)," *Sensors Actuators, B Chem.*, vol. 66, no. 1, pp. 178–180, 2000, [https://doi.org/10.1016/S0925-4005\(00\)00368-3](https://doi.org/10.1016/S0925-4005(00)00368-3)
- [6] M. S. Dahiya, V. K. Tomer, and S. Duhan, *Metal-ferrite nanocomposites for targeted drug delivery*. Elsevier Inc., 2018
- [7] N. Alghamdi *et al.*, "Structural, magnetic and toxicity studies of ferrite particles employed as contrast agents for magnetic resonance imaging thermometry," *J. Magn. Magn. Mater.*, no. October, 2019, <https://doi.org/10.1016/j.jmmm.2019.165981>
- [8] A. Meidanchi and H. Ansari, "Copper Spinel Ferrite Superparamagnetic Nanoparticles as a Novel Radiotherapy Enhancer Effect in Cancer Treatment," *J. Clust. Sci.*, vol. 32, no. 3, pp. 657–663, 2021, <https://doi.org/10.1007/s10876-020-01832-5>

- [9] Y. J. Tu, C. K. Chang, C. F. You, and S. L. Wang, "Treatment of complex heavy metal wastewater using a multi-staged ferrite process," *J. Hazard. Mater.*, vol. 209–210, pp. 379–384, 2012, <https://doi.org/10.1016/j.jhazmat.2012.01.050>
- [10] G. Kumar, R. Rani, V. Singh, S. Sharma, K. M. Batoo, and M. Singh, "Magnetic study of nano-crystalline cobalt substituted mg-mn ferrites processed via solution combustion technique," *Adv. Mater. Lett.*, vol. 4, no. 9, pp. 682–687, 2013, <https://doi.org/10.5185/amlett.2013.1409>
- [11] N. Rezlescu and E. Rezlescu, "Dielectric properties of copper containing ferrites," *Phys. Status Solidi*, vol. 23, no. 2, pp. 575–582, 1974, <https://doi.org/10.1002/pssa.2210230229>
- [12] M. Dhiman, S. Rana, Sanansha, N. Kumar, M. Singh, and J. K. Sharma, "Influence of Ho^{3+} substitution on structural and magnetic properties of Mg–Mn ferrites," *J. Mater. Sci. Mater. Electron.*, vol. 32, no. 7, pp. 8756–8766, 2021, <https://doi.org/10.1007/s10854-021-05547-9>
- [13] H. Wang, Y. Song, X. Ye, H. Wang, W. Liu, and L. Yan, Asymmetric Supercapacitors Assembled by Dual Spinel Ferrites@Graphene Nanocomposites as Electrodes, vol. 1, no. 7. 2018
- [14] M. Dhiman, S. Rana, K. Batoo, J. K. Sharma, and M. Singh, "Synthesis and characterization of Y and Sm doped Mg nanoferrites," *Integr. Ferroelectr.*, vol. 184, no. 1, pp. 151–157, 2017, <https://doi.org/10.1080/10584587.2017.1368634>
- [15] H. Shokrollahi and K. Janghorban, "Influence of additives on the magnetic properties, microstructure and densification of Mn-Zn soft ferrites," *Mater. Sci. Eng. B Solid-State Mater. Adv. Technol.*, vol. 141, no. 3, pp. 91–107, 2007, <https://doi.org/10.1016/j.mseb.2007.06.005>
- [16] M. Tadic, S. Kralj, M. Jagodic, D. Hanzel, and D. Makovec, "Magnetic properties of novel superparamagnetic iron oxide nanoclusters and their peculiarity under annealing treatment," *Appl. Surf. Sci.*, vol. 322, pp. 255–264, 2014, <https://doi.org/10.1016/j.apsusc.2014.09.181>
- [17] Y. Matsuoka McClain, *Handbook of Modern*. 1981
- [18] A. Globus, H. Pascard, and V. Cagan, "and Fundamental Properties in Ferrites," no. 4, pp. 163–168, 1977
- [19] R. M. Bozorth, E. F. Tilden, and A. J. Williams, "Anisotropy and magnetostriction of some ferrites," *Phys. Rev.*, vol. 99, no. 6, pp. 1788–1798, 1955, <https://doi.org/10.1103/PhysRev.99.1788>

