ACERP: Vol. 6, No.1, (Winter 2020) 1-15

Advanced Ceramics Progress

Review Article

Journal Homepage: www.acerp.ir

An Overview of Cobalt Ferrite Core-Shell Nanoparticles for Magnetic Hyperthermia Applications

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PAPER INFO

Paper history:

Received 14 August 2019
Accepted in revised form 15 February 2020

Keywords:

Hyperthermia
Cobalt Ferrite
Rare-earth Elements
Surface Modification

ABSTRACT

Cobalt ferrite nanoparticles ($CoFe_2O_4$) are well known for some distinctive characteristics such as high magnetic permeability and coercive force, good saturation magnetization, excellent physical, and chemical stability, which make them so attractive for magnetic storage, magnetic resonance imaging (MRI), drug delivery, optical-magnetic equipment, radar absorbing materials (RAM), and magnetic hyperthermia applications. According to these particularities, cobalt ferrite-based core-shell nanoparticles have been reviewed focusing on hyperthermia applications. Promoting anisotropic constant and magnetic permeability, increasing the chemical and physical stability of nanoparticles, the proper distribution of particles in aquatic environments to prevent agglomeration, sedimentation, and obstruction in a specific position, as well as enhancing biocompatibility and avoiding the disadvantages, are essential for better efficiency in hyperthermia aspect. For this purpose, the synthesis of magnetic nanoparticles of cobalt ferrite with preferentially smaller sizes, as well as a narrower range of particle size distribution, is the primary objective of the synthesis process. Hence, it is important to identify the influence of effective parameters on the size and shape of nanoparticles, the substitution mechanisms of rare-earth elements, and changing the structure and behavior of the magnetic properties by these elements and finally, the thermal properties. Moreover, surface modifications and coating are other significant parameters in hyperthermia field that are investigated to achieve a suitable and stable distribution in aqueous media, and how they behave against the magnetic field.

1. INTRODUCTION

Metallic oxide nanoparticles are very much attractive due to their unique optical, electronic, and magnetic properties. Cobalt ferrite nanoparticles ($CoFe_2O_4$) with spinel structure have high magnetic permeability, high coercive force (greater than 50KOe), good saturation magnetization (M_S) ($80 emu.g^{-1}$), mechanical hardness, and excellent stability of physical and chemical properties. Therefore, this material is a suitable candidate for high-density magnetic storage, magnetic fluid technology, drug delivery, magnetic resonance imaging (MRI), magnetic hyperthermia (MH) for killing cancerous cells, and radar absorbing materials (RAM) applications [1]. It should be noted that the magnetite iron oxide nanoparticles (Fe_3O_4) are the most commonly used materials due to their lower toxicity, magnetic properties, relatively easy synthesis, and stability in many colloidal environments [2]. On the other hand, Fe_3O_4 has a high M_S and low anisotropic constant (K), and its practical application causes some kinds of aches and pains that are difficult to control. This problem can be solved through using complex magnetic oxides, whose physical, chemical, and magnetic properties can be modified with a variety of elements [3]. Hence, its anisotropic constant and magnetic permeability are modified by cationic substitution [3,4]. One of the substituted elements is cobalt. This element improves the thermal properties for the sake of enhanced anisotropic magnetic constant, chemical, and physical stability [5]. Furthermore, cobalt ferrite nanoparticles have special spatial and stronger linkages of albumin proteins compared to magnetite. Therefore, cobalt ferrite nanoparticles are considered as the best candidate that meet all expected conditions [3].

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The other thing about magnetic nanoparticles is the high ratio of the surface to the volume of the particles, which tends to accumulate and absorb plasma proteins during use. Besides, magnetic nanoparticles are mainly collected in the liver due to hydrophobic surfaces. In fact, unmodified nanoparticles in the bloodstream system are rapidly flooded. It is essential to extend the flow time of nanoparticles and reduce peptidase to improve the use of magnetic nanoparticles in various biological applications. Additionally, biocompatibility will decrease due to the presence of cobalt. Therefore, cobalt ferrite nanoparticle coatings are used to prevent possible damages to biocompatibility provide chemical and physical stability and appropriate distribution of particles in the fluid system. The surface modification of magnetic nanoparticles with a variety of coatings and surface modifiers, such as hydrophilic polymeric compounds, significantly prolongs the time of nanoparticle circulation in the blood through reducing or eliminating Protein adsorption [3,6].

Regarding biological applications, nanoparticles should (1) be less than 100nm (in some references up to 200nm) with a narrow size distribution, so that particles exhibit uniformity in physical and chemical properties; (2) have high saturation magnetization; and (3) require a special surface modification to improve their biocompatibility, and allow them to release at a specific position [3,6,7].

Therefore, the synthesis and coating of spinel cobalt ferrites are desirable for multiple applications including magnetic hyperthermia. It is important to study the parameters affecting powder synthesis and their mechanism of action to achieve optimal properties. Moreover, the type of shell applied to the nanoparticle and how it forms on the surface of nanoparticles will be considered to the final properties of the product. Accordingly, the magnetic hyperthermia and the mechanisms and factors influencing hyperthermia are initially discussed. Cobalt ferrite core-shell nanoparticles are then studied. In this paper, the mechanism of action and the effects of various rare-earth elements on the structure, as well as the magnetic properties of cobalt ferrite and its thermal properties, are comprehensively discussed due to the importance of the doping in the structure and their effects on the properties. The polymer coating of nanoparticles is also investigated with an emphasis on experimental papers.

2. MAGNETIC HYPERTHERMIA

Magnetic materials are used in a variety of applications, including computers, electronics, chemical and mineral industries, automotive, etc. [8-9]. In addition, magnetic nanoparticles produce high thermal energy at different magnetic fields in the medical scope. Local heat in the biologic tissues stops the growth of the tumors and destroys them. Also, these materials can also be used in diagnostic applications such as magnetic resonance imaging (MRI) and drug delivery to the removal of cancerous cells [10]. This issue is discussed considering the application of magnetic nanoparticles in magnetic hyperthermia.

The term hyperthermia is used to explain a therapeutic approach in which a defective and cancerous tissue is subjected to a heat treatment that is higher than the normal physiological temperature (about 37°C) [11-13]. In conventional hyperthermia, heat may be generated by various sources such as microwave, supersonic, or radio waves. The hyperthermia of magnetic particles, known as MH, employs magnetic nanoparticles against an alternating magnetic field (AC). According to the published reports of Cristiano Blanco Andujuar (2016), Hatami (2018), Alison E. Deatsch (2014), and M. Dalal (2018), this method is originally introduced by Gilchrist et al (1957) with the localized heat of lymph nodes by magnetic nanoparticles. Since then, many researchers have considered it in the development of MH and MNPs as heat agents [11-14].

