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RESEARCH PAPER

Magnetic Fe_3O_4@Poly Vinyl Alcohol@Vitamin C Nanocomposite and Its Application in Gradually Drug Release

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ABSTRACT

In recent years, the use of nanoparticles in the field of medicine has attracted many attentions. The surface coating of nanoparticles by biocompatible polymers improves their bioavailability. Due to the compatibility of bio-polymers with the environment and human body, these materials are used as carrier agents. In this research, magnetic nanoparticles were synthesized by microwave and hydrothermal methods. The iron oxide nanoparticles (Fe_3O_4) were coated with polyvinyl alcohol (PVA) to prepare nanocomposite and load the drug (vitamin C) from the mechanical agitator. The nanoparticles crystal structure was studied using X-ray diffraction (XRD). The nanoparticles size was determined by scanning electron microscopy (SEM). Vibrating sample magnetometer (VSM) was used for magnetic analysis, and the purity of the material was determined by applying Fourier transform infrared spectrometer (FT-IR). Evaluation of drug release was investigated by ultra violet-visible (UV-Vis) spectroscopy.

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INTRODUCTION

Application of nanostructures in anticancer therapeutics and drug delivery systems promises an excellent potential to revolutionize the future of treatmant. For bio-medicinal goals, nanoparticles should have mono-disperse distribution with high magnetization values. In the 1970s the introduction of superparamagnetic nanoparticles created a new transport vehicle for the drug delivery, that can be operate with external magnetic field]1-3[.

Between all the achievments, magnetic structures (such as magnetite and maghemite) seem to be appropriate for being a drug targeted carrier, because of their ability of delivering pharmaceuticals to a specific location of body with a gradient magnetic field [4-8]. Superparamagnetic nanoparticles has attracted attention of researchers for two reasons: (i) decrease the drugs dispersion side effects, (ii) reduction of the drug consumption. Due to high magnetic interaction and high surface area the naked magnetites, get agglomerated. In addition, in the biological media, magnetite might show oxidation and make undesired phases. The human body reticuloendothelial system (RES) takes bigger (>300 nm) magnetite nanoparticles more quickly

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than which of the smaller sizes [9-13].

It would be needful to modifying the surface of magnetite nanoparticles or cover them by other biocompatible material to avoid them from aggregation. However, in order to ensure endurance and biocompatibility, as well as special localization at the biological target sites, an optimal surface coating is desired. On the other hand, the nanoparticles are ineffective carriers because of their limitations in drug loading, release rates and retention time in the blood circulation system]14-17[. This problem can be overcome by encapsulating magnetic nanoparticles with biocompatible materials. In order to avoid the aggregation of nanoparticles, some sort of coatings have been applied. When a drug–particle system is concentrated at a desired location, drug release process takes place and the variation of pH value, diffusion, and temperature change, causing of enzymeactivity or physiological feature of cells [18-21]. Meantime, the polymer coated drug can delay the releasing speed, so it is an effective method to target the cancer cells.

iron oxide nanoparticles, with suitable surface modification, are commonly well-tolerated in vivo, and their core–ligand composition can play definite roles in physiological answers. Coating these nanoparticles with dextran, or polyvinyl alcohol (PVA), increase their stability in physiological media, and reduces toxicity, and significantly increases the blood circulation half-life by minimizing the protein absorption on the NP surface [22,23].

PVA is water-soluble synthetic polymer and with abundant hydroxyl groups is noticeable. Other advantages of PVA for coating nanoparticles include aqueous solubility, biodegradability and high chemical resistancy, safety, and stability. Some feasible applications of PVA coated magnetic nanoparticles are: drug delivery, targeting chemotherapy, and magnetic resonance imaging contrast agents. Ascorbic acid is found in fresh fruits and is a famouse water soluble nutrient is the essential of vitamin C. Due to low cost and biological application it is one of the most famouse nutrients. It acts as reducing agent and scavenger of free radicals to prevent the deficiency disease and scurvy. Ascorbic acid with hydroxyl groups can act as a ligand for protection of NPs agglomeration. Because of its fundamental role in the prevention of shortage diseases, for example, scurvy for a long time [24-26]. Vitamin C has attracted considerable attentions for its role in the upgrade of healthy brain aging and potential in cancer treatment.

MATERIALS AND METHODS

Materials and instruments

$Fe(NO_3)_3.9H_2O$, $FeCl_2.4H_2O$, NaOH, deionized water, poly vinyl alcohol (PVA), ascorbic acid (Vitamin C) with molar mass 176 g/mol, were prepared from Sigma-Aldrich or Merck company.

