

A Comprehensive Study of $Zn_xFe_{2-x}O_3$ Nanoparticles for Magnetic Fluid Hyperthermia

Gizachew Diga Milki*

Abstract

Magnetic nanoparticles are the bottlenecks of nanomedicine. They are a wide area of study in nanotechnology. In this review, the role of nanotechnology in transforming $Zn_xFe_{2-x}O_3$ nanoparticles into biomedical applications and smart healthcare systems is demystified. The synthesis and characterization of $Zn_xFe_{2-x}O_3$ nanoparticles are scrutinized, with a focus on the advantages of hydrothermal methods and the revealing capabilities of high-resolution electron microscopy, which enable a deeper understanding of these nanoparticles' unique characteristics. This review presents parameters that influence the functional properties of magnetic nanoparticles. In this regard, the effect of both internal and external parameters that influence the biomedical application of $Zn_xFe_{2-x}O_3$ is discussed. When designing nanoparticles for in vivo or in vitro applications, a crucial set of properties must be carefully considered, including biocompatibility, reactivity, biosensitivity, and biodegradability, to ensure the nanoparticles' safety, efficacy, and compatibility with living systems. An emphasis is given to the potential applications of the three most important $Zn_xFe_{2-x}O_3$ nanostructures namely; nanoparticles, nanocomposite, and double walled iron oxide nanotube. The result indicates that Zn-substituted αFe_2O_3 nanoparticles investigated for effective hyperthermia (thermotherapy) and a smart health care system.

Keywords: Cancer therapy, magnetic nanoparticles, magnetic hydrothermal, medical imaging, and Nanotechnology

INTRODUCTION

Nanotechnology is one of the top three emerging technologies: 3D printing, digital technology, artificial intelligence, and nanotechnology. Nanotechnology encompasses the art and science of nanomaterials, their synthesis, properties, characterization, fabrication, and computation. It also involves the generation, analysis, and quantitative description of the nanostructures. Common nanostructures that pave the way for innovation in nanotechnology include magnetic nanoparticles, nanocolloids, nanotubes, nanodots, nanowires, nanobelts, nano-stars, and nanocomposites. These structures play pivotal roles in nanomedicine and smart healthcare systems. The focus of this review is

limited to magnetic nanoparticles and their functions in magnetic fluid hyperthermia.

Magnetic nanoparticle science is one of the most focused areas of review in nanotechnology. To put this technology forward, the analysis, engineering, and utilization of diluted magnetic semiconductor oxide nanoparticles is of primary importance. Among these nanoparticles, $Zn_xFe_{2-x}O_3$ meets such requirements.

Owing to their unique magnetic properties, excellent biocompatibility, and significant role in

*Author for Correspondence

Gizachew Diga Milki
E-mail: Phygidg@gmail.com

Associate Professor, Department of Physics, Jimma University, Ethiopia

Received Date: September 06, 2024
Accepted Date: September 09, 2024
Published Date: September 19, 2024

Citation: Gizachew Diga Milki. A Comprehensive Study of $Zn_xFe_{2-x}O_3$ Nanoparticles for Magnetic Fluid Hyperthermia. Journal of Nanoscience, Nanoengineering & Applications. 2024; 14(2): 1–9p.

cancer therapy, and drug delivery, Sophie Laurent et al. 2011 [1] reported that iron oxide nanoparticles have attracted considerable attention in pharmaceutical and industrial communities. $Zn_xFe_{2-x}O_3$ nanoparticles are critically important for the treatment of carcinogens, Alzheimer's disease, diabetes, and other infectious diseases. Hence, a systematic study was conducted by pinpointing the nanoscale and thermodynamic properties of the $Zn_xFe_{2-x}O_3$ nanoparticles. $Zn_xFe_{2-x}O_3$ nanoparticles can be combined with DNA to form nanovectors for regenerative medicine. Alvazer, 2004 [2] used single-core iron oxide nanoparticles coated with a silica monolayer and silica beads with embedded iron oxide nanoparticles for purifying DNA. The $Zn_xFe_{2-x}O_3$ nanoparticle-based nanobiosensor helps sense and monitor body temperature and pressure. Conversely, $Zn_xFe_{2-x}O_3$ nanoparticles can generate heat, creating suitable conditions for therapeutic techniques. They are also used for controlling, treating, and bio-labeling diabetes, Alzheimer's disease, cancer, and Covid-19.

