Fabrication of Magnetic Nanocomposites using Natural Polymer Coating to Grain and Ciprofloxacin

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ABSTRACT---- ***In this study, we try to stabilize magnetic nanoparticles (Fe_3O_4) with natural granular polymer (granular mucilage as a natural, biocompatible and biodegradable coating) and then load the drug ciprofloxacin on these nanoparticles. Then, structural, magnetic, physicochemical, colloidal and antibacterial properties of the samples using various characterization tools and tests such as X-ray diffraction (XRD) analysis, transmission electron microscopy (TEM) analysis, FEE-SEM field scanning electron microscopy (SEM) Vibrating Sample Magnetometry (VSM), Infrared Fourier Analysis (FTIR), Optical Spectroscopy (UV-Vis), Dynamic Light Scattering (DLS), Nanoparticle Specific Surface (BET) and Testing The antibacterial property of disk diffusion must be investigated [21]. XRD results as well as structural analysis of the samples confirm the magnetite phase with high purity. The results of FE-SEM and TEM analyzes indicate spherical morphology and very small size of magnetite nanoparticles (average 13 nm). The results of DLS analysis show a hydrodynamic diameter of 81.9 to 119.2 nm for magnetic nanoparticles with different structures. Zeta potential values for magnetic nanoparticles are between -0.28 and -55.2 mV, indicating suitable colloidal stability of the nanoparticles for biological applications. The VSM results indicate the high saturation magnetization of the samples as well as the small amounts of the forcing field and the residual magnetization of the samples, which indicates the superpromagnetic property of the nanoparticles.***

Keywords---- Magnetic nanoparticles; Natural Polymer; Physicochemical; Antibacterial property

1. INTRODUCTION

The first theories and experiments on the use of magnetic nanoparticles in targeted drug delivery applications were presented in the 1960s. Freeman et al. (1960) suggested that magnetic nanoparticles were able to pass through the vascular system and focus on a specific part of the body by applying a magnetic field [1]; However, the first experiments with the use of magnetic microparticles and nanoparticles to deliberately deliver chemotherapeutic agents to target tissue began in the 1970s. In 1978, Wieder et al. Coated a temperature-sensitive targeted drug delivery system by coating magnetite nanoparticles 10 to 20 nanometers in diameter with albumin microspheres and loading the anticancer drug doxorubicin into the albumin matrix to investigate the performance of nanoparticles within They paid. After intravenously injecting the nanoparticles, they were able to concentrate more than 99% of the nanoparticles injected into the capillaries at the target tissue site by applying a magnetic field of 1800 orthostats. Their studies also showed that approximately 50% of the drug attached to the target tissue remained in place for hours after the magnetic field was removed [2].

In another study, Ashjari et al. In 2012 synthesized magnetite nanoparticles by co-precipitation and encapsulated them with cisplatin with a coating of polylactic glycolic acid (PLGA) and the effect of the preparation conditions on size, morphology and They studied the surface properties of PLGA nanocapsules, including drugs and magnetic nanoparticles. In this study, in order to dry the samples, they used two methods of slow drying in environmental conditions and fast drying using pressure reduction. The results of their research showed that the change in morphology as well as the reduction of particle diameter in the drying method in the environment is more obvious than the pressure reduction method. They also observed that the effective drug loading on these nanostructures was significantly related to the drying method of the samples. Also, the DLS results of the samples showed that the hydrodynamic diameter of the nanocapsules is in the range of 142 to 384 nm with zeta potential in the range of -10.5 to 16.5 mv. In this study, it was found that the effective loading of cisplatin in these nanostructures depends on the sample preparation conditions and its value is between 41 to 62% [3].
In 2013, Filipusi et al. Synthesized magnetite magnetic nanoparticles using the co-precipitation method and coated them with polymers synthesized from poly (ethylene glycol) and poly (propylene saxinate) polymer blocks and loaded the anticancer drug taxol on the nucleus of this nano. they paid. The characterization results of the nanoparticles showed that their diameter is about 250 nm and also the drug loading occurred effectively inside the polymer matrix of these core-shell nanostructures. They also investigated drug release from these nanostructures over a period of 15 days and found that the drug release profile was affected by the nature of the hydrophobic part of this polymer matrix [4].