Magnetic properties were investigated using vibrating sample magnetometer (VSM) device at room temperature, (Kavir Company (Iran)) in magnetic field from -10000 to +10000Oe. The Tube anode of XRD device was Cr, Generator tension 40 kV, Generator current 30mA, Wavelength alpha 2.289 Å.

Scanning electron microscopy (SEM) images were used with a voltage of 25kV to generate a magnetic field around the device column (accelerating electrons and increasing their speed and energy). SEM images were obtained using a KYKY instrument model EM-3200. the samples were coated by a very thin layer of Pt (using a BAL-TEC SCD 005 sputter coater) to make the sample surface conducting and prevent charge accumulation, and obtaining a better contrast. For EDS analysis, FE-SEM device specifications: ZEISS Germany SIGMA VP model EDS and Mapping Detector Specifications: Oxford Instrument Company, UK.

FT-IR spectra for samples were recorded on a Jasco-680 (Japan) spectrophotometer and vibration transition frequencies were chosen in the range of 400–4000 cm^{-1}.

UV–vis measurements of the NCs were carried out on a UV–vis/NIR spectrophotometer, JASCO, V-570 with films of the NCs in the spectral wavelength range between 200 and 800 nm.

Synthesis of Fe_3O_4 NPs

Synthesis of Fe_3O_4 NPs by Microwave method

1.2 g of $Fe(NO_3)_3.9H_2O$ with a molecular weight of 404 g/mol were dissolved in 200 ml of deionized water. Then 0.5 g of $FeCl_2.4H_2O$ was added to the solution and wait a little until it has dissolved. In less than 5 minutes, of NaOH solution (1M) was slowly added to the solution until reaching pH to around 10. After that the microwave on the 510 power and 5 minutes, after every 30 seconds, rest 1 minute to the device for up to 5 minutes. The obtained precipitate is then dried to the oven at 60 °C for 24 hours. It is observed that Fe_3O_4 NPs are

attracted to the magnet by bringing the magnet closer to the container.

Synthesis of Fe_3O_4 NPs by chemical precipitation method

Exactly thise stage was done like method in part (2.3.1), but after that addition of NaOH, the temperature is given so much that the temperature is set to 80 °C, and then it will wait for 1 hour to pass. The collected precipitate is then dried to the oven at 60 °C for 24 hours.

Synthesis of Fe_3O_4 NPs by hydrothermal method

Again, similar to the previous mentioned section all the precursors were mixed and then the solution is placed in an autoclave and autoclave is placed in an oven at 170 °C for 5 hours. The manufactured precipitate is then dried to the oven at 60 °C for 24 hours.

Synthesis of Fe_3O_4 NPs by magnetic field method

The precipitate was prepared according to explained method just before precipitation 10 ml of dissolved saffron was added to the solution. Next the solution is placed between two coils (magnet) and In less than 5 minutes, of NaOH solution (1M) was slowly added to the solution until reachingpH to around 10. Using the mechanical stirrer, the solution stirred for 1 hour. This synthesis was done two times under a magnetic field of 200 mT once