- [20] S. Singhal and K. Chandra, "Cation distribution and magnetic properties in chromium-substituted nickel ferrites prepared using aerosol route," *J. Solid State Chem.*, vol. 180, no. 1, pp. 296–300, 2007, <https://doi.org/10.1016/j.jssc.2006.10.010>
- [21] M. Gorgizadeh, N. Azarpira, M. Lotfi, F. Daneshvar, F. Salehi, and N. Sattarahmady, "Sonodynamic cancer therapy by a nickel ferrite/carbon nanocomposite on melanoma tumor: In vitro and in vivo studies," *Photodiagnosis Photodyn. Ther.*, vol. 27, no. March, pp. 27–33, 2019, <https://doi.org/10.1016/j.pdpdt.2019.05.023>
- [22] P. Sharma *et al.*, "Nanomaterial Fungicides: In Vitro and In Vivo Antimycotic Activity of Cobalt and Nickel Nanoferrites on Phytopathogenic Fungi," *Glob. Challenges*, vol. 1, no. 9, p. 1700041, 2017, <https://doi.org/10.1002/gch2.201700041>
- [23] P. L. Venugopalan, R. Sai, Y. Chandorkar, B. Basu, S. Shivashankar, and A. Ghosh, "Conformal cytocompatible ferrite coatings facilitate the realization of a nanovoyager in human blood," *Nano Lett.*, vol. 14, no. 4, pp. 1968–1975, 2014, <https://doi.org/10.1021/nl404815q>
- [24] M. S. Al-Qubaisi *et al.*, "Cytotoxicity of nickel zinc ferrite nanoparticles on cancer cells of epithelial origin," *Int. J. Nanomedicine*, vol. 8, pp. 2497–2508, 2013, <https://doi.org/10.2147/IJN.S42367>
- [25] M. Maaß, A. Griessner, V. Steixner, and C. Zierhofer, "Reduction of eddy current losses in inductive transmission systems with ferrite sheets," *Biomed. Eng. Online*, vol. 16, no. 1, pp. 1–18, 2017, <https://doi.org/10.1186/s12938-016-0297-4>
- [26] M. Ansari, A. Bigham, and H. A. Ahangar, "Super-paramagnetic nanostructured CuZnMg mixed spinel ferrite for bone tissue regeneration," *Mater. Sci. Eng. C*, vol. 105, no. August, p. 110084, 2019, <https://doi.org/10.1016/j.msec.2019.110084>
- [27] G. C. Lavorato, R. Das, J. Alonso Masa, M. H. Phan, and H. Srikanth, "Hybrid magnetic nanoparticles as efficient nanoheaters in biomedical applications," *Nanoscale Adv.*, vol. 3, no. 4, pp. 867–888, 2021, <https://doi.org/10.1039/d0na00828a>
- [28] A. Vashist, A. Vashist, Y. K. Gupta, and S. Ahmad, "Recent advances in hydrogel based drug delivery systems for the human body," *J. Mater. Chem. B*, vol. 2, no. 2, pp. 147–166, 2014, <https://doi.org/10.1039/c3tb21016b>
- [29] K. M. L. Taylor-Pashow, J. Della Rocca, R. C. Huxford, and W. Lin, "Hybrid nanomaterials for biomedical applications," *Chem. Commun.*, vol. 46, no. 32, pp. 5832–5849, 2010, <https://doi.org/10.1039/c002073g>
- [30] T. N. Pham, T. Q. Huy, and A. T. Le, "Spinel ferrite (AFe₂O₄)-based heterostructured designs for lithium-ion battery, environmental monitoring, and

- biomedical applications,” *RSC Adv.*, vol. 10, no. 52, pp. 31622–31661, 2020, <https://doi.org/10.1039/d0ra05133k>
- [31] L. H. Reddy, J. L. Arias, J. Nicolas, and P. Couvreur, “Magnetic nanoparticles: Design and characterization, toxicity and biocompatibility, pharmaceutical and biomedical applications,” *Chem. Rev.*, vol. 112, no. 11, pp. 5818–5878, 2012, <https://doi.org/10.1021/cr300068p>
- [32] J. S. Smart, “The Néel Theory of Ferrimagnetism,” *Am. J. Phys.*, vol. 23, no. 6, pp. 356–370, 1955, <https://doi.org/10.1119/1.1934006>