This method is considered as an alternative and attractive treatment for cancer due to the lack of side effects compared with other therapies such as chemotherapy and radiotherapy. Most of the known hyperthermia methods suffer from certain limitations in the tumor or the control of the exact amount of thermal energy, or that the entire body is under heat and still challenging for specific tissues and tends to significant heat around tissue or inadequate heat. In contrast, it is possible to achieve a beneficial therapeutic effect with the lowest concentration of magnetic nanoparticles in magnetic hyperthermia due to the high specific absorption rate (SAR) from an optimal combination of destructive magnetic nanoscale materials [10].

Magnetic nanoparticles in sustained colloidal suspensions can be released without invasive properties through a variety of drug release pathways. After release, these particles can be heated with an alternating magnetic field at frequencies that have no negative effect on healthy tissue. This action creates sufficient heat in deep tissues along with the release of negligible energy in the path. Also, magnetic nanoparticles may be directed to some surfaces with the external magnetic field. Direction and substitution of nanoparticles in a particular tissue are also available using a suitable chemical agent. Also, it has been shown that magnetic nanoparticles are selectively collected in certain types of tumors. Finally, as noted above, magnetic nanoparticles are used for drug delivery and for hyperthermia. Therefore, multifaceted treatment is possible [13-14]. The rules governing magnetic nanoparticles for hyperthermia are investigated to properly understand the magnetic hyperthermia. The capacity of a material for producing heat under the influence of an AC magnetic field with a specific absorption rate (SAR) or specific loss power (SLP) is defined as Equation (1):

$$SAR = (\frac{\Delta T}{\Delta t})(\frac{C}{mFe}) \quad (1)$$

C is the heat capacity of the liquid per unit mass, mFe is the concentration of the colloid solution (g.l^{-1} of iron), and ΔT/Δt is the increase of the measured temperature relative to the time. The SAR value is widely used to describe the ability of heat production of a system. However, the SAR value cannot be directly compared for a given sample of different experiments because it depends on the field and frequency of the applied magnetic field. As a result, intrinsic loss power (ILP) is proposed to normalize the SAR value using an alternative parameter, which allows direct comparison of the results from different groups as an independent parameter (Equation 2):

$$ILP = P/(\rho \mathrm{H}^2\mathrm{f}) = \mathrm{SAR}/(\mathrm{H}^2\mathrm{f}) \quad (2)$$

P is the volumetric power dissipation $P = \mu_0\pi\chi''(f)\, fH^2$, $\chi''(f)$ is the imaginary part of the magnetic susceptibility, ρ is the magnetic field density, H is the magnetic field strength, and f is the frequency [11].

In magnetic hyperthermia, three independent mechanisms including Neel relaxation, Brownian relaxation, and hysteresis loss have been identified. Each of them depends strongly on the size, shape, crystalline anisotropy, and agglomeration of the nanoparticles [11,13]. It has been shown that the heat-related to the hysteresis loss results from the displacement of the domain walls, which occur in magnetic particles larger than 100nm; it is necessary to explain that the two characteristics of coercivity and remanence strongly depend on the volume of particles that suddenly disappear for smaller particles. In particular, coercivity is defined as $Hc=(2K/M_S)[1-(V_C/V)^{1/2}]$ for $V>V_C$, so that V_C is the critical volume of the particle, and the relaxation mechanisms are dominate below it.

In the hysteresis magnetic behavior, the energy lost in each cycle P can be obtained from the multiple of the surface area under curve A at the frequency (Equation 3). A is determined by the coercive force and a remanence magnetization of the nanoparticle:

$$P = \mu_0 f \oint H dM = Af \quad (3)$$

No hysteresis is observed when superparamagnetic particles are exposed to the magnetic field, which means there is no heat dissipation through this mechanism. Therefore, thermal losses predominate by relaxation mechanisms [11]. In this case, heating is created by rotating the magnetic moment of each particle against an energy barrier. If the conditions are such that this spin causes the whole particle to rotate, the particles are placed under the Brownian mechanism, and thermal energy is released through shear stress in the fluid medium. In any case, if the moment spins while the particle stays constant, the particle is in the Neel state, and the thermal energy inside the crystal is dissipated by rearrangement of the bipolar atomic momentum [13].

At the Neel relaxation mechanism, the characteristic time to return to the equilibrium is defined as [11]:

$$\tau_N = \tau_0\, e^{(KV/k_B T)} \quad (4)$$

Where τ_N is the Neel relaxation time, τ_0 is the exponential parameter ($\tau_0=10^{-9}$-$10^{-3}s^{-1}$), K is the effective anisotropy constant, V is the volume of nanoparticles, K_B is Boltzmann constant, and T is the temperature (K_BT is thermal energy). This time is modified by Brownie [13] as follow:

$$\tau_N = \tau_0\, (\pi kT/KV)^{0.5}\, e^{(KV/k_B T)} \quad (5)$$

V is the volume of the particle and K is an anisotropy constant.

In the Brownian motion, which causes the magnetic field to rotate the nanoparticle physically in the fluid and thus, to the shear friction, Brownian relaxation time strongly depends on the viscosity of the solution η and the hydrodynamic volume of the particle (V_H), and is expressed via the following equation [11,13]:

$$\tau_B = (3\eta\, V_H/\, kT) \quad (6)$$

In general, the dynamic volume of the particle (V_H) is greater than the particle size due to the interaction of the liquid or the adsorbed modifiers [11,13].

The Neal and Brownian mechanisms may occur in parallel and simultaneously; therefore, the effective relaxation time (τ) of the system is given as Equation 7 [11,13]:

$$1/\tau = 1/\tau_B + 1/\tau_N \quad (7)$$

As described above, the size of the nanoparticles determines the main mechanism. The Brown mechanism is predominant in low viscosity conditions for large nanoparticles, while the Neel mechanism is dominant in systems with smaller nanoparticles in viscose solutions [11,13]. However, the phenomenon, which is dominant in relaxation time, is heavily dependent on the anisotropy constant of the nanoparticle, the mainly magnetocrystalline anisotropy, and morphology effects [11]. Moreover, the concentration of nanoparticles in the suspension is one of the parameters that influence the production of heat. Generally, the magnetic relaxation time is reduced and the thermal performance is affected by increasing the concentration of nanoparticles in both Brownian and Neel mechanisms [11, 13].

2.1. The effective factors on magnetic hyperthermia

One of the remarkable points in magnetic hyperthermia is to ensure that the nanoparticle magnetic array is reversible in a medium-range magnetic field (H_0<100-200Oe), since assuming the use of a strong magnetic field requires a sufficiently large electric current generation, which may be dangerous in clinical treatment [10].

Several factors influence the heat generated by a group of magnetic nanoparticles. These variables are discussed as extrinsic and intrinsic parameters [11,13].