As stated by McManus et al. 2019 [3], nanotechnology involves imaging, measuring, modeling, manipulating, and engineering matters at the nanoscale. Currently, nanomedicine is an effective treatment mechanism because of the introduction of magnetic nanoparticles, such as $Zn_xFe_{2-x}O_3$ nanoparticles, for efficient drug delivery. Most importantly, $Zn_xFe_{2-x}O_3$ nanoparticles-based detection, therapy, imaging, and targeted drug delivery systems have become promising. Studies by S. Malekie et al. 2020 [4] indicated that decreasing the size of magnetic nanoparticles increases the temperature of tumor cells during hyperthermia. As discussed by Farnaz Assa et al. 2016 [5], magnetic iron nanoparticles (IONPs) can absorb large amounts of magnetic energy by hysteresis loss to generate thermal energy, which can kill cancer cells.

METHODS

Experimentally, $Zn_xFe_{2-x}O_3$ nanostructures can be synthesized using different methods. Among these, the usual synthesis methods are co-precipitation, hydrothermal methods, solvothermal methods, and biological (green) methods. These methods are preferred because nanostructures synthesized using these methods have a high crystal quality and exhibit measurable physicochemical properties. Moreover, green-synthesized $Zn_xFe_{2-x}O_3$ nanoparticles have outstanding biomedical applications, are cost-effective, eco-friendly, and undergo simple synthesis routes. In this study, the hydrothermal method is preferred because it is better at describing the thermal properties of $Zn_xFe_{2-x}O_3$ nanoparticles for thermotherapy. Hence, more emphasis has been placed on the hydrothermal synthesis methods for magnetic fluid hyperthermia (thermotherapy).

Hydrothermal Method

The hydrothermal method involves the incorporation of an aqueous solution as a reaction system in confined vessels by creating high-pressure and high-temperature differences. This effect is governed by the following statistical equation of state: Iron (II) chloride tetrahydrate, iron (II) chloride hexahydrate, and iron (III) chloride hexahydrate were used as precursors. Chan Oeurn Chey, 2015 [6] prepared $Zn_xFe_{2-x}O_3$ nanoparticles without morphological deformation. Hence, the quality of magnetite is controlled by monitoring the concentration of iron chloride tetrahydrate. Mohapatra and Anand, 2010 [7] stated that the high-temperature decomposition of an iron precursor shows that Zn-doped alpha iron oxide has a high level of mono disparity and manageable size. Sibera et al. 2009 [8] also discussed the possibility of synthesizing ZnO-doped iron oxide using a microwave-assisted hydrothermal method.

Why Hydrothermal Method is Preferred?

This method is used for synthesizing advanced nanomaterials and $Zn_xFe_{2-x}O_3$ nanocomposites. In addition, they are used to produce nanostructures that are undoubtedly applicable to nanozymes, biomedicine, and regenerative medicine.

The hydrothermal method was performed in a pressure furnace (autoclave) under controlled pressure and temperature. Typically, the autoclave was coated with Teflon. This process was performed in an aqueous solution. By varying the temperature beyond 100°C, one can attain the saturation vapor pressure governed by the statistical equation of states. This pressure is referred to as the internal pressure, and it depends on the concentration of the input solution.

The hydrothermal method is advantageous because it can be performed anywhere. It is also advantageous because it is used to recycle nano-waste. In addition, the hydrothermal synthesis process enables the control of many physical parameters such as concentration, pressure, temperature, and particle morphology. Hayashi et al. 2010 [9] verified that hydrothermal synthesis is advantageous for the synthesis of multimetal oxides at the supercritical point of water. Yong et al. 2020 [10] also demonstrated that hydrothermal synthesis method can generate nanomaterials that are unstable at elevated temperatures and maintain the minimum material loss. It enables particle production with highly controlled diffusivity in a strong solvent medium in a closed system.

Characterization Methods

Nanoparticles synthesized using hydrothermal techniques can be characterized by X-ray diffraction (XRD), Mossbauer spectroscopy, and high-resolution transmission electron microscopy (HRTEM). However, HRTEM is preferred because it can perform the characterization process at more than three different accelerating voltages. Thus, it can exhibit enhanced image viability and contrast and improve image quality.