- [33] K. M. Krishnan, “Biomedical nanomagnetics: A spin through possibilities in imaging, diagnostics, and therapy,” *IEEE Trans. Magn.*, vol. 46, no. 7, pp. 2523–2558, 2010, <https://doi.org/10.1109/TMAG.2010.2046907>
- [34] L. Zhou *et al.*, “Development of carbon nanotubes/CoFe₂O₄ magnetic hybrid material for removal of tetrabromobisphenol A and Pb(II),” *J. Hazard. Mater.*, vol. 265, pp. 104–114, 2014, <https://doi.org/10.1016/j.jhazmat.2013.11.058>
- [35] A. A. Abd Elrahman and F. R. Mansour, “Targeted magnetic iron oxide nanoparticles: Preparation, functionalization and biomedical application,” *J. Drug Deliv. Sci. Technol.*, vol. 52, no. May, pp. 702–712, 2019, <https://doi.org/10.1016/j.jddst.2019.05.030>
- [36] C. Su, “Environmental implications and applications of engineered nanoscale magnetite and its hybrid nanocomposites: A review of recent literature,” *J. Hazard. Mater.*, vol. 322, pp. 48–84, 2017, <https://doi.org/10.1016/j.jhazmat.2016.06.060>
- [37] I. Sharifi, H. Shokrollahi, and S. Amiri, “Ferrite-based magnetic nanofluids used in hyperthermia applications,” *J. Magn. Magn. Mater.*, vol. 324, no. 6, pp. 903–915, 2012, <https://doi.org/10.1016/j.jmmm.2011.10.017>
- [38] C. S. S. R. Kumar and F. Mohammad, “Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery,” *Adv. Drug Deliv. Rev.*, vol. 63, no. 9, pp. 789–808, 2011, <https://doi.org/10.1016/j.addr.2011.03.008>
- [39] A. Sohail, Z. Ahmad, O. A. Bég, S. Arshad, and L. Sherin, “Revue sur le traitement par hyperthermie médiée par nanoparticules,” *Bull. Cancer*, vol. 104, no. 5, pp. 452–461, 2017, <https://doi.org/10.1016/j.bulcan.2017.02.003>
- [40] Suriyanto, E. Y. K. Ng, and S. D. Kumar, “Physical mechanism and modeling of heat generation and transfer in magnetic fluid hyperthermia through Néelian and Brownian relaxation: a review,” *Biomed. Eng. Online*, vol. 16, no. 1, p. 36, 2017, <https://doi.org/10.1186/s12938-017-0327-x>

- [41] Z. Hedayatnasab, F. Abnisa, and W. M. A. Wan Daud, "Investigation properties of superparamagnetic nanoparticles and magnetic field-dependent hyperthermia therapy," *IOP Conf. Ser. Mater. Sci. Eng.*, vol. 334, no. 1, 2018, <https://doi.org/10.1088/1757-899X/334/1/012042>
- [42] "coley1891[42].pdf."
- [43] R. K. GILCHRIST, R. MEDAL, W. D. SHOREY, R. C. HANSELMAN, J. C. PARROTT, and C. B. TAYLOR, "Selective inductive heating of lymph nodes," *Ann. Surg.*, vol. 146, no. 4, pp. 596–606, 1957, <https://doi.org/10.1097/00000658-195710000-00007>
- [44] Z. Hedayatnasab, F. Abnisa, and W. M. A. W. Daud, "Review on magnetic nanoparticles for magnetic nanofluid hyperthermia application," *Mater. Des.*, vol. 123, pp. 174–196, 2017, <https://doi.org/10.1016/j.matdes.2017.03.036>
- [45] D. C.F. Chan, D. B. Kirpotin, and P. A. Bunn Jr., "Synthesis and evaluation of colloidal magnetic iron oxides for the site-specific radiofrequency-induced hyperthermia of cancer," *J. Magn. Magn. Mater.*, vol. 122, no. 1–3, pp. 374–378, 1993, [https://doi.org/10.1016/0304-8853\(93\)91113-L](https://doi.org/10.1016/0304-8853(93)91113-L)
- [46] "shinkai1996[46].pdf."
