Targeted Drug Delivery through the Synthesis of Magnetite Nanoparticle by Co-Precipitation Method and Creating a Silica Coating on it

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Abstract:- Billions of dollars are spent annually in the world to treat and investigate problems caused by drug side effects. According to the estimation of health researchers, a huge part of people who take medicine suffer from complications caused by it. In this way, the necessity of using a targeted system in order to deliver medicine to the targeted place without damaging healthy tissues is felt more than before. In recent years, targeted drug delivery systems based on nanoparticles have received much attention. In the same direction, in this research, co-precipitation method was used to prepare magnetic nanoparticles using iron(|) and iron(||) oxides, and further, according to the synthesis steps of magnetite nanoparticles (MNPs) and the mechanism of formation and identification of magnetite nanoparticles (Fe_3O_4) by examining the infrared pattern (FT-IR) obtained from Fe_3O_4 nanoparticles, the results of the magnetometric test (VSM) of Fe_3O_4 nanoparticles, X-ray diffraction pattern (XRD) of Fe_3O_4 nanoparticles, Field Emission Scanning Electron Microscope (FE-SEM) images obtained from Fe_3O_4 nanoparticles was discussed. After this stage, silica-coated iron nanoparticles ($Fe_3O_4@SiO_2$) were prepared, and the infrared (FT-IR) pattern of $Fe_3O_4@SiO_2$) was also investigated. It is worth mentioning that the mechanism of formation and identification of magnetic silica-coated iron nanoparticles ($Fe_3O_4@SiO_2$) has been described in detail. Therefore, the obtained results indicate that the drug can be guided in a controlled and targeted manner by the magnetic field, and the results of the FE-SEM images show that the obtained product has a spherical morphology and the particle size distribution was less than 100 nm. Therefore, spherical shape and the symmetry of these particles can be helpful for their movement in the liquid mediu.

Keywords:- Targeted Drug Delivery - Magnetite Nanoparticle - Co-Precipitation Method - Silica Coating

I. INTRODUCTION

In general definition, it can be said that the particles of sizes in the range of (10-100) nanometers are called nanoparticles. Nanoparticles, due to their very small size and high surface-to-volume ratio, can be used to attach multiple ligands to the surface due to their tendency to create multiple covalent bonds. Other characteristics of nanoparticles include chemical and biological stability, the ability to bind to both hydrophilic and hydrophobic drugs, and the ability to be administered by different routes such as oral, inhalation, and injection [1] These nanoparticles have the ability to carry substances such as drugs in the form of dissolved, trapped, encapsulated or attached to the nanoparticle matrix [2].

A group of nanoparticles that have an inorganic origin and are widely used in drug delivery systems are magnetic iron nanoparticles that are chemically or biologically synthesized. Due to their magnetic properties, these particles can be directed to a specific place in the body by an external magnetic field, therefore they are very useful and valuable in the field of targeted drug delivery. From this category, we can mention magnetite and maghemite nanoparticles, which have received a lot of attention in drug delivery. One of the most important advantages of magnetic nanoparticles is that they can be easily modified [3].

In recent years, many methods have been designed and introduced for the production of magnetic nanoparticles, and in most of them, the focus is on obtaining a controlled shape, high stability and size of nanoparticles. The method used for the synthesis of magnetic nanoparticles depends on the type of properties of the desired material, which can be chosen after determining the properties of the desired product according to the shape, distribution and economic aspects. Among the methods that have been designed so far, we can mention the sol-gel method 5, co-precipitation, hydrothermal, combustion, sonochemical and microemulsion methods [4-5].