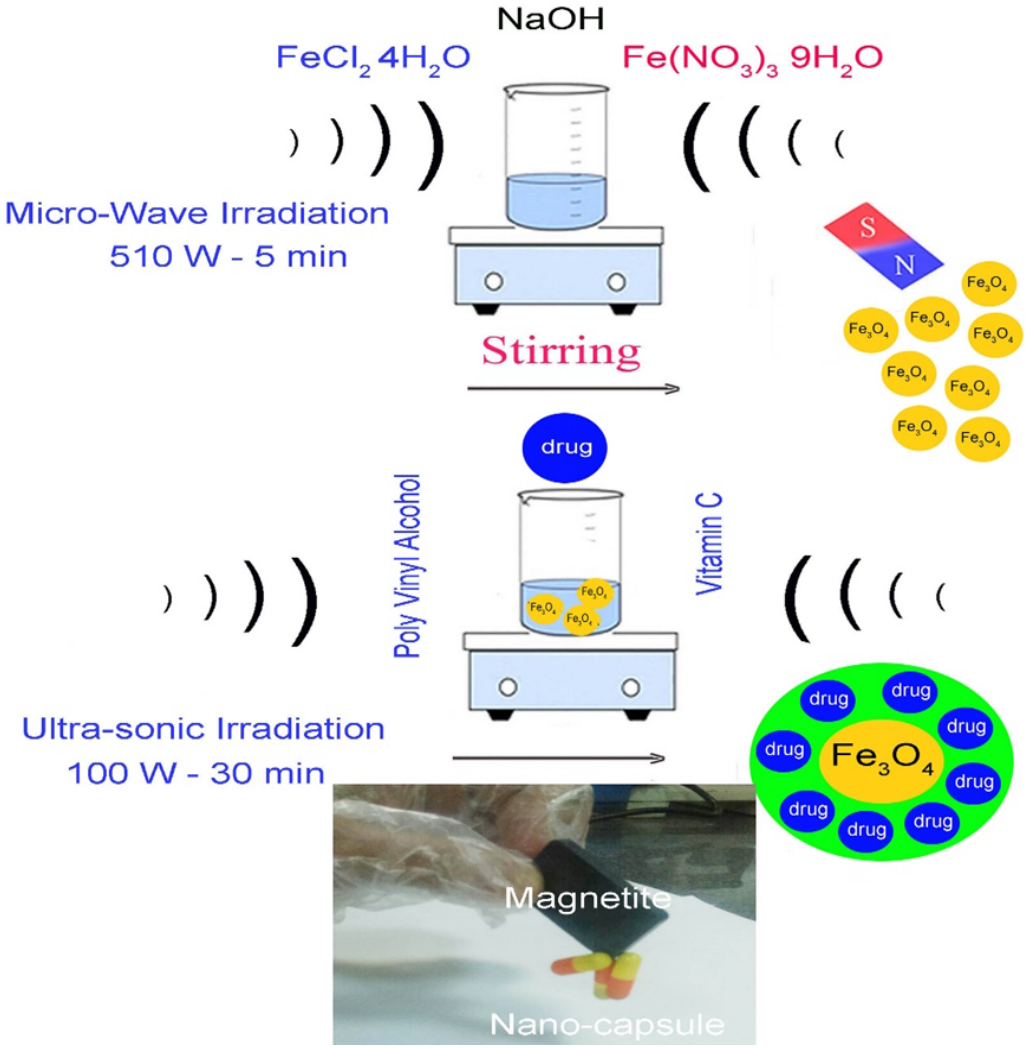

Fig. 1. The schematic of synthesis of core-shell and vitamin C

again under the 400 mT field. The gain precipitate is then dried to the oven at 60 °C for 24 hours.

Coating of Fe_3O_4 NPs with Poly vinyl alcohol (PVA) (Core-shell)

First, 0.2 g of Fe_3O_4 which was synthesized by microwave method, was dissolved in 5 ml of deionized water and then 0.4 g of polyvinyl alcohol in 10 ml of deionized water, Solved with help of microwave. After that, iron ferrite solution was added to the polymer solution and mixed with mechanical stirrer for 8 hours and then it dried to make appropriate analyzes. This part was done in the same way, only by changing the time parameter (2 hours).

Polymeric film making

1g of polyvinyl alcohol was added in 20 cc of water by microwave oven, then the iron oxide nanoparticles described in section (2.3.1) were added to the polyvinyl alcohol solution as much as 0.1 g. The solution was agitated for 3 hours by a mechanical stirrer, then the viscous solution was poured onto a 4 cm (4 cm) area, which was completely dried at room temperature for about 72 hours.

Drug loading

In this section, the iron ferrite synthesized by the microwave method was used wet (wet ferrite has better dispersing spread). 0.2 g of polyvinyl alcohol is dissolved in 10 ml of deionized water. 0.4 g of vitamin C was dissolved in 10 ml of deionized water and was added to the dissolved polymer. Then, 0.2 g of Fe_3O_4 was added and the solution was stirred mechanically for about 8 hours. The solution was then poured in an isinglass container that was open from one side (because the solutionwas not sufficiently dense) and dried at