- [47] A. Jordan *et al.*, "Effects of Magnetic Fluid Hyperthermia (MFH) on C3H mammary carcinoma in vivo," *Int. J. Hyperth.*, vol. 13, no. 6, pp. 587–605, 1997, <https://doi.org/10.3109/02656739709023559>
- [48] "J.1349-7006.1996.Tb03129.X.Pdf."
- [49] R. Hergt *et al.*, "Physical limits of hyperthermia using magnetite fine particles," *IEEE Trans. Magn.*, vol. 34, no. 5 PART 2, p. 37453754, 1998
- [50] H. Y. Son, A. Nishikawa, T. Ikeda, T. Imazawa, S. Kimura, and M. Hirose, "Effect of functional magnetic particles on radiofrequency capacitive heating: An in vivo study," *Japanese J. Cancer Res.*, vol. 93, no. 1, pp. 103–108, 2002, <https://doi.org/10.1111/j.1349-7006.2001.tb01071.x>
- [51] S. Lee and K. Na, "Oleic acid conjugated polymeric photosensitizer for metastatic cancer targeting in photodynamic therapy," *Biomater. Res.*, vol. 24, no. 1, pp. 1–8, 2020, <https://doi.org/10.1186/s40824-019-0177-7>
- [52] P. B. Kharat, S. B. Somvanshi, P. P. Khirade, and K. M. Jadhav, "Induction heating analysis of surface-functionalized nanoscale CoFe₂O₄ for magnetic fluid hyperthermia toward noninvasive cancer treatment," *ACS Omega*, vol. 5, no. 36, pp. 23378–23384, 2020, <https://doi.org/10.1021/acsomega.0c03332>

- [53] S. B. Somvanshi *et al.*, “Hyperthermic evaluation of oleic acid coated nano-spinel magnesium ferrite: Enhancement via hydrophobic-to-hydrophilic surface transformation,” *J. Alloys Compd.*, vol. 835, p. 155422, 2020, <https://doi.org/10.1016/j.jallcom.2020.155422>
- [54] C. E. Demirci Dönmez, P. K. Manna, R. Nickel, S. Aktürk, and J. Van Lierop, “Comparative Heating Efficiency of Cobalt-, Manganese-, and Nickel-Ferrite Nanoparticles for a Hyperthermia Agent in Biomedicines,” *ACS Appl. Mater. Interfaces*, vol. 11, no. 7, pp. 6858–6866, 2019, <https://doi.org/10.1021/acsami.8b22600>
- [55] C. Fisher, A. E. Rider, Z. Jun Han, S. Kumar, I. Levchenko, and K. Ostrikov, “Applications and nanotoxicity of carbon nanotubes and graphene in biomedicine,” *J. Nanomater.*, vol. 2012, 2012, <https://doi.org/10.1155/2012/315185>
- [56] P. Seal, M. Hazarika, N. Paul, and J. P. Borah, “MWCNT-MnFe₂O₄ nanocomposite for efficient hyperthermia applications,” *AIP Conf. Proc.*, vol. 1942, 2018, <https://doi.org/10.1063/1.5028714>
- [57] A. Bhardwaj, K. Parekh, and N. Jain, “In vitro hyperthermic effect of magnetic fluid on cervical and breast cancer cells,” *Sci. Rep.*, vol. 10, no. 1, pp. 1–13, 2020, <https://doi.org/10.1038/s41598-020-71552-3>
- [58] J. Sánchez, M. Rodríguez-Reyes, D. A. Cortés-Hernández, C. A. Ávila-Orta, and P. Y. Reyes-Rodríguez, “Heating capacity and biocompatibility of Pluronic-coated manganese gallium ferrites for magnetic hyperthermia treatment,” *Colloids Surfaces A Physicochem. Eng. Asp.*, vol. 612, no. July 2020, 2021, <https://doi.org/10.1016/j.colsurfa.2020.125986>
- [59] M. S. A. Darwish, H. Kim, H. Lee, C. Ryu, J. Y. Lee, and J. Yoon, “Engineering core-shell structures of magnetic ferrite nanoparticles for high hyperthermia performance,” *Nanomaterials*, vol. 10, no. 5, pp. 1–16, 2020, <https://doi.org/10.3390/nano10050991>
