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SYNTHESIS AND CHARACTERIZATION OF MAGNETIC ZINC FERRITE NANOPARTICLES FOR COMBINED TREATMENTS IN BIOMEDICINE

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ABSTRACT
The coprecipitation process has been used to create zinc ferrite ($ZnFe_2O_4$) nanoparticles. The nanoparticles were synthesised at three distinct temperatures: room temperature, 60°C, and 90°C. Furthermore, three different NaOH concentrations were used: 1 M, 1.5 M, and 2 M. X-ray diffraction and transmission electron microscopy were used to examine the crystal structure and morphology of the samples. The results show that the nanoparticles are made of a ZnFe2O4 phase with a normal and inverse spinel crystal structure. The Scherrer equation calculations revealed that changing the concentration of NaOH and the synthesis temperature resulted in smaller particles. Depending on the concentration of NaOH, the particle size ranges from 10.4nm; 16.5nm and 18.0 nm. It also varies from 15.6 nm to 16.8 nm and 18.2 nm depending on the temperature of synthesis (room temperature, 60°C, and 90°C). The crystals resulting from the synthesis of $ZnFe_2O_4$ nanoparticles were then tested for antibacterial action, namely against Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria with a positive control in the form of ciprofloxacin which is active against both gram-positive and gram-negative, Antibacterial efficacy was then calculated by measuring the diameter of the clear zone produced; this method yielded results of 15 mm for E. coli and 20 mm for S. aureus. Saturation of the liquid medium with nanoparticles is likely to occur within 5 minutes, as shown by the results of the release capacity of nanoparticles.
Keywords: Zinc nano ferrites, precipitation method, characterization, medical applications

1. Introduction

Spinel ferrite is used in many applications including drug delivery, biomolecular sensors, in biomolecule separation processes and purification and hyperthermia therapy [1]. Soft Ferrite, has the formula MFe_2O_4 where M is Cu, Zn, Ni, Co, Fe, Mn, Mg with a crystal structure like the mineral spinel. The properties of this material have high permeability and resistance and low coercivity [2]. Zinc ferrite is classified as a soft magnet or paramagnetic (does not have a remanent field). Zinc ferrite material has material properties where the resultant atomic magnetic field of each atom or molecule is not zero. But the resultant total atomic magnetic field of all atoms or molecules in the material is zero [3]. A valuable purpose directed to the field of nanomedicine is the targeting and release of a therapeutic substance into the human body. Such a system, known as a drug delivery system, can be defined as a process that allows

controlling the release of a drug in the body, in a specific location, after exposure to a trigger such as: pH, enzymes or temperature. This release of content is carried out only in the target tissue, under controlled conditions, increasing its safety and therapeutic efficacy since the drug remains in the therapeutic zone [4].

Various methods have been developed to synthesize magnetic nanoparticles, including coprecipitation, thermal decomposition, microemulsion and hydrothermal methods [5]. Apart from that, there are also polyol methods, sonochemistry, and other methods [6]. Among these methods, the coprecipitation method is a method that is quite effective and relatively simple compared to other methods. This method produces a relatively narrow grain size distribution and can be carried out under normal environmental conditions [5]. Coprecipitation methods include wet chemical methods. This method generally uses precipitating substances such as carbonate hydroxide, sulphate and oxalate [6-7]. The main objective of this paper is to develop a magnetic nanomaterial for use as a thermo-sensitizing agent in biomedical treatments against cancer and that at the same time is self-limiting in the generation of heat, thus reducing the possible side effects of the treatment.

2 Materials and methods

The synthesis of $ZnFe_2O_4$particles was carried out using the Coprecipitation Method. The basic ingredients that form the $ZnFe_2O_4$ material are iron sand (Fe_3O_4), hydrochloric acid (HCL) and sodium hydroxide (NaOH). These basic ingredients are called percussion. Based on the chemical reaction for making $ZnFe_2O_4$ using the coprecipitation method, it can be carried out as in the equation.

In accordance with the chemical reaction for the formation of zinc ferrite, two precursor solutions are required, namely iron chloride and zinc chloride, both of which are used as the initial solution. After the chloride solution is formed, the next process is to mix the two solutions in a ratio of 1:1. Then the solution was mixed with a NaOH solution with a concentration of 20% using a dropper pipette. This process is called the precipitation process.