Rasouli et al. In 2018 announced a green, fast and cheap synthesis of magnetite magnetic nanoparticles, during which magnetite nanoparticles were synthesized by coating gold nanoparticles using natural honey and hydrothermally. In this synthesis, natural honey has been used as a reducing and stabilizing agent. They also analyzed and characterized the nanoparticles using different characterization tools. The TEM results showed the formation of the core-shell structure of gold-coated magnetite nanoparticles with very fine sizes in the range of 3.49 to 4.11 nm with a very uniform size distribution. VSM results also indicate a decrease in the magnetic properties of coated nanoparticles compared to uncoated nanoparticles due to the non-magnetic coating of gold and natural honey nanoparticles on magnetite nanoparticles. The researchers also performed a cytotoxicity test (MTT) on magnetite nanoparticles coated with gold nanoparticles. The results of this test indicate the non-toxicity of these nanoparticles and make them suitable for biological applications such as targeted drug delivery [5].

In another study, Free et al. In 2017 synthesized magnetite magnetic nanoparticles by co-precipitation and coated them with natural basil seed polymer (basil seed mucilage) and loaded the antibiotic cephalexin on these nanoparticles to study adsorption. And drug release in vitro. The nanoparticle characterization results also indicate that the synthesized magnetite nanoparticles are superparamagnetic and also have a diameter of 12 nm for uncoated magnetite nanoparticles and 6 nm for magnetite nanoparticles coated with basil seed mucilage. According to these results, it seems that the placement of basil seed mucilage coating on magnetite nanoparticles reduces their size, which is one of the reasons to prevent the agglomeration of magnetic nanoparticles by basil seed mucilage. Also, by examining drug uptake at different PH, it was found that the highest amount of drug uptake occurs at pH = 2.5. In addition, drug release study indicates the existence of two different phases in drug release, so that in the first phase a rapid release occurs with the release of about 52% of the drug loaded in the first 2 hours and in the second phase about 38% of drug release The charge is released from the drug-carrying nanoparticles within 88 hours. The results of antibacterial test also showed that the samples had a good antibacterial effect on four different bacteria and coating the magnetite nanoparticles with basil mucilage not only did not have a negative effect on the antibacterial properties of the samples but also increased the antibacterial properties of the samples [6].

In another 2016 study, Kriminia et al. Loaded the antibiotic ciprofloxacin onto chitosan-coated magnetite nanoparticles. In their research, magnetite nanoparticles were coated with chitosan during synthesis and the method used for synthesis is co-precipitation method. The results of this study showed that the highest drug loading occurs at pH = 5 and the drug loading capacity decreases sharply with increasing the ratio of nanoparticles coated with chitosan to the drug, so that the highest drug uptake occurs in the ratio of 20 to 1 nanocarrier to the drug. And its amount is about 99% and the lowest drug loading rate in the ratio of 5 to 1 nanocarrier to the drug occurs with an effective loading rate of 50%. Also, the study of the relationship between drug uptake and time shows a linear trend, so that the maximum amount of drug is absorbed by the nanoparticles after 48 hours and no significant change is observed after that. The researchers also examined the drug release in vitro using two methods, ultrasonic and non-ultrasonic. The results of their study indicate a stable and gentle release of the drug over a period of 5 days in the second method, and in the other case, the use of low-frequency ultrasonics increased the release rate of the drug in such a way that more than 95% by weight of the drug It is released from nanoparticles in less than 60 minutes [7].

In this study, after synthesizing magnetite magnetic nanoparticles and coating the nanoparticles and loading the drug on them, in order to study the structure and also to obtain information about size, morphology, physicochemical properties, colloidal stability properties, antibacterial properties and also to study the behavior. Magnetic nanoparticles, these nanoparticles were tested using various tests and characterization tools. These include X-ray diffraction (XRD) analysis, transmission electron microscopy (TEM), field emission scanning electron microscopy (FE-SEM), vibrational sample magnetometry (VSM), red Fourier spectroscopy (FOIR) spectroscopy. (UV-Vis), dynamic light scattering technique (DLS) to measure the hydrodynamic diameter and zeta potential of nanoparticles, the specific surface area measurement technique (BET) as well as the antibacterial property test of disk diffusion.