II. CO-PRECIPITATION METHOD TO PREPARE MAGNETIC NANOPARTICLES

It is one of the oldest methods of synthesis of magnetic nanoparticles, which was used for the first time to produce magnetite nanoparticles. Among the advantages of this method, it can be mentioned that it is a single step, easy, cost-effective and fast, which produces a small and uniform product. In this method, iron(II) and iron(III) oxides and a base are used and magnetite nanoparticles can be synthesized. Among the effective parameters in the production of these

nanoparticles, we can mention the ionic strength, the type of salt used, the reaction temperature, pH, the speed of stirring the reaction and adding base, and the ratio of iron (II) and iron (III) ions, which are effective in the size, shape and composition of the synthesized nanoparticles [6].

$$Fe^{2+} + 2Fe^{3+} + 8OH^- \longrightarrow Fe(OH)_2 + 6Fe(OH)_3 \longrightarrow Fe_3O_4 + 4H_2O$$

> *Steps of of Magnetite Nanoparticles (MNPs) Synthesis:*

Co-precipitation method was used for the synthesis of nanoparticles in this research [7]. For this purpose, 4.5 grams of $FeCl_3.6H_2O$ and 2 grams of $FeCl_2.4H_2O$ in 100 ml of double-distilled water were added to a fume hood equipped with nitrogen inlet and outlet, The resulting mixture was vigorously stirred with a magnetic stirrer under reflux conditions and a temperature of 85°C for 15 minutes, then 15 ml of 30% ammonia solution was added drop by drop to the mixture, the color of the mixture immediately changed from orange to black. The resulting solution was refluxed for 30 minutes. After the reaction is over, the precipitate was separated by a magnet and washed 3 times with double-distilled water. The black precipitate of Fe_3O_4 obtained from this step was identified by FT-IR, VSM and SEM analyses

III. MECHANISM OF FORMATION AND IDENTIFICATION OF MAGNETITE NANOPARTICLES (FE₃O₄)

To prepare these nanoparticles, a co-precipitation method was used, in which iron (II) and iron (III) salts were used with stoichiometric ratios of 1 to 2 according to the following reaction:

By adding ammonia to the reaction solution containing iron salts, spherical shape and black iron nanoparticles are obtained as follows.

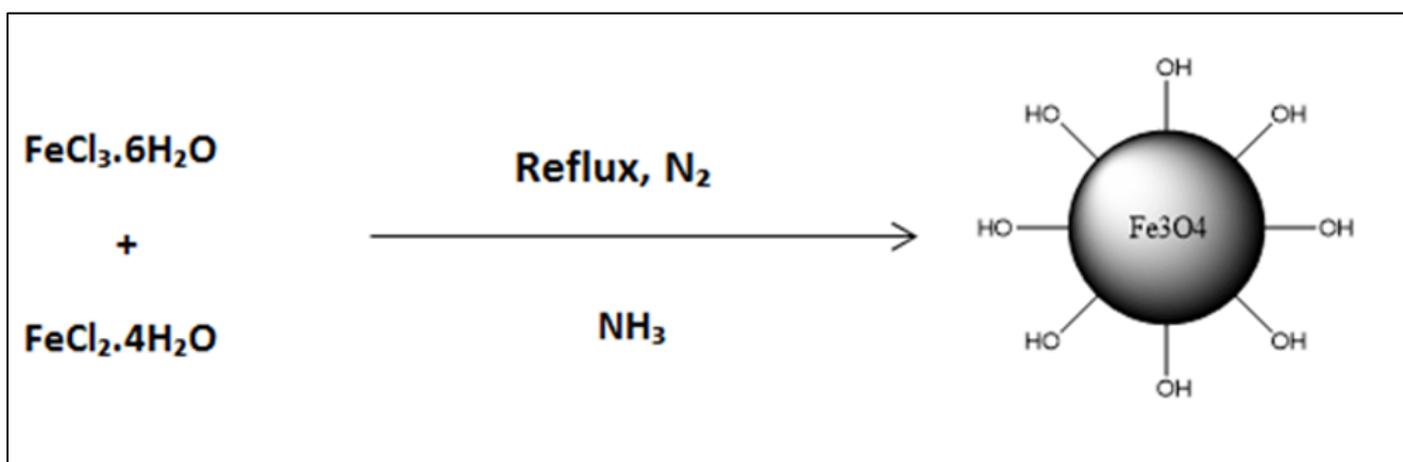Fig 1: Magnetite preparation reaction

$$Fe^{2+} + 2Fe^{3+} + 8OH^- \longrightarrow Fe_3O_4 + 4H_2O$$

Fig 2: General Scheme of Preparation of Magnetite Nanoparticles

Magnetic iron nanoparticles are oxidized in air and produce $Fe(OH)_3$ according to the reaction shown below. To prevent oxidation, nanoparticles were synthesized in the presence of nitrogen gas.