The result of adding the NaOH solution (precipitate) is a brown precipitate. This brown color indicates that ferrite deposits have formed. The resulting precipitate was then left for 24 hours. Then filter the precipitate, wash with distilled water, and dry at 80°C. With the end of this process, the ferrite precipitate is ready to be heated to varying temperatures of 100°C, 300°C and 500° C. This powder is then characterized using XRD to determine its properties.

2.1 Ferrite Purification: The synthesis product was macerated, dissolved in distilled water, centrifuged at 3000 rpm for 5 minutes, with the supernatant discarded. Subsequently, the material was subjected to a muffle furnace at a temperature of 500°C for 4 hours followed by slow cooling at room temperature. 7g of zinc nanoferrites were reserved for freeze-drying, and the remainder was used for characterization using the following techniques: scanning electron microscopy, to evaluate the morphology and average size of agglomerates, chemical analysis and XRD.

Freeze Drying of Nanoparticles: 0.100g of the antibiotic known as Cephalexin ($C_{16}H_{17}N_3O_4S$) was weighed and dissolved in 100mL of deionized water, subsequently 3mL of this solution was reserved in a falcon tube. Furthermore, 7g of this sample of ferrites synthesized was weighed and added to the falcon tube with the drug. This solution was homogenized manually and continued to be lyophilized at -50°C for 10 hours in the lyophilizer.

To characterize these nanoparticles, studying and analyzing their size, Scanning Electron Microscopy (SEM) techniques were used in Numpex on the TESCAN VEGA 3 LMU equipment operating in scanning transmission electron microscopy mode at 30 kV. The elementary and chemical analyses of the samples reached by the technique implemented in the Tescan VEGA 3 LMU with the X-Max type detector, used an acceleration voltage of 30 kV and an acquisition time of 19.2 seconds.

The results of XRD characterization are obtained in the form of a spectrum which is

equipped with information regarding the characteristics of each sample. The spectrum is in the form of a peak which indicates the intensity relative to the angle (2θ). To obtain the diffraction angle, you can use the Bragg equation. Grain size can also be identified using the Scherer formula (Cullity, 2009).

It was characterized by X-ray Diffraction (XRD) (Shimadzu model XD-3H) using monochromatic CuKα radiation (wavelength, λ = 1.5406 Å). The sample crystal grain size was calculated by taking the broadening of the (311) peak using the Scherrer equation,

$$k = \frac{0.9\lambda}{B\cos\theta} \quad (1)$$

where t is the crystal grain size, k is Scherrer's constant (0.9), λ is the X-ray wavelength (in Å), D is the half-peak width (in radians), and θ is the Bragg diffraction angle (in radians). The calculation results will be confirmed by Transmission Electron Microscopy (TEM) observations (JEOL TEM 1400).

2.2 Biomedical applications-

Preparation of nanocomposite variable stock: The variable used in this research was $ZnFe_2O_4$ nano ferrite, 1:1 with a negative control in the form of water, and a positive control in the form of a Ciprofloxacin disk which is a broad-spectrum antibiotic so it is suitable for inhibiting the growth of gam-positive and gam-negative bacteria. A positive control was made by dissolving 0.05 gram of Ciprofloxacin tablet in 50 mL of distilled water. Next, take 1 mL of the Ciprofloxacin solution and then put it in a 10 mL measuring flask, add distilled water until it reaches the tera mark. The solution is then placed on a blank disk, namely a petri dish containing NA. Negative controls were prepared by adding 10 mL of distilled water to the prepared blank disk.

Bacterial culture: Making bacterial stock is carried out to multiply and rejuvenate bacteria, by inoculating 1 dose of pure bacterial culture *E. coli* and *S. aureus* into nutrient agar, then incubated at 37 °C for 24 hours in an incubator.

Making nutrient agar (NA) growing media and sterilizing tools: A total of 8.2 grams of NA was dissolved in 300 mL of distilled water, then the NA solution that had been made along with 8 petri dishes and glassware that would be used in this test were put into an autoclave at a temperature of 121°C for 30 minutes for sterilization.