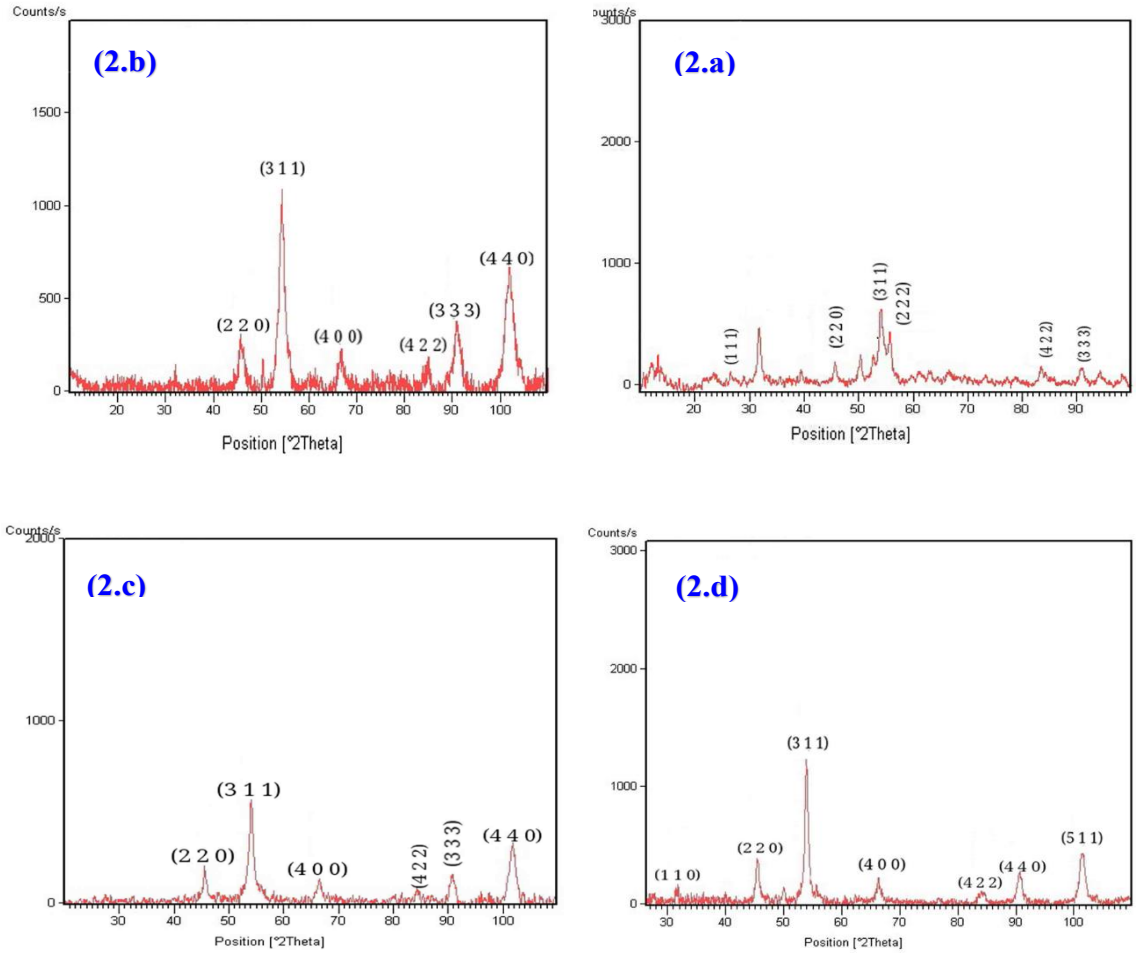

Fig. 2. XRD patterns of the nano-products

about ambient temperature for about 48 hours to analyze it. Fig. 1 illustrate schematic of core-shell and vitamin C.

Release Drug

The solid product obtained at the loading stage of the drug was poured in necessary amount of deionized water, then it was stired with a mechanical stirrer and, at different intervals, the solution was sampled to analyze of gradual release of drug . Once again this was done once with the simulation of the stomach environment (by acidifying the solution with HCl).

RESULTS AND DISCUSSION

X-ray diffraction

The Fe_3O_4 nanoparticles was investigated its crystallinity with X-ray diffraction. Fig. 2.a shows XRD pattern of Fe_3O_4 (synthesized by chemical precipitation method). Peak list table shows