$$4Fe_3O_4 + O_2 + 18H_2O \longrightarrow 12Fe(OH)_3$$

➢ *Examining the infrared pattern (FT-IR) of Fe_3O_4 nanoparticles:*

Diagram 1- shows the FT-IR spectrum of the prepared Fe_3O_4 compound. The two bands appearing at 430 Cm^{-1} and 560 Cm^{-1} correspond to the vibrations of the Fe—O bonds of the compound [8]. The band related to surface OH groups can also be seen in the range of Cm^{-1} 3400.
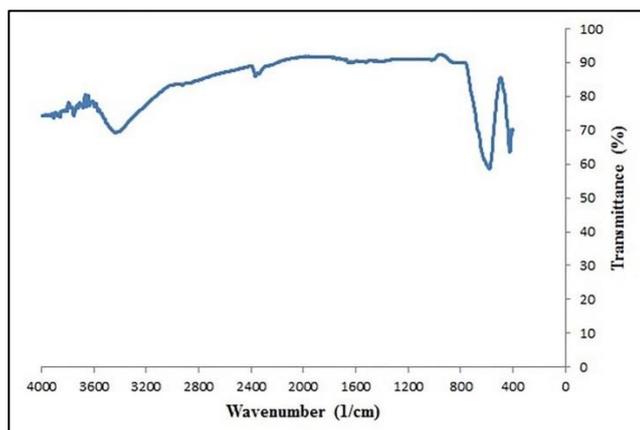

Diagram 1: FT-IR Spectrum of Magnetite Nanoparticles

➢ *Examining the Results of the Magnetometery Test (VSM) of Fe_3O_4 Nanoparticles:*

In paramagnetic materials, the arrangement of atomic magnetic moments is completely random and separate, so that the magnetic moment of the entire crystal structure is zero. In this case, if these materials are exposed to an external magnetic field, some of these separate atomic magnetic moments will find the same orientation and the structure will have a small amount of magnetic moment. In the ferromagnetic state, the atomic magnetic moments have the same orientation relative to each other. Therefore, the crystal structure has a total magnetic moment. This is despite the fact that in an antiferromagnetic crystal, half of the atomic magnetic moments are directed upwards and the other half are directed downwards. Therefore, the total magnetic moment for an antiferromagnetic crystal is zero. Figure 2 shows the magnetic susceptibility diagram of a ferromagnetic material with magnetic strength M in the presence of an external magnetic field with strength H. As it can be seen, with the increase of H, the amount of M increases until it reaches its highest level, which is called the saturation magnetization (M_s). The resulting diagram shows a residual magnetic value after removing the external field, which is called "hysteresis loop ". The presence of this loop indicates that after the removal of the external magnetic field, some magnetic property remains in the material and all the magnetic property of the ferromagnetic material is not lost. Because after the removal of the external magnetic field, the orientation of the atomic magnetic moments in all areas do not return to their original arrangement. Therefore, even when the value of the external field H reaches zero, there is still some residual magnetization MR in the material, which can only be removed by applying a coercive HC field, opposite to the initial field direction. In the magnetization diagram of single-domain magnetic materials, no hysteresis loop is observed, such compounds are called super-paramagnetic. Magnetite nano-oxides smaller than 100 nm have superparamagnetic properties at room temperature. [9]
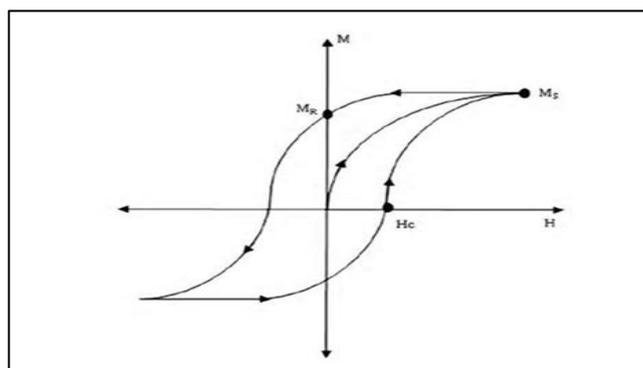