- [60] A. Das, S. Mohanty, R. Kumar, and B. K. Kuanr, “Tailoring the Design of a Lanthanide Complex/Magnetic Ferrite Nanocomposite for Efficient Photoluminescence and Magnetic Hyperthermia Performance,” *ACS Appl. Mater. Interfaces*, vol. 12, no. 37, pp. 42016–42029, 2020, <https://doi.org/10.1021/acsami.0c13690>
- [61] O. M. Lemine, N. Madkhali, M. Hjiri, N. A. All, and M. S. Aida, “Comparative heating efficiency of hematite (α -Fe₂O₃) and nickel ferrite nanoparticles for magnetic

- hyperthermia application,” *Ceram. Int.*, vol. 46, no. 18, pp. 28821–28827, 2020, <https://doi.org/10.1016/j.ceramint.2020.08.047>
- [62] A. Mallick, A. S. Mahapatra, A. Mitra, J. M. Greneche, R. S. Ningthoujam, and P. K. Chakrabarti, “Magnetic properties and bio-medical applications in hyperthermia of lithium zinc ferrite nanoparticles integrated with reduced graphene oxide,” *J. Appl. Phys.*, vol. 123, no. 5, 2018, <https://doi.org/10.1063/1.5009823>
- [63] D. Lachowicz *et al.*, “Enhanced hyperthermic properties of biocompatible zinc ferrite nanoparticles with a charged polysaccharide coating,” *J. Mater. Chem. B*, vol. 7, no. 18, pp. 2962–2973, 2019, <https://doi.org/10.1039/c9tb00029a>
- [64] S. O. Aisida *et al.*, “The role of polyethylene glycol on the microstructural, magnetic and specific absorption rate in thermoablation properties of Mn-Zn ferrite nanoparticles by sol–gel protocol,” *Eur. Polym. J.*, vol. 132, no. May, p. 109739, 2020, <https://doi.org/10.1016/j.eurpolymj.2020.109739>
- [65] H. Nehoff, N. N. Parayath, L. Domanovitch, S. Taurin, and K. Greish, “Nanomedicine for drug targeting: Strategies beyond the enhanced permeability and retention effect,” *Int. J. Nanomedicine*, vol. 9, no. 1, pp. 2539–2555, 2014, <https://doi.org/10.2147/IJN.S47129>
- [66] S. Biswas and V. P. Torchilin, “Nanopreparations for organelle-specific delivery in cancer,” *Adv. Drug Deliv. Rev.*, vol. 66, pp. 26–41, 2014, <https://doi.org/10.1016/j.addr.2013.11.004>
- [67] H. Maeda, “The enhanced permeability and retention (EPR) effect in tumor vasculature: The key role of tumor-selective macromolecular drug targeting,” *Adv. Enzyme Regul.*, vol. 41, no. 1, pp. 189–207, 2001, [https://doi.org/10.1016/S0065-2571\(00\)00013-3](https://doi.org/10.1016/S0065-2571(00)00013-3)
- [68] H. Maeda, G. Y. Bharate, and J. Daruwalla, “Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect,” *Eur. J. Pharm. Biopharm.*, vol. 71, no. 3, pp. 409–419, 2009, <https://doi.org/10.1016/j.ejpb.2008.11.010>
- [69] P. Kumari, B. Ghosh, and S. Biswas, “Nanocarriers for cancer-targeted drug delivery,” *J. Drug Target.*, vol. 24, no. 3, pp. 179–191, 2016, <https://doi.org/10.3109/1061186X.2015.1051049>
- [70] J. Su *et al.*, “Long Circulation Red-Blood-Cell-Mimetic Nanoparticles with Peptide-Enhanced Tumor Penetration for Simultaneously Inhibiting Growth and Lung Metastasis of Breast Cancer,” *Adv. Funct. Mater.*, vol. 26, no. 8, pp. 1243–1252, 2016, <https://doi.org/10.1002/adfm.201504780>