The heat generated from magnetic nanoparticles is not only related to the structure and composition of nanoparticles (intrinsic parameters), but also the frequency and intensity of the magnetic field (H) applied (extrinsic parameters). SAR values enhance with increasing frequency and/or applied field. Most SAR values have reported at a frequency of 300-700kHz and a range of 10 to 30KA^{-1} for the applied field. However, it is still unclear whether these values are safe at the clinical treatments. The Brizovic criterion published Atkins and Brizovic (1988) reported a safety margin to avoid eddy current effects for magnetic hyperthermia. The Hf should be smaller than 4.85×10^8A.ms^{-1}, which have been considered as a consensus standard for all the researchers and further studies have not been reported [11,13].

The role of the frequency in SAR is considerably more complicated than the field amplitude. However, its effect is subtle and delicate in the range of frequencies raised. Therefore, this issue has not been the focus of hyperthermia studies [13].

Intrinsic factors are also important in addition to external parameters that influence the function of magnetic hyperthermia. The first in this field is the type/composition of materials. In fact, magnetic properties such as saturation magnetization, coercive force, and anisotropic magnetocrystalline constant, which have been linked to hyperthermia in previous relationships, depend greatly on the type of composition and size. On this basis, the influence of rare-earth metals on the structure and magnetic properties of ferrites have attracted the attention of many researchers. However, in section 3.1, the mechanism of the substitution elements operation in the structure and effect on magnetic properties, the role of different elements and their effect on the size and magnetic properties are discussed briefly.

In fact, different elements have different electron arrangements and ionic radii. These doped elements fall into tetrahedral or octahedral spaces by incorporating elements into the structure of ferrite, depending on the atomic arrangement, ionic radius, and even, doped element concentration. This can also cause changes in the magnetic moment of the material in addition to changing the lattice parameter of the structure and size of the particle [9]. Studies have shown that changes in saturation magnetization by chemical composition can be justified by the exchange reactions between the cations distributed in octahedral and tetrahedral sites [15].

On the other hand, the particle size parameter is one of the most important factors affecting magnetic properties. Changing the size of the particle can change the magnetic domains. Also, changes in magnetic domains can have a significant effect on magnetic properties such as M_S, H_C, and SAR. A ferromagnetic material that has a significant coercive force can be converted to a superparamagnetic material with a H_C near zero by reducing the particle size.

Regarding the investigation of the effect of particle size on saturation magnetization, it should be noted that the greater the surface area of a particle to its volume ratio (the smaller the particle size), the less saturation magnetization is predicted to occur because the spins on the surface of the particles have many perturbations. Therefore, when the effects of these surface perturbations can be mitigated the Ms further increases. Therefore, the saturation magnetization also increases as the particle size increases [16,17]. The coercive force will increase as the grain size decreases. This is because as the grain reduces, the volume fraction of defects will increase, and as a result, the domain walls would be changed harder and the H_C will increase. Equation 8 expresses the relation between H_C and D [18-20]:

$$Hc = a + b/D \tag{8}$$

Where H_C is the coercive force, a and b are the constant numbers and D is the particle size.

On the other hand, the coercive field depends on the anisotropic magnetocrystalline and the distribution of cations in the interstitials. For instance, high anisotropic magnetocrystalline in cobalt ferrite is mainly due to the presence of cobalt ions in octahedral sites, while this ion is placed in octahedral sites with the substitution of an element like Gd and cobalt ions move to tetrahedral sites, reducing the K [15].

There is also a relationship between saturation magnetization, coercive force, and anisotropic magnetocrystalline known as Wuhlfarth theory (Equation 9) [21-23]. This relationship well indicates the direct correlation of the H_C and K, and their inverse ratio to the M_S. As it was stated, there will be a decrease in the M_S and an increase in the H_C along particle size reduction and vice versa:

$$Hc = 0.98K/Ms \tag{9}$$

Where H_C is the coercive force, K is the anisotropic magnetocrystalline, and M_S is the saturation magnetization.

On the other hand, as obvious in Equation 6, Brownian relaxation time is proportional to fluid viscosity. In extremely viscous environments, its relaxation time is longer and heating is dominated by the Neel mechanism. It has been empirically proved that the mechanism governing the heat dissipation in small nanoparticles is the Neel mechanism, while Brownian motion plays an important role for larger nanoparticles [11].

Determining the mechanism for heat generation is largely dependent on the size of the particles. The hysteresis loss in large particles (>100nm) predominates [11,13], but these sizes of particles are too large for many clinical treatments. These particles do not form a stable colloidal system and do not easily penetrate and dissipate in tumors; Also, large particles may activate the mechanisms of bacterial defense in the body [13]. In smaller particles, the hysteresis loss is negligible. In this range, the relaxation times of the Neel and Brownie are proposed as a suitable mechanism for particles. Generally, the Brownian relaxation time is important in larger particles in this area and the Neel relaxation time is noticeable in smaller particles. However, exactly where this division occurs is strongly dependent on the anisotropy constant of the particle [11,13].

To optimize the hyperthermia system of a particle, magnetic anisotropy control of the particles is critical. In general, magnetic anisotropy may exist from two distinct sources: crystalline anisotropy and shape anisotropy. It is possible to some extent control magnetic anisotropy by choosing the crystalline structure and the shape of the nanoparticles [11,13]. Anisotropy may be increased by substitution of other transition metals such as cobalt, manganese, or nickel in the inverse spinel structure [11].

As evident in Equation 5, any change in the anisotropy constant can be compensated by the corresponding change in the volume of the particle (V) in a system under the mechanism of the Neel. Regardless of this, it is clear that poor control of anisotropy is a major obstacle to the effective optimization of nanoparticle systems for hyperthermia treatments. It is worth noting that hysteresis is also affected by anisotropy since anisotropy is attributed to the coercivity of the sample [13].

In high concentration solutions, magnetic anisotropy is more complicated than single-particle behavior. In these solutions, the interaction between adjacent particles may stimulate the formation of a chain, which then creates an axial anisotropy along the chain that is independent of the anisotropy of single-particles. In a study by Dennis, this kind of particle interaction significantly increased SAR in dextran-coated iron oxide nanoparticles. Generally, concentration dependence is created due to interdimensional bipolar interactions. As the concentration increases, the distance between the particles decreases and increases the bipolar interaction, thus changing the magnetic response of the magnetic fluid. This interaction directly affects the relaxation time of Neel and is the dominant mechanism in the hyperthermia studies. However, numerous contradictory models describe the effects of these bipolar interactions on the relaxation time [13]. These types of particle interactions are rarely well studied in hyperthermia nanoparticles, although they may have a significant effect on SAR [11,13].

3. COBALT FERRITE-BASED CORE-SHELL NANOPARTICLES

Various materials are thought to be hyperthermia agents due to different thermal sources in the field of hyperthermia, most notably nanoparticles include; gold, silicon, palladium, cobalt, carbon base nanoparticles, iron oxide, and substituted iron oxide nanoparticles with other elements [24]. Some materials can act as hyperthermia agents in different heating sources. Ferrite core-shell nanoparticles are the most important materials among the materials highlighted for this purpose. The nanocomposite material has both the advantages of minerals cores (including hardness, thermal stability, etc.) in the core-shell nanoparticles based on the cobalt ferrite core and organic shell, and the benefit of organic shells (including, flexibility, dielectric, toughness, process ability, etc.). Therefore, the final properties of the nanocomposite is a combination of the properties of organic and inorganic materials [25].