Fig 3: Changes of Magnetic Susceptibility in a Ferromagnetic Material

Diagram 2- shows the magnetic behavior of magnetite nanoparticles, which was investigated by performing vibrational magnetometer analysis of the VSM sample. As can be seen, the obtained magnetite particles show the characteristic of super para magnetism with a maximum magnetic susceptibility of 70 emu/g. The absence of a hysteresis loop in the magnetic susceptibility diagram is a confirmation of the superparamagnetic behavior of magnetite in the presence of an external magnetic field.
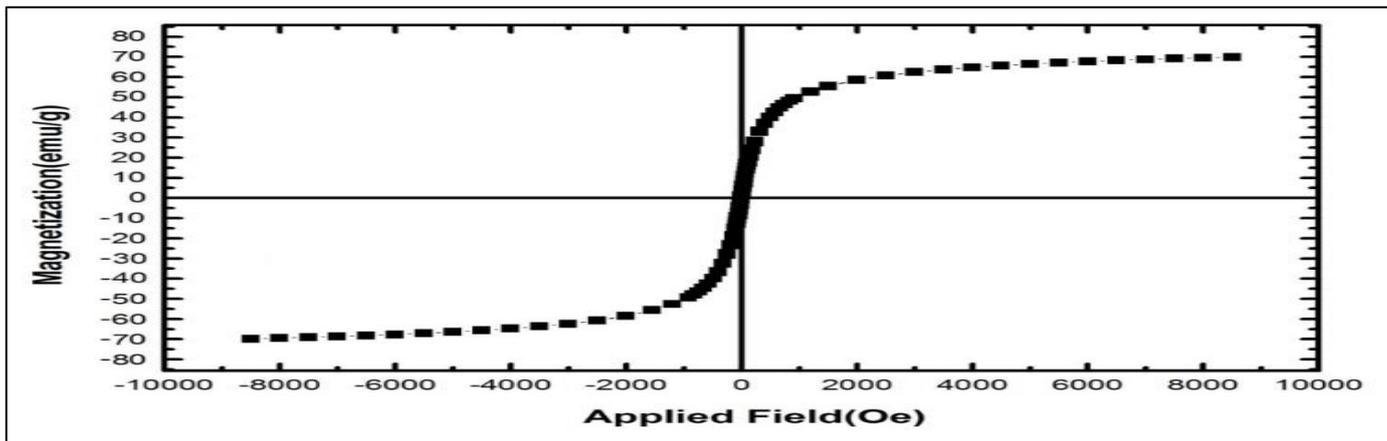
Diagram 2: Magnetometric Diagram of Magnetite Nanoparticles

> *Examining the X-Ray Diffraction (XRD) Pattern of Fe₃O₄ Nanoparticles*

The X-ray diffraction pattern of Fe_3O_4 compound is shown in Figure 3. Comparing this pattern with the reference magnetite pattern in the aforementioned device with JCPDS No. 0629-19, which belongs to Fe_3O_4, determined that all the diffraction signals related to the prepared magnetite structure are consistent with the diffraction related to the reference magnetite structure in terms of the position and intensity of vibrations, which is a confirmation of the formation of the Fe_3O_4 compound.
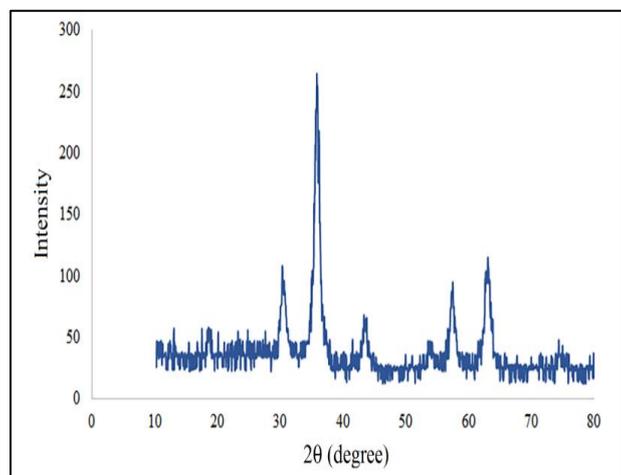