This technique is also used to characterize the electrical and optical properties of a sample. It was also used to determine the lattice parameters of the nanocrystals. Kumar et al. 2019 [11] used HRTEM and found that the average crystallite size of Zn-doped iron oxide nanostructures was 20 nm. This size is suitable for optimizing contrast and image viability. It is also suitable for fluorescence imaging, such as in quantum dots.

Theoretical Method

To investigate its sensing activity, it is important to determine the optimum temperature, pressure, surface effects, and surface-area-to-volume ratio. However, in the classical limit, the equation of motion is used to describe particles undergoing circular harmonic motion as follows:

$$P\Delta A = m \frac{d^2x}{dt^2} + n\rho\Delta v \frac{d^2x}{dt^2} \quad (1)$$

$$P\Delta A = (m + n\rho\Delta v) \frac{d^2x}{dt^2} \quad (2)$$

$$\frac{d^2x}{dt^2} = -\omega^2 x \quad (3)$$

$$P\Delta A = -(m + n\rho\Delta v)\omega^2 x \quad (4)$$

$$P\Delta A = \frac{nRT}{\Delta x} \quad (5)$$

$$\frac{nRT}{\Delta x} = -(m + n\rho\Delta v)\omega^2 x \quad (6)$$

$$nRT = -(m + n\rho\Delta v)\omega^2 x^2 \quad (7)$$

$$\omega = -\frac{nR}{(m+n\rho\Delta v)} \frac{\sqrt{T}}{x} \quad (8)$$

By making the lattice parameter, volume of primitive cell, and density of electrons constant, we determine the frequency of vibration directly from equation (8). This equation shows that the vibration frequency is directly proportional to the square root of the thermodynamic temperature.

$$\omega = C \frac{\sqrt{T}}{x} \quad (9)$$

where $C = -\frac{nR}{(m+n\rho\Delta v)}$, is the constant of proportionality describing the thermoelectric interactions between the nanoparticles and body fluids. This equation is an alternative and more accessible than DLVO theory, which is complex and requires energy expenditure. To realize thermotherapy, nanoparticles are made to oscillate at a frequency that is tuned by the action of heat. Then, by measuring the temperature rise, the resonance frequency can be adjusted to perform the therapeutic process.

Alternatively, using a nanoneedle will increase the pressure because of the extremely narrow area. To visualize this effect, thermodynamic relationships were developed by combining the first, second, and third laws of thermodynamics.

$$P\Delta A = \frac{T\delta S - dU}{dx} \quad (10)$$

Equating equation 10 with equation 4 we have

$$\frac{T\delta S - dU}{dx} = -(m + n\rho\Delta v)\omega^2 x \quad (11)$$

$$Tds = -(m + n\rho\Delta v)\omega^2 x^2 + du \quad (12)$$

Limiting conditions

1. For isothermal conditions, $du = 0$, $Tds = -(m + n\rho\Delta v)\omega^2 x^2$
2. For isochoric condition, $dv = 0$, $Tds = -m\omega^2 x^2 + du$

Where T is the temperature in Kelvin, which is the therapeutic temperature for which the nanobiosensor works, ρ is the volume density, ω is the frequency of the particle, dU is the increase in internal energy, and dS is the infinitesimal change in entropy. For a monatomic electron gas, the infinitesimal change in internal energy is $\frac{3}{2}nRT$

$$Tds = -m\omega^2 x^2 + \frac{3}{2}nRdT \quad (13)$$

$$\text{With } ds = \frac{nRdT}{T}$$

$$m\omega^2 x^2 = \left(\frac{3}{2} - 1\right)nRdT \quad (14)$$

$$m\omega^2 x^2 = \frac{1}{2}nRdT \quad (15)$$

$$\omega = \sqrt{\frac{nRT}{m} \frac{\sqrt{T}}{x}} \quad (16)$$

$$\omega = C \frac{\sqrt{T}}{x} \quad (17)$$

The result is in agreement with the first case, as in equation (9), except for the constant. $C = \sqrt{\frac{nRT}{m}}$, in this case. This result is a consequence of the interaction between magnetic nanoparticles and body fluids (tissues). The relationships between these parameters are illustrated in the Figure 1.