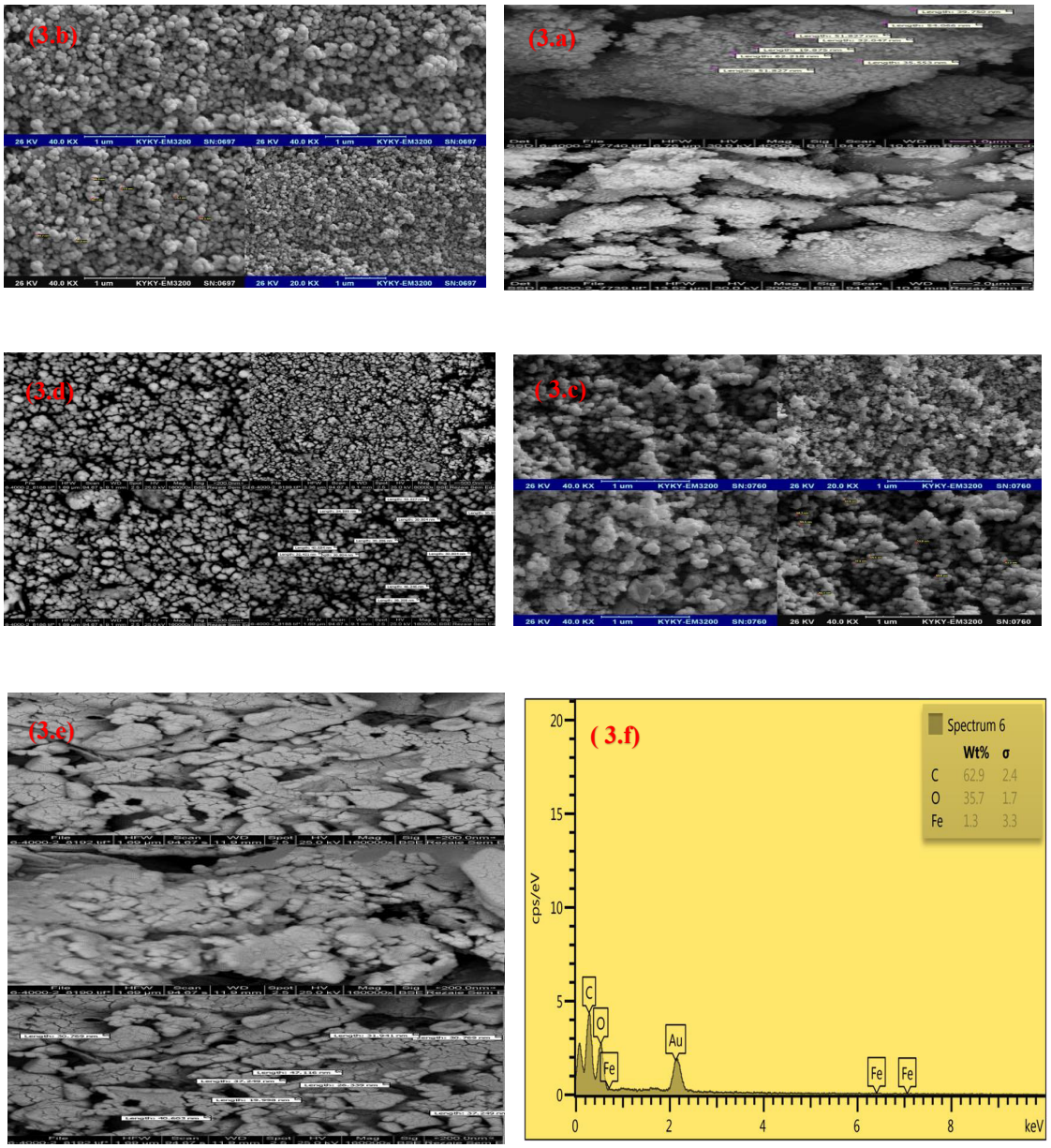

Fig. 3. SEM images of samples prepared by a) Microwave method b) Chemical precipitation method c) Hydrothermal method d) Field method, 200 mT e) Field method, 400 mT and F) EDS spectra of core-shell drug

different phases that indicate that magnetite nanoparticles are not well formed. The sharp peaks observed in the figure represent the fact that the magnetite nanoparticles are well crystallized. The average crystalline size of Fe_3O_4 NPs was calculated using Debye–Scherrer formula ($D = k\lambda/\beta \cos\theta$) as calculated from the three diffraction peaks observed in XRD spectrum, where D is the average crystallite size, k is the Scherrer constant (0.9), λ is the X-ray wavelength of Cr (2.289 Å), β is the line broadening at half the maximum intensity (FWHM) in radians, and θ is the Bragg angle. Also Fig. 2.b illustrates pattern of Fe_3O_4 that prepared by microwave method, it has agreement with standard peak. Fig. 2.c depicts X-ray pattern of Fe_3O_4 that is obtained under magnetic field method. Fig. 2.d shows diffraction pattern of Core-shell structure, the average crystallite size in nanocomposite for three-peak with a maximum intensity is 38nm. The average crystallite size in microwave, precipitation and magnetic field method for 400mT field are ~18nm, ~17nm and