- [71] X. Yang *et al.*, “Tumor Microenvironment-Responsive Dual Drug Dimer-Loaded PEGylated Bilirubin Nanoparticles for Improved Drug Delivery and Enhanced Immune-Chemotherapy of Breast Cancer,” *Adv. Funct. Mater.*, vol. 29, no. 32, pp. 1–12, 2019, <https://doi.org/10.1002/adfm.201901896>
- [72] O. C. Olson and J. A. Joyce, “Cysteine cathepsin proteases: Regulators of cancer progression and therapeutic response,” *Nat. Rev. Cancer*, vol. 15, no. 12, pp. 712–729, 2015, <https://doi.org/10.1038/nrc4027>
- [73] Z. Karimi, L. Karimi, and H. Shokrollahi, “Nano-magnetic particles used in biomedicine: Core and coating materials,” *Mater. Sci. Eng. C*, vol. 33, no. 5, pp. 2465–2475, 2013, <https://doi.org/10.1016/j.msec.2013.01.045>
- [74] M. Angelakeris, “Magnetic nanoparticles: A multifunctional vehicle for modern theranostics,” *Biochim. Biophys. Acta - Gen. Subj.*, vol. 1861, no. 6, pp. 1642–1651, 2017, <https://doi.org/10.1016/j.bbagen.2017.02.022>
- [75] M. Arruebo, R. Fernández-Pacheco, M. R. Ibarra, and J. Santamaría, “Magnetic nanoparticles for drug delivery The potential of magnetic NPs stems from the intrinsic properties of their magnetic cores combined with their drug loading capability and the biochemical properties that can be bestowed on them by means of a suitab,” vol. 2, no. 3, pp. 22–32, 2007, [Online]. Available: <https://pdfs.semanticscholar.org/1844/8eb43dc235f82cb591983bc8df5ed799984c.pdf>
- [76] F. Xiong, S. Huang, and N. Gu, “Magnetic nanoparticles: recent developments in drug delivery system,” *Drug Dev. Ind. Pharm.*, vol. 44, no. 5, pp. 697–706, 2018, <https://doi.org/10.1080/03639045.2017.1421961>
- [77] J. Kudr *et al.*, “Magnetic nanoparticles: From design and synthesis to real world applications,” *Nanomaterials*, vol. 7, no. 9, 2017, <https://doi.org/10.3390/nano7090243>
- [78] S. Ahadian *et al.*, “Micro and nanoscale technologies in oral drug delivery,” *Adv. Drug Deliv. Rev.*, vol. 157, pp. 37–62, 2020, <https://doi.org/10.1016/j.addr.2020.07.012>
- [79] J. Cao, D. Huang, and N. A. Peppas, “Advanced engineered nanoparticulate platforms to address key biological barriers for delivering chemotherapeutic agents to target sites,” *Adv. Drug Deliv. Rev.*, vol. 167, pp. 170–188, 2020, <https://doi.org/10.1016/j.addr.2020.06.030>
- [80] F. Laffleur and V. Keckeis, “Advances in drug delivery systems: Work in progress still needed?,” *Int. J. Pharm. X*, vol. 2, no. March, 2020, <https://doi.org/10.1016/j.ijpx.2020.100050>

- [81] K. Park, “Controlled drug delivery systems: Past forward and future back,” *J. Control. Release*, vol. 190, pp. 3–8, 2014, <https://doi.org/10.1016/j.jconrel.2014.03.054>
- [82] P. Fomby *et al.*, “Stem cells and cell therapies in lung biology and diseases: Conference report,” *Ann. Am. Thorac. Soc.*, vol. 12, no. 3, pp. 181–204, 2010, <https://doi.org/10.1002/term>