Preparation of test bacteria: Bacteria are diluted by mixing 1 dose each of *S. aureus* and *E. coli* bacterial suspensions into a test tube containing 5 mL of 0.9% NaCl solution. Then homogenize using a vortex until it becomes cloudy.

Bacterial inhibition test: A total of 20 mL of NA solution was put into a petri dish and then left for 15 minutes until the NA solution hardened. Then 0.1 mL of the bacterial solution that was made earlier was applied to the NA growth medium. After that, 0.1 mL of negative control was placed, 0.1 mL of positive control, and 0.1 gram of sample (2 repetitions). The media that had been made was incubated in an incubator at 37 °C for 24 hours, and measured the next day by observing the diameter of the clear zone formed using a calliper.

***In Vitro* Release Test:** The samples were subjected to the release test where it was divided into two stages:

In step one, 80 mg of the sample already lyophilized with the drug was weighed on a precision balance and diluted in a beaker containing 500 mL of deionized water under stirring at room temperature. Aliquots (1ml) were removed at pre-defined times (5, 10, 20 and 30 minutes), without replacing the volume, by collecting the dissolution medium, the collections were analyzed in the spectrophotometer at a wavelength of 311 nm. In the second stage, a second release test was carried out like the previous one with the following modifications, reducing the concentration of Nanoferrites by half (40 mg) and modifying the subsequent time periods: 5, 30 and 60 minutes.

3. Results and Discussion

Test the powder's response to an external magnetic field: Addition of a base solution to a chloride solution produces a brown powder as shown in figure 1 (a). The powder resulting from precipitation has magnetic properties (responds to an external magnetic field) as shown in figure 1 (b).

(a) **(b)**

Figure 1. (a) Precipitation process (b) Precipitated ferrite powder

Figure 2 and Figure 3 show the X-ray diffraction patterns of samples synthesized with varying concentrations of NaOH, namely 1M, 1.5 M, and 2M and variations synthesis temperature from room temperature, 60°C, and 90°C. The results of XRD characterization of $ZnFe_2O_4$ nanoparticles from peaks recorded from 27° to 75° show that the synthesized samples have a cubic spinel structure. This can be seen clearly in the main diffraction peaks of the sample, namely at an angle of 2θ of around 35°, which is related to the (311) plane. Other peaks with lower intensity corresponding to the (220), (400), (511), and (440) planes respectively were also observed in the $ZnFe_2O_4$ samples synthesized in this study.

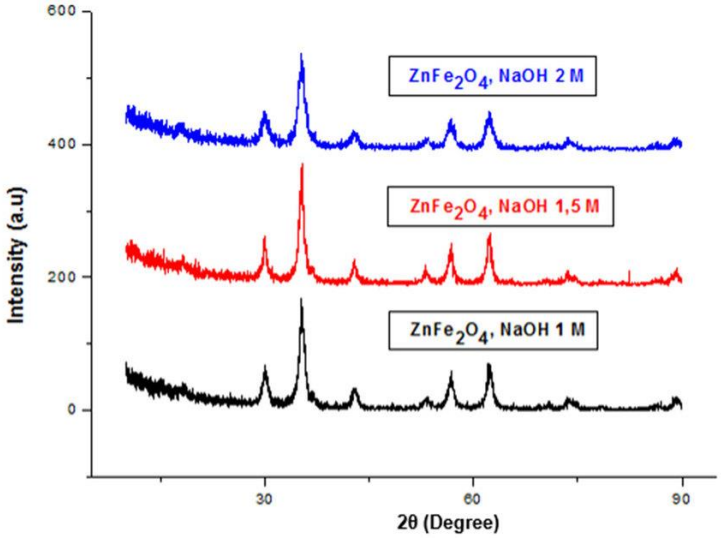

Figure 2: XRD pattern of $ZnFe_2O_4$ nanoparticles with varying NaOH concentrations