DISCUSSION

Magnetic nanoparticles (MNPs) are powerful tools for magnetic fluid hyperthermia. Magnetic fluid hyperthermia is a method of treating cancer using the induced heat caused by the quantum confinement

effect. This method, also referred to as thermotherapy, is a better method to kill carcinogens. For in vivo and in vitro applications, iron oxide nanoparticles must be engineered to exhibit high magnetic saturation, stability, biocompatibility, and surface functionality. To ensure the biomedical application of magnetic nanoparticles, it is important to analyze the pivotal role of nanotechnology and the thermodynamic properties of magnetic nanoparticles.

Here, emphasis is placed on the significant role of nanotechnology in magnetic fluid hyperthermia. Most importantly, the role of magnetic $Zn_xFe_{2-x}O_3$ nanoparticles in magnetic fluid hyperthermia was discussed.

The Role of Nanotechnology in Thermotherapy

Nanotechnology provides new methods for synthesizing and characterizing magnetic nanoparticles with improved quality, sensitivity, reactivity, biocompatibility, and quality. Nanotechnology enables the utilization of nanoparticles and nanodevices for therapy, imaging, drug delivery, and painless injection methods such as nano-needles. This enables the fabrication of nanosensors for the detection, monitoring, and treatment of cancerous cells and tissues. Industrial nanotechnology enhances the production and quality of drugs at the nanometer scale for use in nanomedicine and medical treatment.

Nanofilms, nanofluids, and ferrofluids exhibit remarkable magnetic and thermal properties. The ferrofluid of $Zn_xFe_{2-x}O_3$ nanoparticles and nanocomposites can kill cancer cells using guided magnetic fields. As discussed by Yuyun Yang et al. 2023 [12], nanocomposites offer significant applications in diagnosis, therapeutics, theranostics, anticancer, and antimicrobial. Semiconductor nanoparticles with low size and high fluorescence are promising for diagnostic, imaging, and therapeutic applications.

However, in this study, we focused on Zn-substituted iron oxide nanoparticles for medical applications. This is because (1) the toxicity of Zn is very low; (2) Zn is found in many human body organs; (3) Zn is environmentally friendly and used for safety purposes; (4) it is cheap compared to other elements; (5) Zn^{2+} is isovalent to Fe^{2+} cations; (6) most Zn-containing compounds exhibit interactions such as van der Waals interactions with body fluids such as DNA, genes, tissues, and hemoglobin; and (7) it exhibits superparamagnetic, ferromagnetic, and multiferroic phases, which are suitable for medical imaging and magnetic fluid hyperthermia.

The Effect of Induced Heat

The analysis of nanoparticle interactions with body cells involves mechanical, thermal, van der Waals, and magnetic interactions. At the nanoscale, the ferrofluid of $Zn_xFe_{2-x}O_3$ nanoparticles can generate heat owing to the quantum confinement effect. The induced heat is proportional to the increase in tissue temperature. This property makes $Zn_xFe_{2-x}O_3$ nanoparticles effective for heat therapy.

Moreover, the effect of the induced temperature on the functional properties of the nanoparticles was investigated. To realize thermotherapy, the oscillation frequency of the nanoparticles must be tuned by the action of heat. Subsequently, by measuring the temperature rise, its resonance frequency can be adjusted to perform the thermotherapy process. Otherwise, the critical temperature is calibrated. Figures 1 (a, b) illustrate the relationship between temperature and oscillation frequency.

The calculated results suggest that as the particle displacement increases, the induced temperature increases owing to the quantum size effects. This is because the $Zn_xFe_{2-x}O_3$ nanoparticles themselves induce heat in proportion to the rise in temperature. This indicates that as the size of nanoparticles decreases, their sensitivity, biocompatibility, and biomedical functionality increase. The results also demonstrate the possibility of monitoring variations in temperature distribution per nanoparticle. The relationships between these parameters are illustrated in the Figure 1.