A wide range of magnetic nanoscale materials has been reported for using in hyperthermia. Manys core-shell nanoparticles have been investigated and their results have been extracted in terms of parameters such as temperature, SAR, frequency, field, time, type of cancer treated the thickness of the shell and core, and the synthesis method. Table 1 shows the SAR value and temperature for different core-shell nanoparticles prepared in various synthesis methods. In summary, iron oxide is the most common material for magnetic hyperthermia, which has attracted the most attention so far due to its biocompatibility. The preparation methods of such particles are varied. The most common approach for synthesizing these materials is known as the co-precipitation method that benefits from iron salts. This process gives ultrafine powder with a narrow size distribution. Also, it is a simple method and takes less time to do [2,4,26-28].

TABLE 1. The SAR value and temperature for different ferrite core-shell nanoparticles prepared via various synthesis methods

core	shell	Temp.(°C)	SAR (w/g)	Synthesis method	Ref.
Zn-Mn and Zn-Co ferrites	maghemite, dimercaptosuccinic acid (DMSA), $MnFe_2O_4$		799	hydrothermal coprecipitation of aqueous solutions	[26, 29-34]
$CoFe_2O_4$	$Zn_{0.4}Fe_{2.6}O_4$		10,600		[16]
$Zn_{0.4}Co_{0.6}Fe_2O_4$	$Zn_{0.4}Mn_{0.6}Fe_2O_4$		3866		[16]
$MnFe_2O_4$	$CoFe_2O_4$		3034		[16]
$CoFe_2O_4$	$MnFe_2O_4$		2274.12		[16]
$(Mn_xFe_{1-x})Fe_2O_4$ (MFO)	SiO_2, mPEG, dimercaptosuccinic acid (DMSA)		1635	co-precipitation	[33, 34, 35]
MWCNTs	$Zn_{0.54}Co_{0.46}Cr_{0.6}Fe_{1.4}O_4$	42.7	1372	coprecipitation	[26]
$Zn_xCo_{1-x}Fe_2O_4$	$MnFe_2O_4$	39-47	530	chemical synthesis	[34]
$MnFe_2O_4$ and $CoFe_2O_4$	oleylamine, dimercaptosuccinic acid (DMSA), DEG and polyacrylic acid		525	solvothermal	[30, 32, 33, 35, 36]
Mn doped iron oxide	DEG and polyacrylic acid		390	chemical route	[36]
$Zn_{0.47}Mn_{0.53}Fe_2O_4$ SPION	ligand (TRAIL)	37-43	347.3	thermal decomposition	[37]
$Li_{0.31}Zn_{0.38}Fe_{2.31}O_4$, (LZFO)-RGO		42–45	300	sol-gel	[26, 37]
$Ni_{0.3}Zn_{0.4}Co_{0.3}Fe_2O_4$	MWCNT, $MnFe_2O_4$		200	co- precipitation	[6, 14, 30, 32, 34 ,38]
manganese-ferrite nanoparticles	dimercaptosuccinic acid (DMSA)	50	128		[33]
$Ni_{1-x}Zn_xFe_2O_4$	Poly(ethyleneglycol)	ΔT=10 °C	92	mechanical milling and subsequent sintering, high-temperature polyol method	[12, 39, 40]
Fe_3O_4, $Ni_{1-x}Zn_xFe_2O_4$		40	92	sol-gel autocombustion technique	[40]
$MgFe_20_4$		50	85		[6, 31, 41]
$Co_{0.2}Fe_{0.8}Fe_2O_4$	dextran, $MnFe_2O_4$		78	co-prcipitation	[4, 6, 26, 30, 34, 38]
$Zn_{0.9}Fe_{2.1}O_4$	$MnFe_2O_4$	38.6	36		[6, 30, 31, 34]
$Ni_{0.65}Zn_{0.35}Fe_2O_4$	Poly(ethyleneglycol)	42	33.47	high-temperature polyol method	[40]
$Fe_{1-x}Mg_xFe_2O_4$	hydrophobic oleic acid, and hydrophilic poly(acrylic acid)	ΔT=10 °C	22.4	solvothermal	[4, 41]
Fe_2O_3:CuO:ZnO:MgO	gold	42.5–43	21.27		[38]
$CoFe_2O_4$	ZnO, $MnFe_2O_4$		9.6	heat-up method	[25, 31, 34, 38]
$Mn_{0.75}[(Zn\ or\ Co)]_{0.25}Fe_2O_4$	citric acid, dimercaptosuccinic acid (DMSA), $MnFe_2O_4$, PEG-phospholipid and a cyclic tripeptide of arginine-glycine-aspartic acid (RGD)		4.5	hydrothermal	[6, 12, 30, 32- 34, 36, 37, 42-44]

cobalt ferrite magnetic nano-articles (MNPs)	folic acid	37 and 44	1	co-precipitation	[28, 45]
$Zn_{0.54}Co_{0.46}Cr_{0.6}Fe_{1.4}O_4$		45.7	0.774		[32- 34, 37, 43, 44 , 46, 47]
$Zn_{0.4}Fe_{2.6}O_4$	nanothin SiO_2 layer, PEG-phospholipid and a cyclic tripeptide of arginine-glycine-aspartic acid (RGD)	44.9 °C		FSP, in situ	[6, 12, 29, 32-34, 37, 43, 44 ,48]
$Mn_{0.5}Zn_{0.5}Fe_2O_4$	PEG coating, ligand (TRAIL), dimercaptosuccinic acid (DMSA), PEG-phospholipid and a cyclic tripeptide of arginine-glycine-aspartic acid (RGD), DEG and polyacrylic acid	40.5 ± 0.3, 37-43		thermal decomposition	[32- 34, 36, 37, 43, 44]
Mg doping in ɣ-Fe_2O_3 ($Mg_{x-c}Fe_2O_3$)		99-184		thermally decomposition synthesis	[4, 6, 31, 41]
$CoFe_2O_4$	SiO_2, PEG	42		hydrothermal approach, pechini method	[7, 12, 30]
$Cu_{0.3}Zn_{0.2}Mg_{0.5}Fe_2O_4$		43		thermal treatment technique	[31, 41]
$Ce_xFe_{3-x}O_4$		42		single step microwave refluxing technique	[49]
$CoFe_{2-x}La_xO_4$ (x = 0.0; 0.2 and 0.5)	oleic acid (OA) & ethylenediamine triacetate trisodium salt	58.8, 51.7 and 56.8		coprecipitation	[2]
$MgFe_2O_4/ZrO_2$ composites		50-120		citrate gel technique	[50]
Mn-Zn ferrite MNCs	PEG-phospholipid and a cyclic tripeptide of arginine-glycine-aspartic acid (RGD)	43~44		thermal decomposition	[44]
cubic spinel cobalt ferrites		50		co-recipitation	[28]
3D-printed b-tricalcium phosphate bioceramic scaffold	Fe_3O_4 nanoparticles/graphene oxide nanocomposite layers	50–80		3D scaffolds of beta-TCP= printing device, Fe_3O_4/GO nanocomposites = in situ forming	[51]
mesoporous bioactive glass/ polycaprolactone MBG/PCL) scaffolds	Fe_3O_4	80	4.7	MBG powders (Si/Ca/P molar ratio 80/15/5)= sol gel, Fe_3O_4 nanoparticles= coprecipitation, Preparation of Fe_3O_4/MBG/PCL scaffolds= by 3D printing	
$ZrFe_2O_5$			0.026	mechanical milling process and Sintering process at 1100°C	[50]
$La_{0.73}Sr_{0.27}MnO_3$ (LSMO)	LSMO nanoparticles were coated with a bilayer surfactant(first layer; oleic acid and SDS; second layer: PNIPAAm and Aam chains)	45–60	27.3, 28.8 and 20.1	citrate gel method	[52]
Fe_3O_4, $Zn_{0.4}Co_{0.6}Fe_2O_4$, $MnFe_2O_4$(core), Co Fe_2O_4	SiO_2 , $Zn_{0.4}Mn_{0.6}Fe_2O_4$, Co Fe_2O_4(shell), $Zn_{0.4}Fe_{2.6}O_4$				[7]