- [83] B. T. Mai, S. Fernandes, P. B. Balakrishnan, and T. Pellegrino, “Nanosystems Based on Magnetic Nanoparticles and Thermo- or pH-Responsive Polymers: An Update and Future Perspectives,” *Acc. Chem. Res.*, vol. 51, no. 5, pp. 999–1013, 2018, <https://doi.org/10.1021/acs.accounts.7b00549>
- [84] Z. Wang, X. Deng, J. Ding, W. Zhou, X. Zheng, and G. Tang, “Mechanisms of drug release in pH-sensitive micelles for tumour targeted drug delivery system: A review,” *Int. J. Pharm.*, vol. 535, no. 1–2, pp. 253–260, 2018, <https://doi.org/10.1016/j.ijpharm.2017.11.003>
- [85] W. Il Choi, A. Sahu, F. R. Wurm, and S. M. Jo, “Magnetoliposomes with size controllable insertion of magnetic nanoparticles for efficient targeting of cancer cells,” *RSC Adv.*, vol. 9, no. 26, pp. 15053–15060, 2019, <https://doi.org/10.1039/c9ra02529d>
- [86] B. D. Cardoso *et al.*, “Magnetoliposomes containing magnesium ferrite nanoparticles as nanocarriers for the model drug curcumin,” *R. Soc. Open Sci.*, vol. 5, no. 10, 2018, <https://doi.org/10.1098/rsos.181017>
- [87] S. Kamaraj, U. M. Palanisamy, M. S. B. Kadhar Mohamed, A. Gangasalam, G. A. Maria, and R. Kandasamy, “Curcumin drug delivery by vanillin-chitosan coated with calcium ferrite hybrid nanoparticles as carrier,” *Eur. J. Pharm. Sci.*, vol. 116, no. January, pp. 48–60, 2018, <https://doi.org/10.1016/j.ejps.2018.01.023>
- [88] J. Panda *et al.*, “Anticancer potential of docetaxel-loaded cobalt ferrite nanocarrier: an in vitro study on MCF-7 and MDA-MB-231 cell lines,” *J. Microencapsul.*, vol. 38, no. 1, pp. 36–46, 2021, <https://doi.org/10.1080/02652048.2020.1842529>
- [89] X. H. Wang, M. Huang, C. K. Zhao, C. Li, and L. Xu, “Design, synthesis, and biological activity evaluation of camptothecin-HAA-Norcantharidin conjugates as antitumor agents in vitro,” *Chem. Biol. Drug Des.*, vol. 93, no. 6, pp. 986–992, 2019, <https://doi.org/10.1111/cbdd.13397>
- [90] I. V. M. V. Enoch, S. Ramasamy, S. Mohiyuddin, P. Gopinath, and R. Manoharan, “Cyclodextrin-PEG conjugate-wrapped magnetic ferrite nanoparticles for enhanced

- drug loading and release,” *Appl. Nanosci.*, vol. 8, no. 3, pp. 273–284, 2018, <https://doi.org/10.1007/s13204-018-0798-5>
- [91] S. Ramasamy, I. V. M. V. Enoch, and S. Rex Jeya Rajkumar, “Polymeric cyclodextrin-dextran spooled nickel ferrite nanoparticles: Expanded anticancer efficacy of loaded camptothecin,” *Mater. Lett.*, vol. 261, p. 127114, 2020, <https://doi.org/10.1016/j.matlet.2019.127114>
- [92] O. Veisich, J. W. Gunn, and M. Zhang, “Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging,” *Adv. Drug Deliv. Rev.*, vol. 62, no. 3, pp. 284–304, 2010, <https://doi.org/10.1016/j.addr.2009.11.002>
- [93] L. Wu, A. Mendoza-Garcia, Q. Li, and S. Sun, “Organic Phase Syntheses of Magnetic Nanoparticles and Their Applications,” *Chem. Rev.*, vol. 116, no. 18, pp. 10473–10512, 2016, <https://doi.org/10.1021/acs.chemrev.5b00687>
- [94] H. Zhang *et al.*, “Ultrasmall Ferrite Nanoparticles Synthesized via Dynamic Simultaneous Thermal Decomposition for High-Performance and Multifunctional T1 Magnetic Resonance Imaging Contrast Agent,” *ACS Nano*, vol. 11, no. 4, pp. 3614–3631, 2017, <https://doi.org/10.1021/acsnano.6b07684>