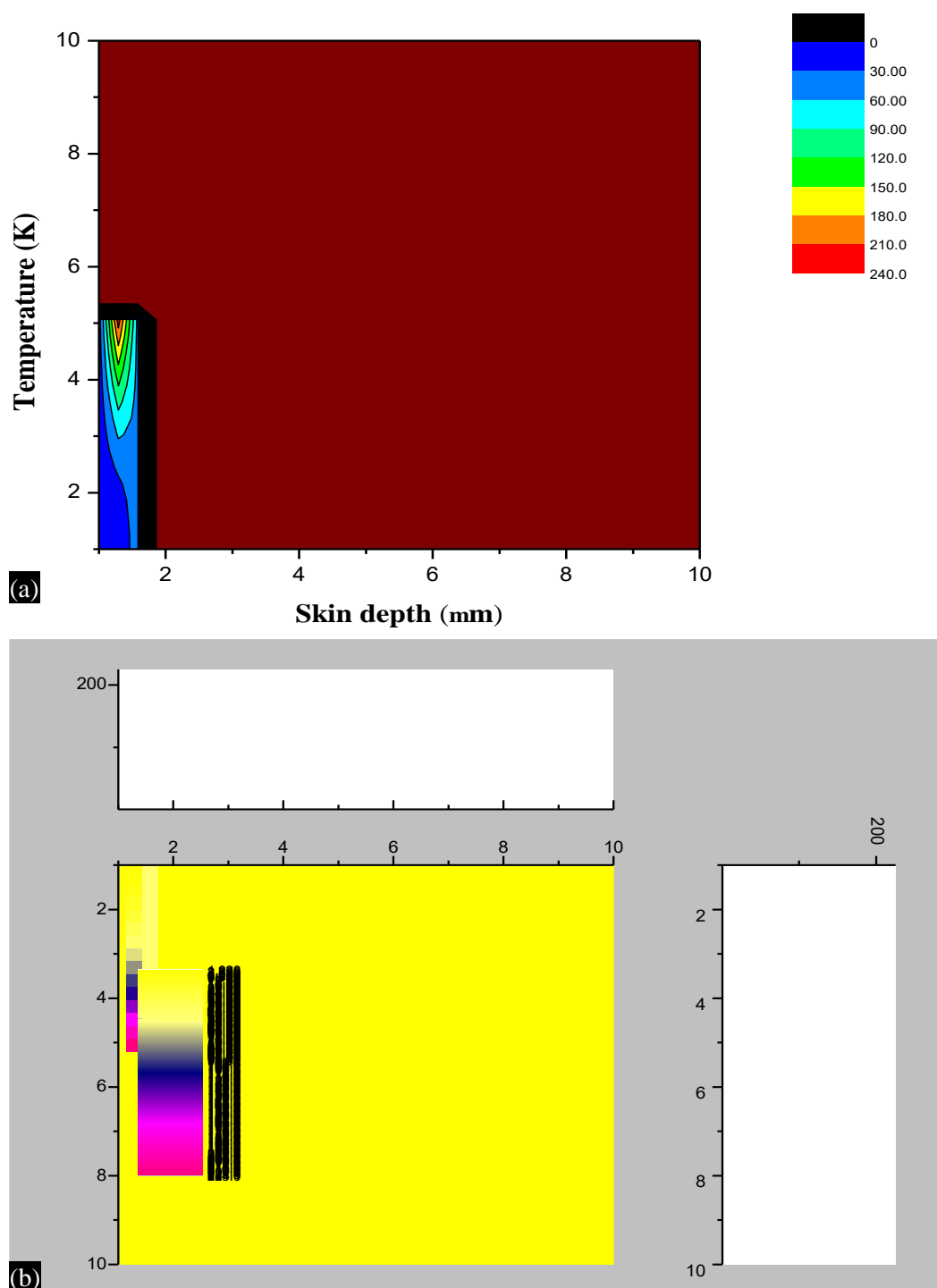


Figure 1. Temperature variations with particle size; (a) the quadratic relations between temperature and frequency and (b) thermo-luminescence caused by the interaction of $Zn_xFe_{2-x}O_3$ nanoparticles and temperature gradient where the frequency is being constant; $\omega \sim 200\text{Hz}$.