It can be seen from the table that various core-shell nanoparticles have been studied. It can be indicated that the highest SAR value in most of the core-shell composite compounds belong to the cobalt ferritic nanoparticles, and most efforts have been relatively focused on the development of these types of compounds. Cobalt ferrite nanoparticles have a relatively high saturation magnetization as well as significant thermal effects. These materials have higher SAR values (up to 720w.g^{-1} and sometimes even much more) than all data reported for iron oxide in recent studies. Since less attention has been paid to these particles compared to iron oxide, the control methods of their size, shape, and size distribution have not yet fully developed. Therefore, the potential for higher heat production is anticipated. One of the factors affecting the properties of ferrite materials, as seen from the above table, is the presence of substituted elements that are present in the structure. Therefore, understanding how to influence these elements will be very helpful. On the other hand, the application of particles containing cobalt, nickel, or other magnetic elements has been somewhat limited due to the complexity of synthesis and reduced biocompatibility, and magnetic nanoparticles are often coated with a mainly polymeric shell or modified with surface treatments to achieve a stable distribution for environmental reasons. There are pieces of evidence that such coatings can greatly affect heating efficiency [13,28,53]. Therefore, the mechanism of the elements substitution and their effect on the properties is discussed in the first step, and then, the coating of these nanoparticles by the polymer shell is described.

3.1. Mechanism of action of doped elements within the structure and influence on magnetic properties

Cations operation within the structure will be discussed to understand the behavior of metal cations within the ferrite structure as the substituted elements regarding the parameters and mechanisms affecting magnetic hyperthermia. The metal elements have different mass, atomic number atomic and ion radii as well as different valences because of their position in the periodic table. Magnetic moments will arise from the presence of an element within the structure due to the electron spin related to each element [9].

It is known that the magnetite structure has the inverse spinel-type, and the iron element is from group VIIIB and the periodic type 4s3d4p (d^6s^2). In this structure, Fe^{2+} occupies the octahedral position, and half of the Fe^{3+} sits in the octahedral space and the other half is located in the tetrahedron site. Therefore, when Fe^{2+} forms, two electrons belong to the 4s electrons are removed, but all the electrons of the 3d level remain. Since four unpaired electrons are in the 3d, the strength of the Fe^{2+} bipolar field is equal to four Bohr magneton. When Fe^{3+} ions are formed, all 4s electrons and one of the 3d electrons are eliminated, so the 5 Bohr magneton will be generated.

The ions in the tetrahedral site of the magnetite are in opposition to the applied field so that their magnetic moment is opposite to the magnetic field, but they amplify the field in the octahedral spaces. As a result, Fe^{3+} ions in the tetrahedral sites neutralize Fe^{3+} ions in the octahedral positions. The Fe^{2+} ions in the octahedral spaces do not contradict any ions, and therefore, strengthens the magnetic field.

Therefore, the magnetic moment per unit volume and the amount of saturation flux density (B_{sat}) for magnetite can be calculated in terms of cation distribution in tetrahedral and octahedral spaces. In a single cell, the total magnetic moment is equivalent to four Bohr magneton resulted from Fe^{2+} ions because the magnetic moments of iron Fe^{3+} eliminate each other. In the overall network cell (spinel structure), there are 8 cells, so the total magnetic moment is 32 Bohr magneton. Regarding the network parameter (8.37×10^{-8}cm) for a magnetite cell, the magnitude of Bohr magneton per unit volume (saturation magnetization) is 10^{22}magnetons.cm^{-3} (5.1×10^{5}A.m^{-1}). As a result, the amount of saturation flux density (B_{sat}) is according to Equation 10 [9]:

$$B_{sat} = \mu_0 \times Ms = (4\pi \times 10^{-7})\,(5.1\times 10^{5}) = 0.64\,Tesla \tag{10}$$

Now, the amount of the Bohr magneton derived from the substitution varies in the system if all or a part of these elements with two or three valences are replaced by other cations with different valences, considering the fact that the electron balance of the elements is different. Therefore, the amount of saturation magnetization and flux density would also be different.

Cobalt ferrite ($CoFe_2O_4$) is the same as magnetite with an inverse spinel structure, in which oxygen ions lie in cubic positions. The tetrahedral sites are filled with Fe^{+3} cations, and Co^{+2} and F^{+3} cations with different ratios are located in octahedral spaces. Magnetic properties of ferrites are usually dependent on the nature and mode of distribution of cations in the tetrahedral and octahedral sites. The exchange of cation distribution causes a change in magnetic moments and then, alters the M_S and H_C. Moreover, magnetic moments can be affected by the replacement of different cations in the spinel structure, as expressed in the magnetite case. Rare-earth elements are good candidates for substitution in cobalt ferrite structure because these elements have large magnetic moments, magnetocrystalline anisotropy, and magnetostriction at low temperatures due to the nature of 4f electrons. In rare-earth elements, electrons of the 4f layer are unpaired and have spin-orbit couplings in angular momentum. Hence, various studies have been done to investigate the effect of rare-earth elements on the magnetic properties of cobalt ferrite. According to the results of these types of research, the substitution of rare-earth ions leads to the migration of cobalt ions from octahedral sites to tetrahedral spaces. As a result, the amount of saturation magnetization and coercive field will also change [54].