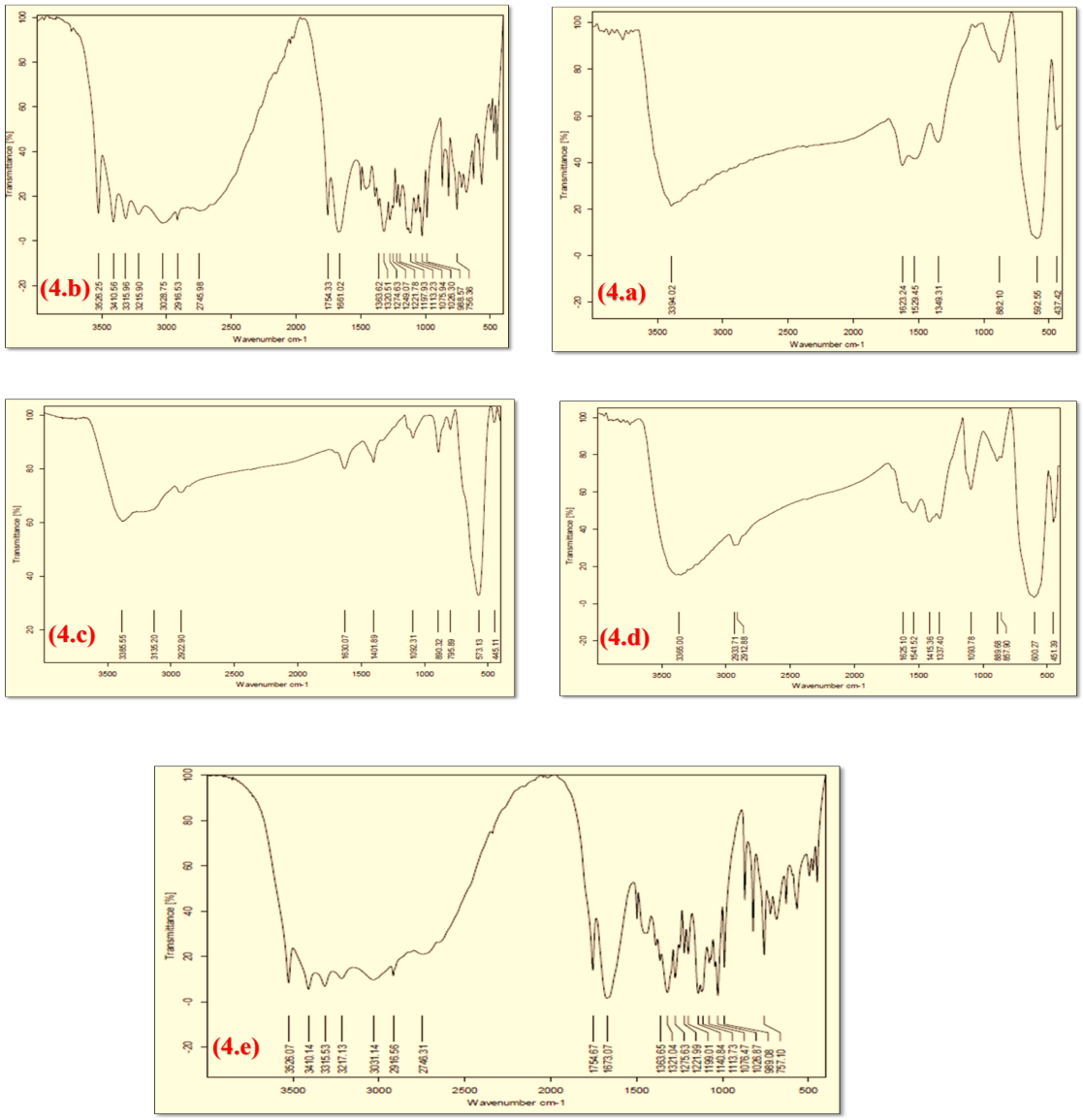

Fig. 4. FT-IR spectra of a) Fe_3O_4 naqnoparticles b) Ascorbic acid (Vitamin c) PVA/ Fe_3O_4 nanocomposites (2 hours) d) PVA/ Fe_3O_4 nanocomposites (8 hours) e) Core-shell drug

~19nm recpectively.

SEM (Scanning electron microscopy)

Scanning electron microscopy was employed for estimation of morphology and particle size of the products. Fig. 3.a shows SEM images of Fe_3O_4 NPs prepared by chemical precipitation method. According to scanning electron microscopy images the average particle size is found to be around 40 nm. The images show that the particles are agglomaration, but this does not mean that the particlesare not nanoparticles, but because of the particle are very small. Fig. 3.b illustrates SEM images of Fe_3O_4 NPs prepared by microwave method. As can be seen in the figure, the average size of nanoparticles is about 80 nm. The nanoparticles are below 100 nm and are spherical and homogeneous. Fig. 3.c depicts the Fe_3O_4 NPs images prepared by the hydrothermal method. Scanning electron microscopy images verify dimensions are less than 53 nm. Fig. 3.d illustrates SEM images of the as-synthesized Fe_3O_4 NPs by the field method. As can be seen in the figure, the average size of nanoparticles is about 35 nm (for 200 mT field). According to the images, the particles are almost uniform in size and the nanoparticles formed are almost single-spray. Fig. 3.e shows the Fe_3O_4 NPs images prepared by the field method (for 400 mT field). The images show that with increasing magnetic field intensity, the agglomeration and linear growth of nanoparticles has increased. The average particle size is about 34 nm. By the EDS analysis, the presence of the desired elements was determined, Fig. 3.f.