As shown in Figure 2, the frequency of the lattice vibrations is directly proportional to the square root of the temperature. However, it decreased linearly as a function of lateral displacement. This is due to the gradual decrease in the heat transfer with the temperature gradient. In addition, although $Zn_xFe_{2-x}O_3$ nanoparticles generate heat at the nanoscale, the surface area is so high that the rate of heat transfer decreases with an increase in surface area. This arises because $Zn_{0.4}Fe_{1.6}O_3$ can persist in either a nano-solid state or a nanofluid state. This condition is also required for magnetic fluid hyperthermia (MFH).

Ferrofluid with sufficient $Zn_xFe_{2-x}O_3$ nanoparticles used in magnetic hyperthermia was injected into the tumor; it was then turned on with a high-frequency AC magnetic field. It generates high heat energy, which is sufficient to kill cancer and tumor cells. It can also be noted that tuning $Zn_xFe_{2-x}O_3$ nanoparticles to the superparamagnetic phase at Larmor frequency enables effective magnetic resonance imaging and magnetic hyperthermia of Glioblastoma cells.

However, for the nanofluid state or nanofilms, the volume charge density ρ plays a dominant role. The ferrofluid of $Zn_xFe_{2-x}O_3$ nanoparticles can also generate heat, so the resulting temperature is related to the square of the frequency of vibration, as shown in Figure 3.

These results show that changing the temperature shown in Table 1 uniformly enhances the sensitivity for the accurate detection of tumor cells. In, the activity of the tumor rapidly decreased owing to the combined effect of heating temperature and oxygen partial pressure. Figure 4 shows the relationship between the change in temperature and skin effect.

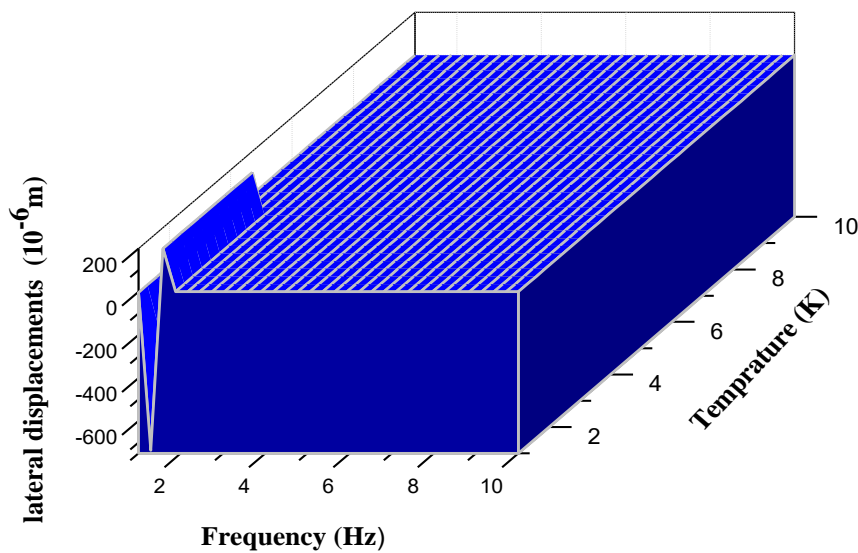


Figure 2. The temperature change is a function of lateral displacement of threshold frequency.