Zhou *et al.* [55] investigated the effect of doping the structure of cobalt ferrite with some rare-earth elements such as Y, Lu, Yb, Tm, Sm, and La. According to the X-ray diffraction pattern, the spinel structures were synthesized with lattice parameters in the range of 8.376 to 8.430°A. There were also no additional peaks arising from rare-earth elements. These observations mean that the added elements are entirely in the spinel structure. Another important point is the decreasing peak intensity and increasing the width of the peaks by increasing dopants elements. This can be attributed to reducing the crystallinity of spinel ferrites. Rare-earth elements prevent the complete crystallization of ferrites due to the high ionic radius. They examine the changes in saturation magnetization and coercive field through the addition of rare-earth elements (Table 2). Accordingly, they reported the amount of saturation magnetization has decreased substantially by adding these elements, which is the reason for decreasing the crystallization. However, the addition of Lu element in contrast to other elements leads to an increase in saturation magnetization. It can be seen from Table 2 that the coercive field and saturation magnetization decreases with increasing the rare-earth elements, and Ho has greatly reduced the amount of coercive field. In general, the changes arising from the presence of rare-earth elements in the structure of manganese cobalt ferrite are attributed to the presence of the 4f layer [55].

Pervaiz *et al.* [56] and Sodaee *et al.* [15] investigated the effect of adding Gd on the magnetic properties of cobalt ferrite in separate studies. The results showed that the M_S and H_C were reduced by increasing Gd and the area of the hysteresis loop decreased significantly. Changes in M_S by chemical composition are explained by the exchange reactions between cations distributed in octahedral and tetrahedral spaces. These exchange reactions depend on the length and angle of the bonding. this cation goes to the octahedral and replaces some of the Fe^{3+} ions by adding Gd^{3+}. This behavior is because Gd^{3+} ions have a very high ionic radius and their probability of being present in tetrahedral is very low. Since the magnetic moments arising from 4f layer's electrons of the rare-earth elements including gadolinium ions originate at temperatures lower than 40K, and these elements exhibit non-magnetic behavior at room temperature, their presence instead of iron ions reduces magnetism in octahedral positions. As a result, the material's M_S decreases [15,56].

TABLE 2. Effect of rare-earth elements on magnetic properties of manganese cobalt ferrite

Elements	Mn-Co ferrite Without element	La	Pr	Nd	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Atomic Number	-	57	59	60	62	63	64	65	66	67	68	69	70	71
Ms (emu.g^{-1})	32.9	30.2	31	30.5	27.5	31.1	32	29.1	29	28.5	28.8	29	32.1	34.5
Bohr magneton (μ_B)		0	3.5	3.5	1	0	8	10	11	10.8	9.5	7.5	4.5	0
H_C (Oe)	340	215	21	195	225	295	280	250	210	155	160	190	215	235

According to Sodaee *et al.* results, Gd increased the crystallite size from 21.2 to 42.4nm. This is due to the replacement of Gd cations instead of Fe in the spinel structure because the ionic radius of gadolinium is 1.07°A, while the iron ionic radius is 0.67°A. For this reason, the strain rate of the network has increased with the replacement of Gd instead of iron. On the other hand, H_C depends on grain size and crystalline defects. The larger the size of the grain, the lower the locking of the wall domain, due to the reduction of the grain boundary fraction. Therefore, the coercive field is also decreased with increasing Gd [15].

Another point is that the coercive field depends on the anisotropy constant and cation distribution in interstitial locations. Strong anisotropy in cobalt ferrite is mainly due to the presence of cobalt ions in octahedral positions. Cobalt ions migrate to tetrahedral sites and reduce anisotropy constant by the replacement of Gd ions in octahedral locations. As a result, macro spins are more easily returned to the previous location, and then, H_C is reduced [15].

In the study of Xavier *et al.* [57], the effect of samarium on the structural and magnetic properties of cobalt ferrite were also investigated. The crystallite size increased from 11.26 to 16.53nm with an increase of Sm^{3+} as 0.25 molar, which is attributed to the higher ionic radius of the samarium. Saturation magnetization and coercive field were also decreased from 52.24emu.g^{-1} to 32.55emu.g^{-1} and from 1379.2Oe to 814.73Oe, respectively. The reason for these changes is the same as explained for other rare-earth elements.

Naik and Salker [58] investigated the effect of temperature on the magnetic properties of cobalt ferrite in the presence of Dy and Gd elements at room temperature (300K) and very low temperature (5K). They observed when the temperature dropped from 300K to 5K, the M_S increased from 73.84emu.g^{-1} to 79.69emu.g^{-1} for cobalt ferrite; 70.29emu.g^{-1} to 79.35emu.g^{-1} for Dy presence in cobalt ferrite; and 60.85emu.g^{-1} to 71.02emu.g^{-1} for gadolinium cobalt ferrite. Moreover, the coercive field for Co-ferrite, Co-Dy ferrite, and Co-Gd ferrite changed from 1.326KOe to 13.939KOe, 1.435KOe to 10.149KOe, and 1.215KOe to 15.602KOe, respectively. The reason for this phenomenon is attributed to the magnetic moments activation of the Dy and Gd ions at temperatures below 40K. It is also observed that the M_S in the cobalt ferrite doped by Dy is much higher than the Gd doped cobalt ferrite. This is related to the higher magnetic moments in Dy ions.

The effect of adding yttrium ion (Y^{3+}) on the structural and magnetic properties of cobalt ferrite nanoparticles was investigated by Alves *et al.* [20]. They showed the increasing the ion Y^{3+} up to 0.04 mole, and the grain size decreased from 35.32nm to 16.05nm. Saturation magnetization is also reduced from 69emu.g^{-1} to 33emu.g^{-1}. This is while the coercive field increased from 1.1KOe to 1.9KOe. The decrease in M_S can be attributed to the non-magnetic Y^{3+} substitution. This behavior is similar to that mentioned for other rare-earth elements discussed in this report. Increasing the H_C can be justified by increasing the amount of Y^{3+}, which causes a smaller grain size. As the grain size is smaller, the defective volume fraction and grain boundary will be greater. Then, changing the magnetic domain walls becomes harder, and H_C increases.

Motavallian *et al.* [4] synthesized $Cd_xCo_{1-x}Zr_{0.05}Fe_{1.95}$ ($0.0\leq x\leq 0.3$) and $CoFe_2O_4$ nanocrystals via Pechini method with average particle sizes in the order of 32-40nm. X-ray diffraction analysis showed only the presence of a cubic spinel phase, and the lattice parameter increased with increasing cadmium substitution in the cobalt ferrite structure (from 8.3348°A for $CoFe_2O_4$ to 8.3975°A for $Cd_{0.3}Co_{0.7}Zr_{0.05}Fe_{1.95}$). The observed change in the lattice parameter is justified by the fact that the ionic radius of Cd^{2+} ion (0.97°A) is greater than that for Co^{2+} ion (0.745°A). Also, the crystallite size of the spinel structure decreased by increasing the amount of cadmium from 40nm to 32nm. Saturation magnetization increased with increasing cadmium up to 0.1 due to the migration of Fe^{3+} ions to octahedral positions, and thus, the reduction of iron ions in tetrahedron spaces. With increasing cadmium, more than 0.1 molar, reduced Ms was observed as 57.33emu.g^{-1} for $Cd_{0.3}Co_{0.7}Zr_{0.05}Fe_{1.95}$, which was attributed to the effect of spin tilting in octahedral spaces.