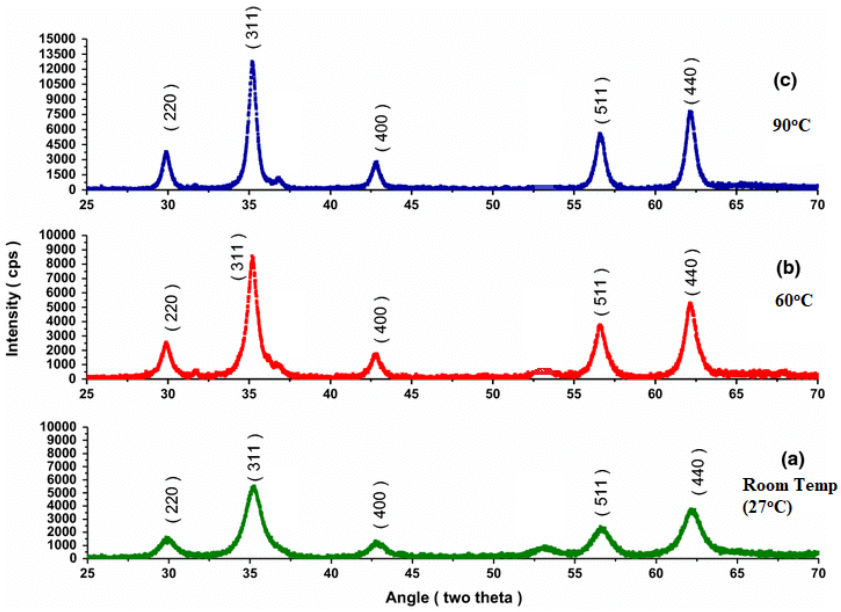

Figure 3: XRD pattern of $ZnFe_2O_4$ nanoparticles with variations in synthesis temperature.

The results of analysis of lattice parameters (a) and particle size (t) of synthesized $ZnFe_2O_4$nanoparticle samples with variations in NaOH concentration and synthesis temperature are shown in Tables 1 and 2.

Table 1. Lattice parameters (a) and grain size (t) of samples with varying NaOH concentrations

Sample	NaOH Concentration (M)	a(Å)	t(nm)
1M	1	8.466	10.4nm
1.5M	1.5	8.476	16.5nm
2.0M	2	8.513	18.0 nm

Table 2. Lattice parameters (a) and grain size (t) of samples with variations in synthesis temperature

Sample	Synthesis temperature (oC)	a(Å)	t(nm)
Room Temprature 27°C	27°C	8.443	15.6 nm
60°C	60°C	8.469	16.8nm
90°C	90°C	8.446	118.2nm

The lattice parameter values increase with increasing NaOH concentration. The lattice parameter value of the synthesized nanoparticle sample was obtained to be greater than the lattice parameter value of bulk $ZnFe_2O_4$, namely 8.441 Å (JCPDS No. 22-1012). This indicates that the $ZnFe_2O_4$ nanoparticle sample is a mixture of normal and inverse spinel structures. This phenomenon of increasing lattice parameter values can be related to the distribution of Zn2+ and Fe3+ cations in interstitial sites. Substitution of several Zn^{2+} cations with a Zn2+ ionic radius of 0.74 Å, greater than the Fe3+ ionic radius of 0.64 Å, results in expansion of the spinel lattice so that the resulting lattice parameters increase further.

However, the samples synthesized at a temperature of 20oC obtained the smallest lattice parameter values. This result was also obtained by

previous researchers, Shahraki et al., 2012 [8], who showed that the lattice parameter value decreased at a synthesis temperature greater than 60oC and at a temperature of 20oC the lattice parameter value was reduced. This is because at room temperature (RT), the cation distribution process is slow.

Table 1 demonstrates an inverse relationship between the NaOH content and the particle size of the synthesised $ZnFe_2O_4$ nanoparticles. Raising the concentration of NaOH leads to a higher rate of precipitation and a lower rate of dissolution, resulting in the occurrence of the nucleation stage. The nucleation phase exerts greater influence than crystal development, resulting in the formation of particles with a tiny size. Furthermore, the observed reduction in particle size as NaOH concentration increases demonstrates the efficacy of NaOH as a potent disintegrating agent.