2. ANTIBACTERIAL TEST STEPS

The purpose of this test is to evaluate the antibacterial effect of antimicrobial agents on pathogenic bacteria and also to measure the susceptibility and resistance of pathogenic bacteria to antibacterial agents. In order to evaluate the antibacterial effect of magnetite nanoparticles and also to investigate the effect of coating and loading of ciprofloxacin on the antibacterial property of nanoparticles, antibacterial effect of magnetite nanoparticle samples, mucilage coated with grain mucilage, magnetite coated with mucilage to grain and load Ciprofloxacin, pure ciprofloxacin and pure mucilage were tested using the antibacterial disk diffusion test, which will be described in the following.

Initially, concentrations of 100 ppm were prepared from the tested samples in sterile distilled water and homogenized using a probe ultrasonic device. Then, using a sterile sampler, 3 µl of each of the prepared nanoparticle suspensions was transferred to 6.4 mm diameter disks. In the next step, two species of gram-positive bacteria called Bacillus cereus and

Staphylococcus aureus and two types of gram-negative bacteria named Salmonella typhimurium and Escherichia coli from the suspension of freshly cultured bacteria with a density of 0.5 McFarland, separately using Sterile cotton swabs were cultured on Müller-Hinton agar medium, then the disks containing each of the above samples were transferred to the Müller-Hinton agar medium cultured with each bacterium using sterile pliers. It should be noted that the sterility of the samples and equipment used in all stages of this test is very important. The plates were then placed in an incubator at 24 ° C for 24 hours and removed from the incubator after 24 hours and the diameter of the growth inhibition zone of the samples was measured.

3. MEASURING AND ANALYZING RESULTS

3.1. Synthesis of magnetite magnetic nanoparticles

In this research, magnetic nanoparticles were first synthesized. Since the synthesis of these nanoparticles is the basis of this research and a prerequisite for the next steps of this research, and with the ideology that successful synthesis and production of magnetite nanoparticles with small size and having suitable physicochemical and physiological properties can be the result of other tests. It has a positive effect, so in this work, a lot of study was done to synthesize high quality magnetic nanoparticles and it yielded results that we will refer to in the following sections. In this study, magnetite magnetic nanoparticles were synthesized, with some modifications, similar to the co-precipitation chemical synthesis method proposed by Saxena et al. [8].

In this method, iron (II) and (III) salts with molar ratios of 2: 1 were used. According to this method, 8.1 g of FeCl3.6H2O and 2.3 g of FeCl2.4H2O were dissolved in 100 ml of distilled water. The resulting solution was stirred under a stream of argon gas for 30 minutes using a magnetic stirrer at 80 ° C. Then 75 ml of 0.1 M profit was added to the solution using a syringe at a very gentle injection rate for 30 minutes. As soon as the sodium was added to the iron salt solution, Fe3O4 nanoparticles formed as a black precipitate according to the following reaction [9].

$$Fe^{2+}+2Fe^{3+}+8OH^{-}\rightarrow Fe_3O_4+4H_2O \quad (4)$$

Half an hour after the formation of the black magnetite precipitate, 2.5 g of ascorbic acid was dissolved in 10 ml of distilled water and added to the magnetite nanoparticle solution. Ascorbic acid was used to control the growth process of nanoparticles during the co-precipitation reaction. The synthesized nanoparticles were then rinsed five times with distilled water using a magnet from a magnetic separation solution and dried in an oven at 80 ° C for 6 hours. They were then manually ground using a mortar to obtain a soft black powder of magnetite nanoparticles.

In general, many factors such as PH, temperature, molar ratios of iron salts, stirring speed of solution, use of inert atmosphere, how to add alkalis to solution, reaction time, etc. can affect the size, morphology and other physical and chemical properties of synthesized nanoparticles. Be effective in this way [10-11]. Therefore, it is very difficult to conduct a comprehensive study focusing on all the factors affecting the properties of iron oxide nanoparticles in the co-precipitation method, and in most studies in this field, usually one or two parameters have been considered together. On the other hand, the study of the effect of each parameter alone is not sufficient to determine the optimal conditions for synthesis. However, one of the important and effective parameters of the synthesis results is PH, which by affecting the protonation and deprotonation of hydroxyl groups can play an important role on the electrostatic surface charge of nanoparticles as well as the hydrolysis of Fe^{3+} and Fe^{2+} ions. Contained in iron salts. PH can also have important effects on the size, morphology, magnetic properties and other physical and chemical properties of nanoparticles produced by this method [8, 11, 12]. Various studies show that the optimal PH for the synthesis of magnetite magnetic nanoparticles using the co-precipitation method is in the range of 9.7 to 14 [13, 14-15]. At lower PH, the formation of other iron oxide phases such as α-Fe2O3 and ε-Fe2O3 is evident [16-18].