Pilati *et al.* [29] synthesized Zn-Mn and Zn-Co ferrite nanoparticles by the hydrothermal method of Fe^{3+}, Zn^{2+}, and Co^{2+} solutions (0.5mol.L^{-1}) in a strongly alkaline environment at 100°C under vigorous stirring. XRD patterns confirmed the cubic spinel structure of the samples. The size of the cubic cell changed with Zn for both samples. Both Zn-Co and Zn-Mn ferrite nanoparticles showed a decrease in crystallite size by increasing the Zn ratio, and this decrease was higher for Zn-Mn ferrites. The distance between atomic Mn-O is greater than that of Zn-O, which leads to a further reduction of the cubic cell. Therefore, the size of the nanoparticles is smaller.

The saturation magnetization of synthetic nanoparticles was investigated at room temperature (300K) and lower temperature (5K). An increase in saturation magnetization from 65emu.g^{-1} to 87emu.g^{-1} was seen for Zn-Mn ferrite nanoparticles, with an increase of Zn up to 0.4 moles at 5k. Afterward, this property decreased to 80emu.g^{-1} by increasing 0.6 mole zinc. The observed magnetization decrease is attributed to the week interaction of rapid changes in octahedral-tetrahedral positions arising from increased zinc concentration in tetrahedron sites. This trend is also observed for Zn-Co nanoparticles. Although, saturation magnetization for Zn-Mn nanoparticles at 300K shows a decreasing trend from 50emu.g^{-1} for 0.1 mole zinc to 30emu.g^{-1} for 0.6 mole. Saturation magnetization changes for Zn-Co nanoparticles are different from Zn-Mn ferrites at this temperature. Saturation magnetization is 40emu.g^{-1} for 0.1 mole zinc. This value decreases to 30emu.g^{-1} for 0.2 mole Zn, and then increases to 40emu.g^{-1} for 0.4 mole, and again decreases to 30emu.g^{-1} at 0.4 mole.

Considering the magnetic properties of nanoparticles, it was found that the replacement of Zn alters anisotropic constant of nanoparticles in different forms. Magnetic anisotropy of nanoparticles based on Zn-Co ferrite varies strongly from K_{ef} $=2.5\times10^5$J.m^{-3} (low zinc content) to $K_{ef}=5.3\times10^4$J.m^{-3} (high Zn content), whereas the anisotropy of nanoparticles based on the Zn-Mn ferrite changes less than 40% for any Zn value (0.9 -1.4× 10^4J.m^{-3}). These differences were related to the thermo-magnetic behavior of nanoparticles as a function of their Zn content. The relaxation time (τ_c) values decreased compared with other iron oxides, especially magnetite as a function of Zn content for both samples have. Reducing τ_c in hyperthermia is very interesting in preventing excessive heat in the biological environment [29].

The SAR results of the samples were evaluated as a function of zinc value. In Zn-Co ferrite nanoparticles, the samples with low content of Zn have the best performance for heat generation (SPA=1230w.g^{-1} for x=0.18) and the SPA reaches zero for more Zn. In this type of specimen with a negligible variation of magnetic anisotropy, this mode is related to a decrease in nanoparticle diameter and saturation magnetization at 300K [29]. It is observed that these nanoparticles provide the same amount of SPA as similar ferrites. The increase in Zn value decreases fast interaction and induces power absorption. Therefore, these nanoparticles are a good candidate for MH behaviors in a more secure and safer strategy because they help prevent excessive heat generation and damage healthy tissues.

It has already been stated that the performance of the nanoparticles in heat generation is influenced by the diameter of the nanoparticles, the magnetic anisotropy constant, and saturation magnetization. The magnetic moment is strongly coupled to the anisotropy field and preferential relaxations through the mechanical rotation for nanoparticles with high anisotropy constant. Increasing the viscosity of the fluid environment disrupts Brownian's rotation and reduces heat production efficiency. Also, higher SPA values are attributed to larger amounts of M_S, which is associated with a less anisotropy barrier induced by increasing zinc content [29].

In a similar study, Dalal *et al.* [14] synthesized $Ni_{0.3}Zn_{0.4}Co_{0.3}Fe_2O_4$, $Ni_{0.4}Zn_{0.4}Co_{0.2}Fe_2O_4$, and $Ni_{0.3}Zn_{0.4}Co_{0.2}Cu_{0.1}Fe_2O_4$ nanoparticles via co-precipitation method. Synthesized nanoparticles were added to the MWCNT matrix to achieve radar absorption properties and to study the SAR characteristic for cancer treatment under alternating current (AC). Through the studied nanoparticles, $Ni_{0.4}Zn_{0.4}Co_{0.2}Fe_2O_4$ with crystallite sizes as much as 34.7nm showed a maximum SAR as 200w.g^{-1} value. The high M_S (~84emu.g^{-1}) was obtained at room temperature [14].

3.2. Coating of nanoparticles by a polymer shell

Magnetic nanoparticles are highly sensitive to oxidation and agglomeration due to their high surface area and are reactive in chemical reactions. Under environmental conditions, the surface of nanoparticles undergoes rapid oxidation, resulting in the formation of a thin layer of oxide, which changes the properties of the particle. The natural agglomeration of nanoparticles in the form of larger clusters is another problem that such particles face. The encapsulation process has been proposed to maintain magnetic properties and to protect against oxidation and agglomeration. Nanoparticle encapsulation has been successfully carried out using carbon, silica, precious metals, metal oxides, organic polymers, and surface modifiers [7,53].

The surface modification of magnetic nanoparticles plays a vital role in the application of these materials. The surface coating improves not only the colloid stability of nanoparticles, but also enhances biocompatibility, bio-safety, and SLP. Hence, the design of multipurpose biocompatible magnetic nanoparticles with upgraded magnetic properties and SLP values is possible by applying coatings [4,5].

Generally, electrostatic or chain repulsion is used to distribute nanoparticles, which keeps them stable. Modifiers or polymers chemically bind nanoparticles or physically absorb them to create single or double layers that generate repulsive forces (mainly repulsive chains) for balancing Vander walls gravity and magnetic forces of nanoparticles. Therefore, with magnetic repulsion and magnetic particles remain stable in suspension [53].