- [95] D. Ni, W. Bu, E. B. Ehlerding, W. Cai, and J. Shi, “Engineering of inorganic nanoparticles as magnetic resonance imaging contrast agents,” *Chem. Soc. Rev.*, vol. 46, no. 23, pp. 7438–7468, 2017, <https://doi.org/10.1039/c7cs00316a>
- [96] J. Wallyn and N. Anton, “Biomedical Imaging : Principles , Technologies , Clinical Aspects , C o n t r a s t A g e n t s , L i m i t a t i o n s a n d F u t u r e T r e n d s in Nanomedicines,” pp. 1–31, 2019
- [97] Y. Miao *et al.*, “Composition-tunable ultrasmall manganese ferrite nanoparticles: Insights into their in vivo T1 contrast efficacy,” *Theranostics*, vol. 9, no. 6, pp. 1764–1776, 2019, <https://doi.org/10.7150/thno.31233>
- [98] Z. Zhou, L. Yang, J. Gao, and X. Chen, “Structure–Relaxivity Relationships of Magnetic Nanoparticles for Magnetic Resonance Imaging,” *Adv. Mater.*, vol. 31, no. 8, pp. 1–32, 2019, <https://doi.org/10.1002/adma.201804567>
- [99] D. Dheer, J. Nicolas, and R. Shankar, “Cathepsin-sensitive nanoscale drug delivery systems for cancer therapy and other diseases,” *Adv. Drug Deliv. Rev.*, vol. 151–152, pp. 130–151, 2019, <https://doi.org/10.1016/j.addr.2019.01.010>
- [100] Y. Wang *et al.*, “Engineering ferrite nanoparticles with enhanced magnetic response for advanced biomedical applications,” *Mater. Today Adv.*, vol. 8, 2020, <https://doi.org/10.1016/j.mtadv.2020.100119>

- [101] D. H. Kim, H. Zeng, T. C. Ng, and C. S. Brazel, “T1 and T2 relaxivities of succimer-coated MFe_2O_4 ($\text{M}=\text{Mn}^{2+}$, Fe^{2+} and Co^{2+}) inverse spinel ferrites for potential use as phase-contrast agents in medical MRI,” *J. Magn. Magn. Mater.*, vol. 321, no. 23, pp. 3899–3904, 2009, <https://doi.org/10.1016/j.jmmm.2009.07.057>
- [102] F. Hyder and S. Manjura Hoque, “Brain tumor diagnostics and therapeutics with superparamagnetic ferrite nanoparticles,” *Contrast Media Mol. Imaging*, vol. 2017, 2017, <https://doi.org/10.1155/2017/6387217>
- [103] H. Shokrollahi, A. Khorramdin, and G. Isapour, “Magnetic resonance imaging by using nano-magnetic particles,” *J. Magn. Magn. Mater.*, vol. 369, pp. 176–183, 2014, <https://doi.org/10.1016/j.jmmm.2014.06.023>
- [104] G. Basina *et al.*, “Water-soluble spinel ferrites by a modified polyol process as contrast agents in MRI,” *AIP Conf. Proc.*, vol. 1311, no. 2010, pp. 441–446, 2010, <https://doi.org/10.1063/1.3530053>
- [105] Y. Sun *et al.*, “High-Performance Worm-like Mn-Zn Ferrite Theranostic Nanoagents and the Application on Tumor Theranostics,” *ACS Appl. Mater. Interfaces*, vol. 11, no. 33, pp. 29536–29548, 2019, <https://doi.org/10.1021/acsami.9b08948>
- [106] L. Ansari *et al.*, “Synthesis, Characterization and MRI Application of Cobalt-Zinc Ferrite Nanoparticles Coated with DMSA: An In-vivo Study,” *Appl. Magn. Reson.*, vol. 52, no. 1, pp. 33–45, 2021, <https://doi.org/10.1007/s00723-020-01220-2>