FT-IR spectroscopy

Fig. 4.a depicts the FT-IR spectrum of Fe_3O_4 NPs by Microwave method. As seen in the figure, iron ferrite nanoparticles with absorption peaks range from 437 cm^{-1} and 582 cm^{-1} related to the iron-oxygen gravity bonding (metal-oxygen bond) indicate the formation of iron ferrite matter. Extensive absorption peak at the 3394 cm^{-1} wavelength corresponds to the oxygen-hydrogen bond strength of the hydroxyl group. Fig. 4.b illustrates the FT-IR spectrum of Ascorbic acid (vitamin C). In this spectrum, absorption peaks range from 3000 cm^{-1} to 3500 cm^{-1}, indicating

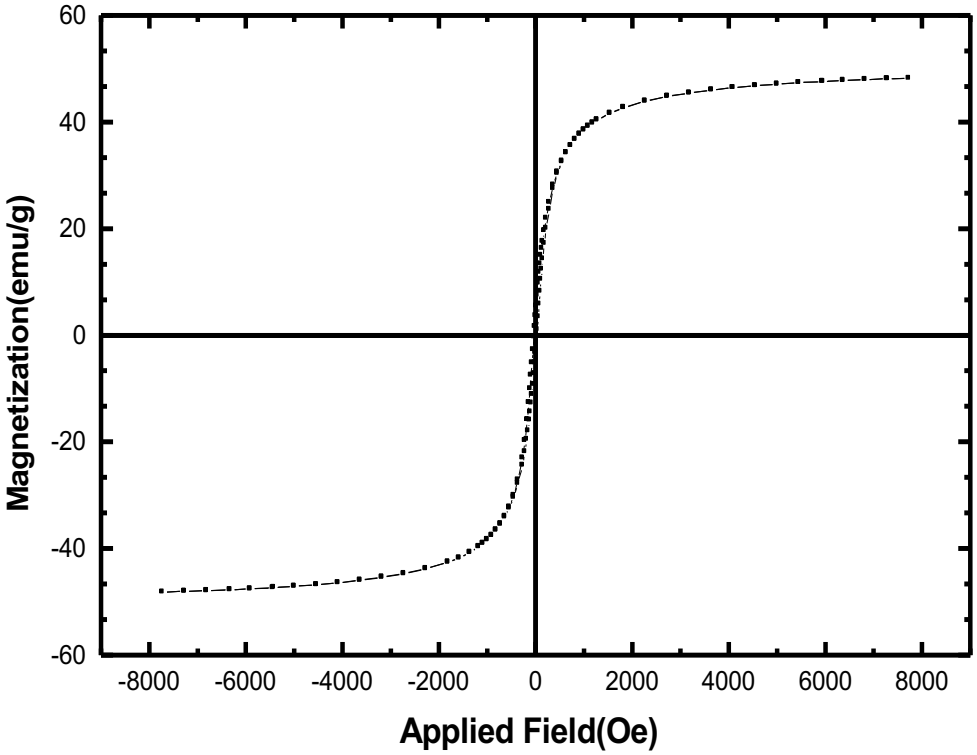

Fig. 5. VSM curve of room- temperature prepared Fe_3O_4 NPs

an O-H bond that usually overlaps with C-H. Absorption in the 1754 cm^{-1} as for the C=O bond and the absorption in the 1661 cm-1 for C = C bond, as well as the absorption peaks in the range of 1000 cm-1 to 1300 cm^{-1}, are related to the C = O bond. Figs. 4.c, 4.d show the FT-IR spectrum of PVA/Fe_3O_4 nanocomposite. As can be seen in the Fig 4.c, peaks of 445cm^{-1} and 573cm^{-1} correspond to the metal-oxygen tensile bond, peak 3385cm^{-1} corresponds to the vibrational O-H bond, peak 2900cm^{-1} indicates a vibrational bond C-H. peak in the range of 1000 to 1100cm^{-1} is related to the C-O tensile bond, and the peak in the range of1500 to 1600cm^{-1} is related to the C=O vibrational dual bond. The bonds found in Fig. 4.d are 451cm^{-1} and 600cm^{-1}, respectively, of the metal-oxygen tensile bond, peak 3365cm^{-1} of the O-H vibrational bond , the peak in the range of 2900 to 2933cm^{-1} represents the C-H vibrational bond, the peak of 1000 to 1100cm^{-1} is related to the C-O tensile bonding, peak of 1500 to 1600cm^{-1} is related to the C=O vibrational dual bond, with comparing Figs. 4c and 4d, the result is that the bonds of PVA/Fe_3O_4 nanocomposite for 8 hours are stronger than of PVA/Fe_3O_4nanocomposite for 2 hours. Fig. 4e shows the FT-IR spectrum of Core-shell-drug. peak in the wavelength range of 400cm^{-1} and 566cm^{-1} is related to the metal-oxygen bond and the bond in the wavelength 1000 to 1100cm^{-1} associated with the C-O single bond, the bond in the wavelength 1455 to 1497cm^{-1} related to the C=O double bond, the peak in the 1673cm^{-1} of the C=C dual bond, the in the 3526cm^{-1} wavelength of the O-H bond, the bond in 3031cm^{-1} it is a C-H bond.