Iron oxide nanoparticles are very sensitive to oxidation due to their small size and very high specific surface area. Increasing the purity of magnetite nanoparticles is essential. However, in some cases, magnetic nanoparticles can be synthesized by changing the molar ratios of iron salts. However, it should be noted that by using inert atmosphere in the sedimentation process, more control can be had on the size, morphology and magnetic properties of nanoparticles [8, 11].

The molar ratios of iron salts are also one of the important and influential factors on the synthesis result; Specifically, for successful synthesis of magnetite nanoparticles, the ratio of Fe^{2+} to Fe^{3+} ions must be 1: 2, and if this condition is not met, the formation of other phases of iron oxide will occur, and if synthesized in air (no use of inert atmosphere) This ratio needs to be considered 2 to 3 [11].

The mixing speed of the solution is also one of the factors affecting the properties such as the size and size distribution of nanoparticles, so that as the mixing speed of the solution increases, its uniformity and homogeneity will increase and nanoparticles with smaller size and more uniform size distribution will be produced. The optimal agitation speed for producing smaller nanoparticles with uniform size distribution and spherical morphology seems to be 10,000 rpm [10].

3.2. Optimal mucilage extraction (QSM)

Obtaining the hydrocarbon content of plants usually begins with extracting them from plant sources such as plant seeds by immersing them in water or alkaline solutions. The extraction efficiency of polysaccharides from plant sources is affected by various parameters such as extraction temperature, time, ratio of raw material to water, etc. [19].

In this study, in order to extract optimized mucilage, first the granules were cleaned and solid impurities were separated from them, figure (1-a); After weighing, some of the seeds were dispersed in distilled water (weight ratio of distilled water to grains was considered to be 50 to 1) and a container containing distilled water and grains was left on a medium speed steer for 24 hours at room temperature. it placed. Mucilage, as soon as the granules are placed in water, separates from the outer surface of the granules and disperses in the water as a viscous substance, creating a relatively stable suspension of granules, mucilage and water (Figure 1-b). After 24 hours, the mucilage solution was passed through metal nets 60, 120 and 180, respectively, to separate the granules and solid impurities. Figure (1-d) and a clear solution containing pure mucilage and water was obtained; In the next step, the PH of the solution obtained for drying using a freeze-drying device was set to 7 and the mucilage solution was frozen at PH = 7 for drying and extraction of dry mucilage.). Finally, dry mucilage was obtained as a white, light, porous powder (Figure 1); This step of mucilage extraction was performed using an ALPHA 1-2 LD freeze-drying device available in the Biotechnology Research Institute of Isfahan University of Technology.