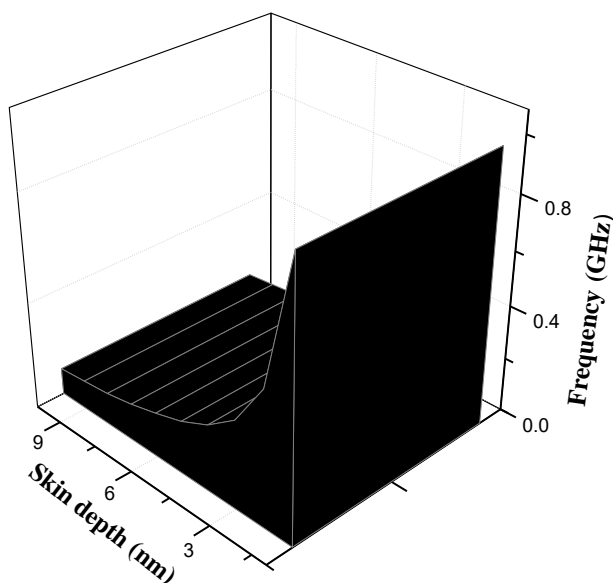
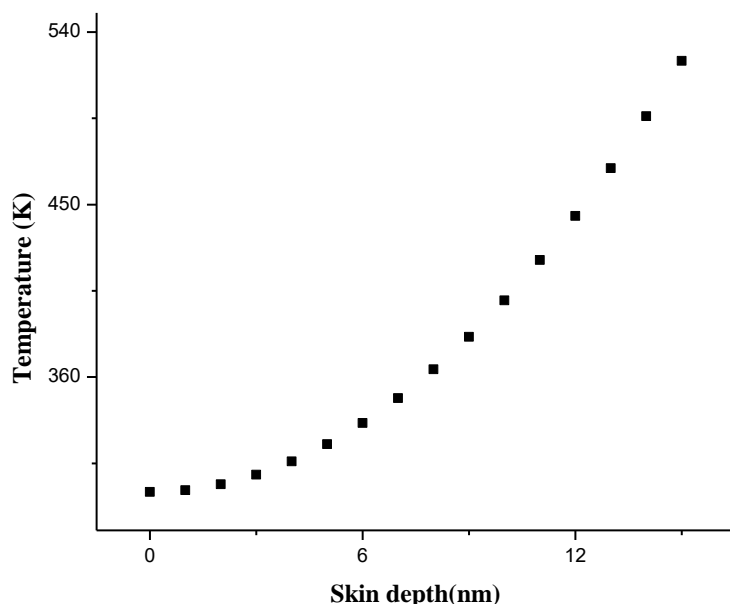


Figure 3. The frequency of crystal vibration varies inversely as a function of skin depth.

Table 1. The minimum and maximum Prostatic temperature of the $Zn_{0.4}Fe_{1.6}O_3$ based nanobiosensor.

Minimum temperature	-273°C	0°C	25°C	37°C	40°C	49°C
Constant Increment	273	273	273	273	273	273
Final temperature	0K	273K	298K	310	313K	322K

**Figure 4.** The change in temperature as the function of skin depth.

As the graph indicates, the temperature varies quadratically as a function of the skin depth. In addition, the heat induced by $Zn_xFe_{2-x}O_3$ nanoparticles increased quadratically as a function of skin depth. Because nanoparticles generate heat, their thermal properties are significantly influenced by the size and shape of the materials. This effect can be applied in therapeutic applications, temperature sensing, and monitoring time.

By improving biocompatibility and magnetic properties, $Zn_xFe_{2-x}O_3$ nanoparticles can be tailored for immune cell regeneration. $Zn_xFe_{2-x}O_3$ nanostructures, ZnO, and Fe_2O_3 play key roles in controlling the biological activity of body cells. To ensure biomedical applications, it is important to test the PH of $Zn_xFe_{2-x}O_3$ nanoparticles with regard to acid-base indicators.

Owing to their magnetic properties, such as superparamagnetism, Zn-doped iron oxides are widely used in magnetic resonance imaging. This property is also suitable for cell imaging and labeling. This idea can be applied to mesenchymal cells. As Li et al. 2019 [13] revealed, iron oxide nanoparticles were engineered to promote the growth of mesenchymal stem cells (MSCs). To improve resonance imaging and MFH, the effects of the magnetic field were analyzed. This is because the external magnetic field helps tune the resonance and Larmor frequencies for ferromagnetic resonance imaging. In addition, the existence of ferromagnetism at the Curie temperature enables MFH.

In general, the effective use of $Zn_xFe_{2-x}O_3$ based nanomedicine helps to reduce the risk effects related to blood contamination, particularly in the case of viral disease and enables prevention, protection, and treatment at its earliest stages. Although the use of nanoparticles, as discussed in this paper, is an efficient and reliable medical treatment, it is important to be aware of policies and ethics concerning the dose, injection methods, and safety rules. In the future, AI-assisted therapy, theranostics, and drug delivery systems are expected to improve the biomedical applications of magnetic $Zn_xFe_{2-x}O_3$ nanoparticles.