Table 2 demonstrates a direct correlation between the synthesis temperature and the particle size of the synthesised $ZnFe_2O_4$ nanoparticles, indicating that higher synthesis temperatures result in larger particle sizes. This phenomenon occurs due to the direct correlation between temperature and the level of nanoparticle growth activity, which is influenced by thermal factors throughout the synthesis process. Consequently, increasing the synthesis temperature leads to an augmented particle size of the material. This is a result of additional phase growth processes, causing the merging of particles and subsequent enlargement. Apart from having a $ZnFe_2O_4$ phase, the sample diffraction pattern also shows the presence of other peaks related to impurities. This peak is characteristic of the α-Fe_2O_3 (hematite) phase which is antiferromagnetic.

Scanning Electron Microscopy (SEM): Figure 4 refers to the SEM of the nanoparticles, on the left the sample synthesized, with a cluster of nanostructures of varying sizes, demonstrating the role of NaOH pH in the formation and growth of Nanoferrites, stabilizing surface charges and thus stabilizing the first Nanoferrites nuclei at the beginning of synthesis. The final morphology of Nanoferrites can vary depending on the pH in the medium, since the higher the pH, the growth of the nuclei in specific planes will be inhibited and favoured in others, varying the morphology, these results being consistent with the results reported in the literature [12].

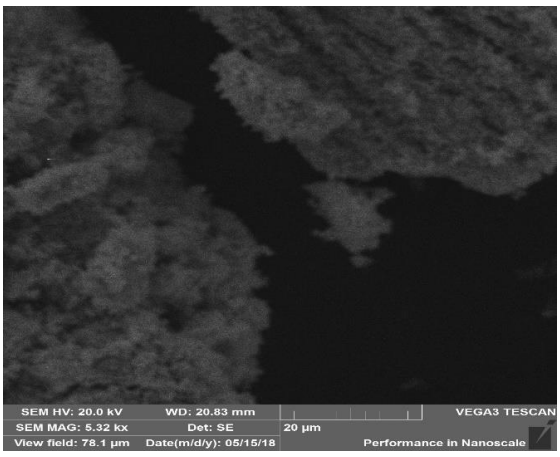

Figure 4: Micrograph obtained by SEM of $ZnFe_2O_4$ powder synthesized

The clusters have a morphology similar to pores, which are of great importance, as therapeutic substances can be transported more easily as they have a large surface area for interactions with the drug [11]. According to observations of the surface morphology of Zn Fe_2O_4 nanoparticles. Shows that the shape of the particles is large and some are square, rectangular and checkered. The morphology of the $ZnFe_2O_4$ particles resulting from this study is similar to that reported by Sathishkumar et al (2013) [10], where the shape of the $ZnFe_2O_4$ particles is also square or checkered.

Elemental Analysis: Chemical analyses of the sample without stabilizer confirmed that there was no distribution of oxygen, zinc, iron and oxygen atoms in the sample, it is possible to observe that where one of these three types of atoms is found there is presence of the others in the same location, implying that ferrite formation occur (figure 5).