Diagram 3: X-ray Diffraction Pattern of Magnetite Nanoparticles

> *Examining the Scanning Electron Microscope (FE-SEM) Images Obtained from Fe₃O₄ Nanoparticles*

Scanning electron microscope is used to determine surface morphology, texture, size and shape of major samples of solid materials. The FE-SEM images obtained from the Fe_3O_4 compound in this project are shown in Figure 3. As can be seen, the obtained nanoparticles are assemblies of spherical particles stuck together with a high surface area and an approximate size of 20-30 nm.
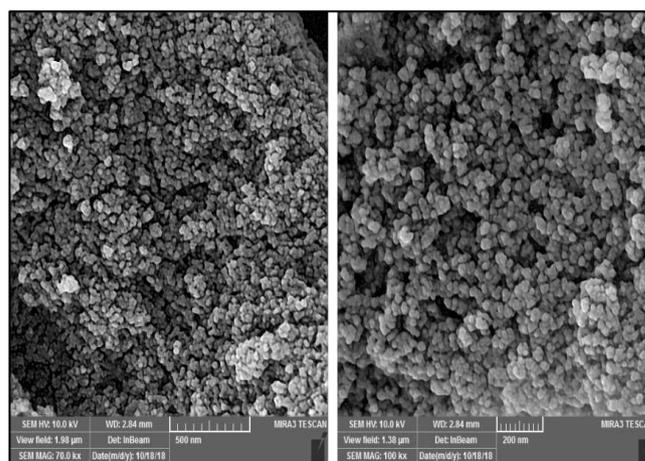

Fig 4: FESEM Images Obtained from Magnetite Nanoparticles

- *Preparation of Silica Coated Iron Nanoparticles (Fe₃O₄@SiO₂)*

Silica coated iron nanoparticles were prepared with a slight change according to the method of Liu et al. [10] In this step, 3 grams of Fe_3O_4 nanoparticles obtained from the previous step were transferred to a double-mouth flask and 80 ml of tetra ethyl ortho silicate (TEOS) solution 10% by volume in deionized water was added to it. Then, 60 ml of glycerol was added to the mixture and the pH of the resulting suspension was adjusted by acetic acid to about 4.5. At the end, the resulting mixture was stirred under reflux at a temperature of 90°C for 2 hours with a magnetic stirrer. At the end, the resulting contents were transferred to a beaker, the sediment was separated by a magnet, and washed with double-distilled water and methanol, respectively. After drying at room temperature, the resulting nanoparticles were identified by FT-IR spectroscopy.

- *Mechanism of Formation and Identification of Silica Coated Magnetic Iron Nanoparticles (Fe₃O₄@SiO₂)*

In order to prevent magnetite nanoparticles from oxidizing, an inert layer of silica is placed between the iron core and the reaction medium. It is possible to perform this operation with the sol-gel technique and by adding the TEOS compound to the solution containing magnetite nanoparticles [11].

Among the effects of silicon coating on magnetite nanoparticles, we can mention protecting them against oxidation, creating a suitable space for modifying the surface of nanoparticles, and also increasing their thermal stability. Another important advantage of this process is the increase in the number of hydroxyl groups on the surface of nanoparticles, which causes better functionalization on the surface of nanoparticles. Also, the silica coating prevents the clumping of nanoparticles and the distribution of particles in the solution environment is better [12].