CONCLUSION

In this study, a comprehensive investigation of $Zn_xFe_{2-x}O_3$ nanoparticles was conducted. This study reveals that a $Zn_xFe_{2-x}O_3$ nanoparticle is a magnetic nanomaterial exhibiting superparamagnetic and ferromagnetic properties. The ferrofluid of $Zn_xFe_{2-x}O_3$ is superparamagnetic, whereas its nanoparticles, nanofilms, and nanocomposite are ferromagnetic. Its thermodynamic properties can be investigated by analyzing the statistical equations of states in the ferrofluid state. These nanoparticles/nanofluids can be engineered for improved thermotherapy or MFH. Researchers have discovered a straightforward correlation between the frequency of vibration and the resulting temperature change in the tissue, demonstrating that as the frequency increases, so does the temperature predictably and linearly. This relationship also indicates that $Zn_xFe_{2-x}O_3$ nanoparticles can be used for improved thermotherapy, magnetic imaging, and drug kinesis. In future work, $Zn_xFe_{2-x}O_3$ will be further investigated for AI-assisted therapy and nano-theranostics.

REFERENCES

1. Laurent S, Dutz S, Häfeli UO, Mahmoudi M. Magnetic fluid hyperthermia: Focus on superparamagnetic iron oxide nanoparticles. *Adv Colloid Interface Sci.* 2011;166:8–23. DOI: 10.1016/j.cis.2011.04.003.
2. 3McManus IP. *Nanotechnology in a Globalized World: Strategic Assessments of an Emerging Technology.* 2014. p. 0704–0188.
3. 2Salazar Alvazer G. Synthesis, characterization, and applications of iron oxide nanoparticles. *J Chem Mater.* 2004;44–67.
4. Malekie S, Rajabi A. Study on Fe_3O_4 Magnetic Nanoparticles Size effect on temperature distribution of tumor in hyperthermia: A finite element method. *Int J Nanoscience Nanotechnol.* 2020;16:181–188.
5. Assa F, Jafarizadeh-Malmiri H, Ajamein H, Anarjan N, Vaghari H, Sayyar Z, et al. A biotechnological perspective on the application of iron oxide nanoparticles. *Nano Res.* 2016;9:2203–25. DOI: 10.1007/s12274-016-1131-9.
6. Chey CO. *Synthesis of ZnO and Transition Metals Doped ZnO Nanostructures, Their Characterization and Sensing Applications.* 2015. ISBN: 978-91-7519-206-2.
7. Mohapatra M, Anand S. *Synthesis and applications of nanostructure iron oxides/hydroxides.* Vol. 2. 2010. p. 127–46.
8. Sibera D, Jędrzejewski R, Mizeracki J, Presz A, Narkiewicz U, Łojkowski W. Synthesis and characterization of ZnO doped with Fe_2O_3 – Hydrothermal synthesis and calcination process. *Acta Phys Pol A.* 2009;116(Suppl). DOI: 10.12693/APhysPolA.116.S-133.
9. Hayashi H, Hakuta Y. Hydrothermal synthesis of metal oxide nanoparticles in supercritical water. *Materials.* 2010;3:3794–817. DOI: 10.3390/ma3073794. PubMed: 28883312.
10. Yong XG, Shuyuan X, Xiumin W, Jia Z, Zehui Z. Hydrothermal synthesis of nanomaterials. *J Nanomater.* 2020;89170:1–3.
11. Kumar M, Sharma A, Maurya IK, Thakur A, Kumar S. Synthesis of ultra-small iron oxide and doped iron oxide nanostructures and their antimicrobial activities. *J Taibah Univ Sci.* 2019;13:280–5. DOI: 10.1080/16583655.2019.1565437.
12. Yang Y, Liu Y, Song L, Cui X, Zhou J, Jin G, et al. Iron oxide nanoparticle-based nanocomposites in biomedical application. *Trends Biotechnol.* 2023;41:1471–87. DOI: 10.1016/j.tibtech.2023.06.001. PubMed: 37407395.
13. Li X, Wei Z, Lv H, Wu L, Cui Y, Yao H, et al. Iron oxide nanoparticles promote the migration of mesenchymal stem cells to injury sites. *Int J Nanomedicine.* 2019;14:573–89. DOI: 10.2147/IJN.S184920. PubMed: 30666115.