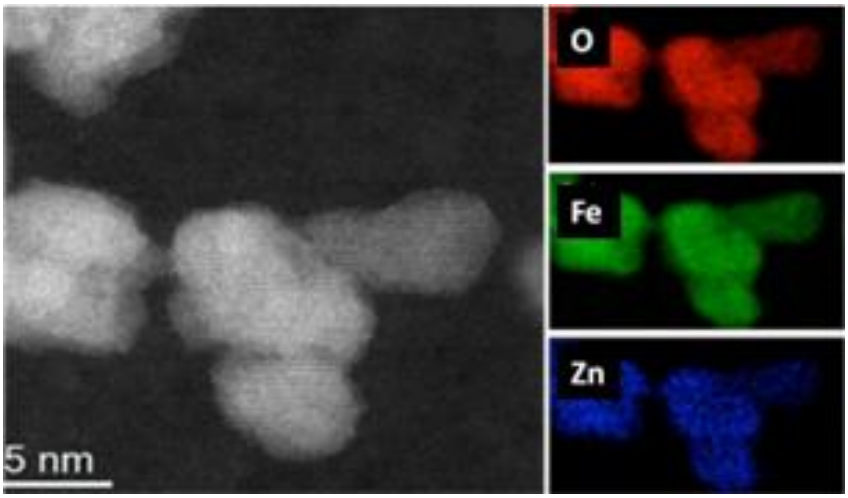

Figure 5. Chemical analysis of powdered $ZnFe_2O_4$ nanoferrite synthesized

Figure 6 shows the results of TEM observations. Figure 6(a) is the morphology of $ZnFe_2O_4$nanoparticles of 1M sample with an average diameter of 10.4 nm with a particle size distribution below 18 nm. This result is quite consistent with the calculation results using the Scherrer equation for XRD analysis, namely 16.5 nm. In Figure 6(b) is a diffraction ring pattern showing the (220), (311), (400), (511), and (440) planes. These results confirm the results of XRD analysis on the 1M sample.

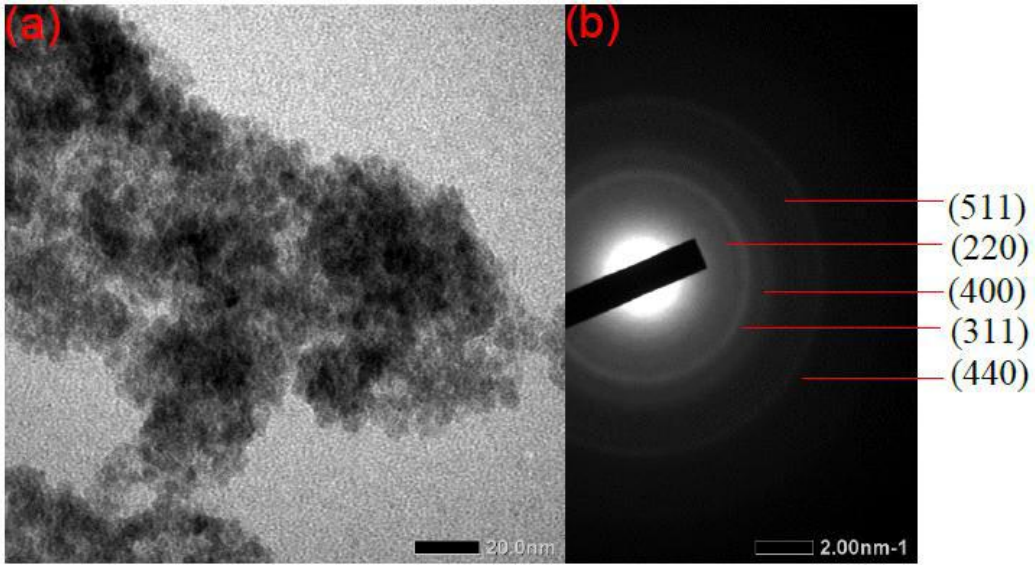

Figure 6: TEM test results (a) morphology (b) diffraction ring pattern of 1.5M sample

3.1 Test of antibacterial activity of $ZnFe_2O_4$ nanoparticles

The crystals resulting from the synthesis of $ZnFe_2O_4$ nanoparticles were then tested for antibacterial action, namely against Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria with a positive control in the form of cyprofoxasin which is active against both gram-positive and gram-negative. The antibacterial activity test is measured based on the inhibition of bacterial growth. Based on results of the antibacterial activity test, when $ZnFe_2O_4$ nanoparticles were added, the inhibitory power increased until it reached 15 mm for *E. coli* bacteria and 20 mm for *S. aureus* bacteria. Basically, nanoparticles stick to the bacterial cell walls and penetrate the cell membrane. This can happen because the size of the bacteria is around 0.7-1.2 µm for *S. aureus* bacteria and around 1.1 µm with a diameter of 0.7 µm for *E. coli* bacteria [13].

As a result of the entry of these particles, the thick and rough bacterial cell walls become damaged, resulting in degeneration and loss of cytoplasm and therefore causing cell death. Wang et al (2017) [14], reported that the ions released from nanoparticles caused oxidative stress in cells which ultimately caused DNA damage. Another comparison that can be seen is that the antibacterial activity of the nanocomposite turns out to be greater against *S. aureus* bacteria than *E. coli* in inhibiting bacterial growth.