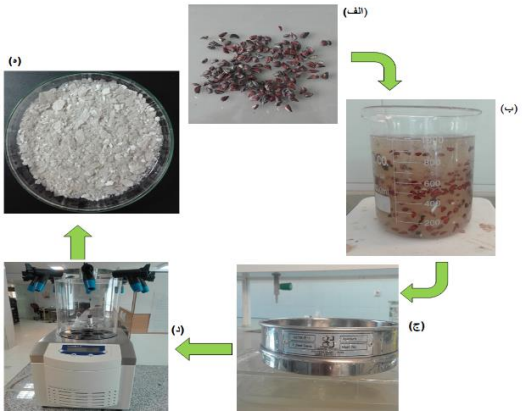

Figure 1. Steps of extracting mucilage to grain

Drying methods are usually divided into two categories: hot methods (for example, the use of an oven) and cold methods such as cold drying method and vacuum or lyophilization. Since the method of drying mucilage can affect its physical, chemical and physiological properties, and due to the many advantages of the method of drying under cold and vacuum compared to other methods, in this study, this method was used to dry mucilage. . Cold and vacuum drying method is a method based on thermodynamic processes during which, by sublimation and phase change of the material, the desired solution extract is extracted as a dry powder.
In this method, the desired solution is first frozen at low temperature. Then, by creating a vacuum, ice is formed, which is the water or solvent used, it is quickly evaporated (sublimated) and using a special refrigerant, it is removed from the device and pure mucilage is extracted as a white, dry, light and porous powder. This method has many advantages compared to the hot method, including reducing the amount of water in the product, preserving the physical and chemical properties of mucilage during the drying process, less impurities in the product, less microbial load of the product, maintaining plant quality, The better solubility of dried mucilage in water, the presence of less ash in the sample, prevention of oxidation or burns and preserving the sugar nature of the materials in the mucilage during the drying process, etc. [20-21]. Of course, some researchers have established new idea and formulation that can be developed for considered subjects [22-27].

3.3. Coating of magnetite nanoparticles with optimal mucilage (Fe_3O_4@QSM)

In order to coat the magnetite nanoparticles, first 100 mg of the magnetite nanoparticles were dispersed in 80 mg of distilled water and placed in a 150 watt proponic ultrasonic for 10 minutes to obtain a homogeneous suspension of the nanoparticles. Then dissolve 20 mg of dry mucilage in 20 ml of acidic solution in volume ratios of 3: 1 from formic acid to acetic acid, and the mucilage solution was added to the suspension of magnetite nanoparticles. The resulting solution was then placed in ultrasonic sonication with a power of 100 watts for ten minutes to disperse the nanoparticles by dispersing the magnetite and polymer nanoparticles and placing the polymer coating on the iron oxide nanoparticles. It should be noted that when coating nanoparticles, the use of high power ultrasonics may destroy the polymer structure and change the mucilage functional groups into granules and iron oxide nanoparticles and have a negative effect on the coating process of iron oxide nanoparticles. The mucilage-coated Fe_3O_4 nanoparticles were then separated using a magnet (Figure 2), and the coated

nanoparticles were washed four times with distilled water to separate the impurities. They were then dried in an oven at 50 ° C for 12 hours. From now on, for the sake of simplicity of writing, we will briefly display nanoparticles coated with grain mucilage as Fe_3O_4@QSM.

Figure 2. Magnetic separation of nanoparticles coated with mucilage into grains

3.4. Obtaining the standard concentration curve of ciprofloxacin

To determine the amount of ciprofloxacin loaded on Fe_3 O_4 nanoparticles, it is necessary to obtain the standard concentration curve of ciprofloxacin. In this process, first standard concentrations of ciprofloxacin (CIP) in distilled water were made and then using spectrophotometry (UV-Vis) the amount of light absorption by the desired solutions was measured with concentrations of 1 to 25 ppm. The results are shown as diagrams in Figure (3).

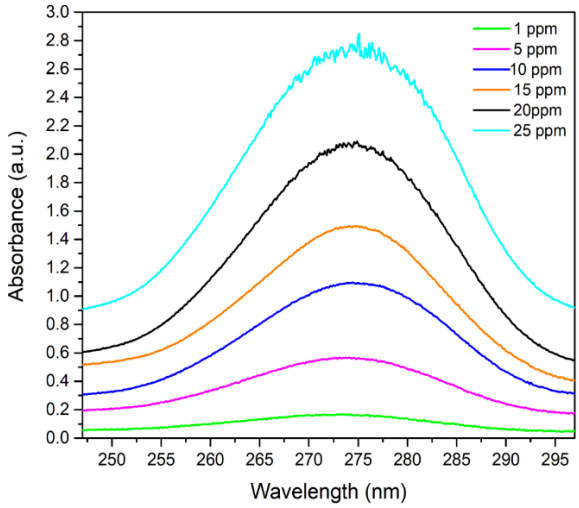

Figure 3. Absorption curves of standard concentrations of ciprofloxacin at different wave lengths

Various studies show that the highest amount of light absorption by ciprofloxacin is in the wavelengths 273 to 277 [88, 104-107]. Measurements performed in this work showed the highest drug absorption at 275 nm, which is consistent with the results of other studies. The results of UV-Vis optical spectroscopy analysis for concentrations up to 25 ppm are shown in Table (1) as follows.