Sun and Murray reported the synthesis of cobalt nanoparticles in the presence of an organic surface modifier such as oleic acid, lauric acid, trioctylphosphonic acid, and pyridine. Among the organic surface modifiers, oleic acid is an organic sealant that can bind to heavy metal surfaces through the carboxyl group. This acid has been widely used in the synthesis of colloidal nanoparticles for a large number of metals. Recently, Lu *et al.* compared several surface modifiers (stearic acid, oleic acid, and ealidic acid) to synthesize cobalt magnetic nanoparticles to investigate the difference between their ability to control the particle size, distribution, and oxidation stability of nanoparticles. They found that the poor performance of stearic acid on mono-particles stability was attributed largely to its linear composition. Unlike the oleic acid or ealidic acid, there is no double bond of C=C in the stearic acid chain. They claimed that the interaction of the dual bond between olefinic acid contributes to the formation of a dense layer on the surface of cobalt nanoparticles. The sharing of binary links between adjacent molecules results in the hardness of the coating layers. There is a formation probability of magnetic gels through polymerization and cross-linking of binary bonds during solvent evaporation due to the presence of dual bonding in olefinic acid [53].

So far, most studies have focused on the development of surface-modifying coatings, which recently have attracted more attention to polymers that make magnetic nanoparticles stable. Polymers can produce more repulsive forces than surface modifiers. In resources, both synthetic and natural polymers are used to cover magnetic nanoparticles. The most common natural polymers are dextran, chitosan, starch, gum arabic, and gelatin. Also, the most usual synthetic polymers are polyethylene glycol (PEG), polyvinyl alcohol (PVA), polylactide acid (PLA), alginate, polyacrylic acid (PAA), and polymethylmethacrylate (PMMA) [53].

Hatamie *et al.* used polyethylene glycol (PEG) to modify the surface of the synthesized cobalt ferrite nanoparticles prepared via the hydrothermal method. The average particle size of this method was 30nm. The M_S and H_C of synthesized nanoparticle were 41.3emu.g^{-1} and 2284Oe, respectively, which changed to 29.8emu.g^{-1} and 2324Oe with PEG coating, respectively. It can be seen that the saturation magnetization decreases and the coercive force increases with surface treatment. Moreover, the maximum SLP was 31.8w.g^{-1} for nanoparticles coated with polyethylene glycol for 0.0025gr.mL^{-1} at 350kHz. The temperature of the coated nanoparticle after 10 minutes was 42°C [12].

Linh *et al.* synthesized core-shell structure from $Co_{0.2}Fe_{0.8}Fe_2O_4$ nanoparticles coated with dextran via coprecipitation method using an ultrasound chemical process. The mean crystallite size was obtained as 10.5±0.7nm using the Scherer equation. The average diameter of the uncoated particles was measured as much as 11.8±1.5nm, while this number for dextran-coated particles was obtained as 50±5nm. This value is suitable for in vivo applications. The magnetization of both samples did not saturate due to the dead layers with paramagnetic properties on the surface of the magnetic nanoparticles. The M_S values of 53 and 48.5emu.g-1 were obtained for uncoated and coated nanoparticles, respectively. Clearly, the Ms decreased by 4.8% after surface coating. This was attributed to the presence of paramagnetic polymer coatings. Additionally, the H_C value for both samples was 116Oe. The highest SAR value for magnetic fluid exposed to the 300Oe field intensity was 78w.g^{-1} [5].

In another study by Gharibshahian *et al.* [7], cobalt ferrite nanoparticles and $CoFe_2O_4/SiO_2$ core-shell nanoparticles were prepared using the Pechini method. They synthesized nanoparticles in an electric furnace and microwave. It was observed that synthesized nanoparticles in the microwave were smaller particles than those prepared in an electric furnace (14nm in comparison with 35.06nm). The M_S value for coated particles was equal to 36.25emu.g^{-1}, while it obtained as much as 64.5emu.g^{-1} for uncoated particles synthesized in the microwave, and 71.51emu.g^{-1} for uncoated powders prepared in an electric furnace. Also, the lower H_C and smaller remnant magnetization (almost zero) and more biocompatibility were observed for silica-coated particles, which makes them suitable for most of the medical applications, such as drug delivery, hyperthermia therapy for cancer cells, cancer cell imaging, and MRI in the diagnosis of cancer.

Salunkhe *et al.* [3] synthesized cobalt ferrite nanoparticles via coprecipitation method and applied oleic acid (OA) and oleic acid- polyethylene glycol acid (OA-PEG) coatings on the particles. The crystallite diameter of the uncoated (CIO) and coated (CIO-OA-PEG) nanoparticles was calculated using the Scherer equation as 10 and 12nm, respectively. The lattice parameter for the uncoated and coated samples was about 0.8377 and 0.8376nm, respectively. There was no significant difference in the lattice parameters, indicating that the crystalline structure is not affected by the OA-PEG coating. TEM images showed uncoated particles were agglomerated, while coated particles were well distributed in the solution. Bipolar interactions in magnetic nanoparticles cause agglomeration of uncoated particles. Reduction in bipolar interactions between magnetic nanoparticles is necessary because it affects SAR. Upgrading SAR or maximizing thermal power often depends on optimal density, which ultimately influenced by the power of bipolar/bipolar interactions. Optimizing the mentioned properties is often important to focus on increasing the density of particles in the tumor through novel targeting designs. Bipolar-dipole interactions can be reduced by the physical and chemical adsorption of the polymer on the nanoparticle surfaces. The increased distribution after the OA-PEG coating is attributed to the presence of dead layers on nanoparticles, which reduces bipolar interactions between particles.

4. CONCLUSION

Magnetic nanoparticles have a high utility in detecting and treating cancer due to their special magnetic properties. For this reason, advanced magnetic hyperthermia has progressed tremendously during the last decade. The present research shows that the type of magnetic nanoparticles had a great effect on hyperthermia performance. Accordingly, it seems that cobalt ferrites were good materials for synthesizing and performing hyperthermia operations based on the extracted data from various papers on the heating of different nanoparticles and their comparison with each other, as well as the suggestions of other authors. The structural and magnetic properties of substituted spinel ferrites depended heavily on the type of substituted elements and their concentration, and these properties could be altered by modifying the size and shape of the nanoparticles, and the chemical composition. Accordingly, the ratio of the raw materials, the type of dopant, the temperature, and time required for optimal nanoparticle synthesis were the factors affecting the structural properties of the nanoparticles, phase formation, density, and lattice parameter.

The use of rare-earth elements and the simultaneous substitution of these elements into the structure of cobalt ferrite had an important effect on the structural and magnetic properties of the nanoparticles as well as the thermal effects of nanoparticles to control the magnetic properties. Furthermore, nanoparticle biocompatibility with physiological conditions, especially biocompatible coatings such as dextran, chitosan, or PEG seemed to be necessary for the proper distribution of nanoparticles, as well as the prevention of agglomeration and particle bonding.

There are many methods for controlled synthesis of nanoparticles for hyperthermia applications and SAR enhancement. Finally, further investigations are needed to improve the uniformity and to synthesize nanoparticles with a narrower size distribution of nanoparticles. Additionally, mass fraction and agglomerations of nanoparticles are the other important parameters that affect the relaxation time and SAR.

5. ACKNOWLEDGEMENTS

The authors would like to thank the Department of Materials Engineering, Babol Noshirvani University of Technology.

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