The mechanism of this process is shown below in Figure 4. First, TEOS molecules are formed in the vicinity of glacial acetic acid and glycerol hydrolysis, followed by hydroxyl groups. Adding glycerol to the solution causes the nanoparticles to be completely separated and the silica coating is done more effectively. The reason for adding acid is to adjust the pH of the solution in order to hydrolyze the OH groups on the surface of nanoparticles and TEOS molecules, and as a result, these molecules are effectively connected to each other. A scheme of silica coating process on magnetite nanoparticles is shown in Figure 5:
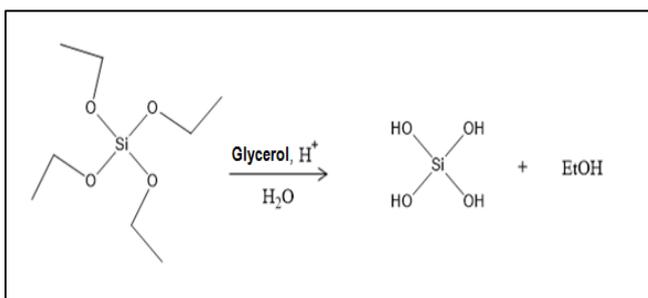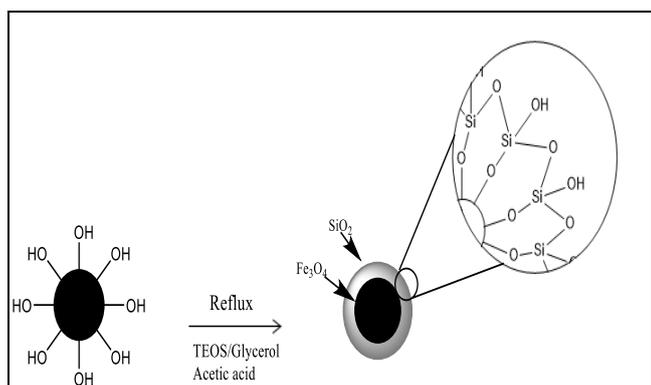

Fig 5: Hydrolysis Mechanism of TEOS Molecules

Fig 6: Schematic of the Silica Coating Process of Magnetite Nanoparticles

➤ *Investigating the Infrared Pattern (FT-IR) Related to $Fe_3O_4@SiO_2$)*

Diagram 4 is the FT-IR spectrum of silica coated magnetite nanoparticles. All bands related to the previous stage are observed in this spectrum. Vibrations related to Fe—O bonds appeared in the range of $Cm^{-1}460$, which overlapped with the bands related to Fe—O—Si bonds located in this range. Therefore, the existence of a silicon network on the surface of nanoparticles is proved by the bands related to the symmetric and asymmetric stretching vibrations of the Si—O—Si bond, which appeared in the range of $Cm^{-1}980$ and $Cm^{-1}1080$, respectively. [13] The broad band appearing in the range of $Cm^{-1}3400$ indicates the presence of OH bonds on the surface of these nanoparticles [14].
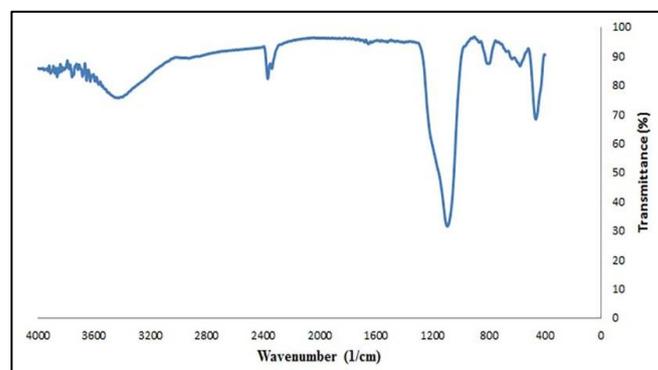

Diagram 4: FT-IR Spectrum of Magnetite Nanoparticles Coated with Silica

IV. CONCLUSIONS

In this research, an attempt has been made to provide a method in which the medicine can be controlled and directed by the magnetic field. The results of examining the FE-SEM images show that the obtained product had a spherical morphology and the particle size distribution was less than 100 nm. The spherical and symmetrical shape of these particles can help them move in the liquid environment. Analysis of the thermal decomposition of the final product also indicates the presence of both organic and mineral substances in the drug part and the magnetic part of the sample.

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