Table 1. Measured absorbance for standard concentrations of ciprofloxacin at 275 nm.

25	20	15	10	5	1	concentrations of (ppm)ciprofloxacin
2/7712	2/0691	1/4951	1/0976	0/5679	0/17062	absorbance

Using the data in Table (1), the standard concentration curve of ciprofloxacin with Equation (2-4) and regression coefficient (R^2=0.9931) was plotted as figure (4). Using this equation, the unknown concentrations of the drug can be determined by placing the absorption values determined by the UV-Vis spectrometer in the equation.

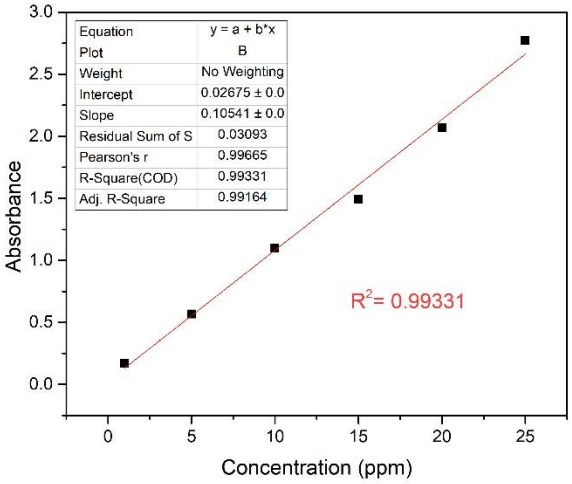

Figure 4. Standard concentration curve of ciprofloxacin

$$Y = 0.10541X(ppm) + 0.02675 \quad (5)$$

In this equation, Y is the amount of adsorption read by the device and X (ppm) is the concentration of the drug not absorbed.

4. CONCLUSIONS

1. The results of PH effect on drug loading show that the highest drug loading on magnetic nanocarriers Fe_3O_4@QSM occurs at PH in the range of 5.5 to 6.5 and the amount of drug loaded is about 85%, which is successful. Indicates the load of the drug on the nanoparticles and the high percentage of drug uptake by these nanoparticles indicates the appropriate potential of the nanocomposites synthesized in this study for targeted drug delivery applications.

2. FESEM and TEM images show that the synthesized magnetite nanoparticles with an average size of 13 nm have a homogeneous distribution and is a confirmation of the nanoparticle structure of the samples synthesized in this research. Considering that the superparamagnetic property for magnetite nanoparticles according to various reports occurs in dimensions less than 25 nm, it can somehow confirm the superparamagnetic property of the samples synthesized in this research; the results of VSM vibration magnetometer analysis also confirm this.

3. VSM vibratory magnetometer analysis showed that by coating magnetite nanoparticles by mucilage and drug loading, the magnetization of nanoparticles was reduced, which could be due to the addition of a non-magnetic substance and the reduction of the magnetic property of nanoparticles on a nanoparticle layer. He pointed to the decrease in bipolar-dipolar interactions and the exchange between them and the increase in the effect of the irregular surface spin layer by reducing the particle size. Also, the shape of the residual loops in the fields close to zero indicates the superparamagnetic properties of the samples and the results show that by coating the nanoparticles with mucilage to the grain and loading the drug on them, the forced field values and magnetism of the retained nanoparticles are reduced. Samples are provided.

4. BET results indicate that the magnetite nanoparticles synthesized in this study have a very high specific surface area that can be due to the very small size of these nanoparticles.

5. DLS results indicate the very suitable hydrodynamic diameter of nanoparticles for biological applications. Also, the results of this analysis show that the hydrodynamic diameter of nanoparticles increases with coating and loading of ciprofloxacin on nanoparticles.

6. The results of zeta potential analysis indicate the colloidal stability of nanoparticles and these results show that coating and loading ciprofloxacin on nanoparticles also reduces their zeta potential values.

7. The results of antibacterial test also indicate the appropriate antibacterial effect of Fe_3O_4@QSM-CIP nanostructures on all four types of bacteria used in this test, which indicates the successful synthesis of these nanoparticles in this study.

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