***In vitro* release test:** The results of the release capacity of nanoparticles over time are available in figures 7 and 8. In figure 7, the Nanoferrites exhibited a release effect of up to 5 minutes and probably reach the degree of saturation due to the number of nanoparticles in the liquid medium. When observing figure 8 where there was a decrease in the amount of nanoparticles in relation to the first test, we can observe a drug release profile over 60 minutes showing a delayed release showing a slow release of the drug over time. It can be observed that there is a relationship between the amount of nanoparticles and the drug and this affects the type of drug release.

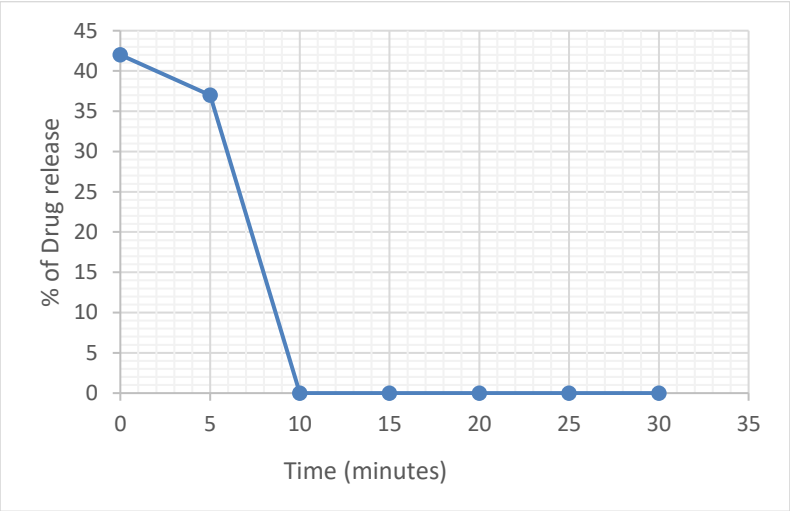

Figure 7. Release profile graph of the drug cephalexin in the aqueous medium over time for Nanoferrites concentration 1.

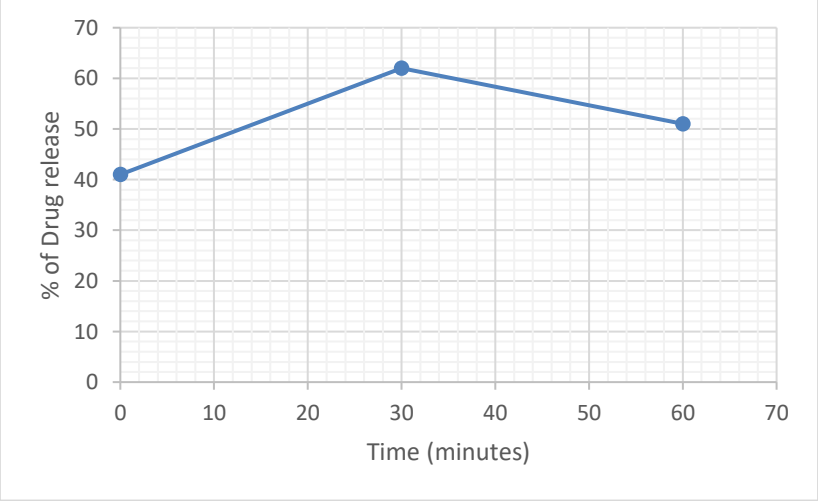

Figure 8. Cephalexin drug release profile graph in the aqueous medium over time for Nanoferrites concentration 2.

4. Conclusion

$ZnFe_2O_4$ nanoparticles have been successfully synthesized using the coprecipitation method at various NaOH concentrations and synthesis temperatures. The results show that the sample is a $ZnFe_2O_4$ phase with a mixed structure of normal and inverse spinel. In addition, the grain size decreases with increasing NaOH concentration and increases with increasing synthesis temperature. Analysis of magnetic properties shows that the coercivity value increases with decreasing grain size and tends to increase with increasing grain size, respectively for samples with variations in NaOH concentration and synthesis temperature. The synthesis of zinc ferrite nanoferrites ($ZnFe_2O_4$) was considered promising since nanoferrites of excellent quality and efficiency were formed as drug carriers via an already known route (co-precipitation) but of lower cost way to use synthetic chemistry in the process.

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