VSM (vibrating sample magnetometer)

Magnetic property of the sample was studied using VSM instrument, and the obtained is shown in Fig. 5. Fig. 5 shows the hysteresis loop of the magnetic nanoparticles synthesized by the microwave. As seen from this curve, this ferrite is a soft ferrite with a saturation magnetization of about 47$emug^{-1}$and remanence magnetization near zero, and a very small coercivity field. Particles have superparamagnetic behavior due to small coercivity field, as can be seen in the figure.

Fig. 6 shows the hysteresis loop of the PVA/Fe_3O_4 nanocomposite. As it seen magnetization has decreased due to the presence of a polymer, but its magnetization has not been eliminated, and it can still be absorbed by the magnet. Saturation magnetization is about 8.5$emug^{-1}$ and remanence magnetization is about 2$emug^{-1}$ and coercivity field is small.

UV–vis spectroscopy

Fig. 7a shows the UV–vis spectrum of the

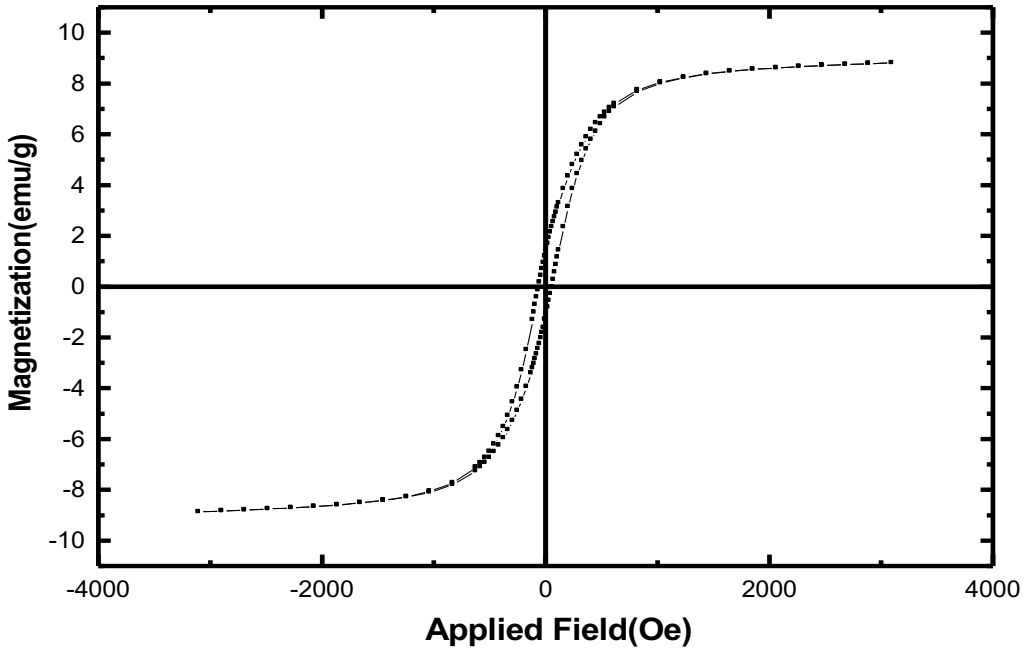

Fig. 6. VSM of PVA/Fe_3O_4 nanocomposite

polymer of polyvinyl alcohol(PVA). In this experiment, 0.003 g of this polymer were dispersed in about 100 mL of water, using a microwave, and a UV-visible spectrum was prepared. As it seen, there is an absorption peak in the wavelength range of 206 nm (ultraviolet). Fig. 7b illustrates the UV–vis spectrum of Ascorbic acid (vitamin C). 0.006 g of vitamin C was dissolved in 100 ml of water. According to Fig. 7, the drug has an absorption peak at 258 nm (ultraviolet) wavelength. Fig. 7c depicts the UV–vis spectrum of Polyvinyl alcohol-vitamin C composition. In this section, 7 ml of the drug solution was added to 7 ml of the polymer solution (with the concentration used for each UV-vis spectrum separately) and then the solution was placed in ultrasonic for one hour, until Well, two solutions are combined together. Fig. 7c clearly shows that the solution has two absorption peaks in the wavelength range of 200 to 350 nm (ultraviolet). Fig. 7d shows the UV–vis spectrum of Fe_3O_4 NPs. As seen in the figure, a little absorption courier is seen at a wavelength of 202 nm. Fig. 7e illustrates the UV–vis spectrum of core-shell-drug. According to the figure, two peaks are found in the wavelength range of 200 to 350 nm. The ultraviolet-visible spectroscopy analysis

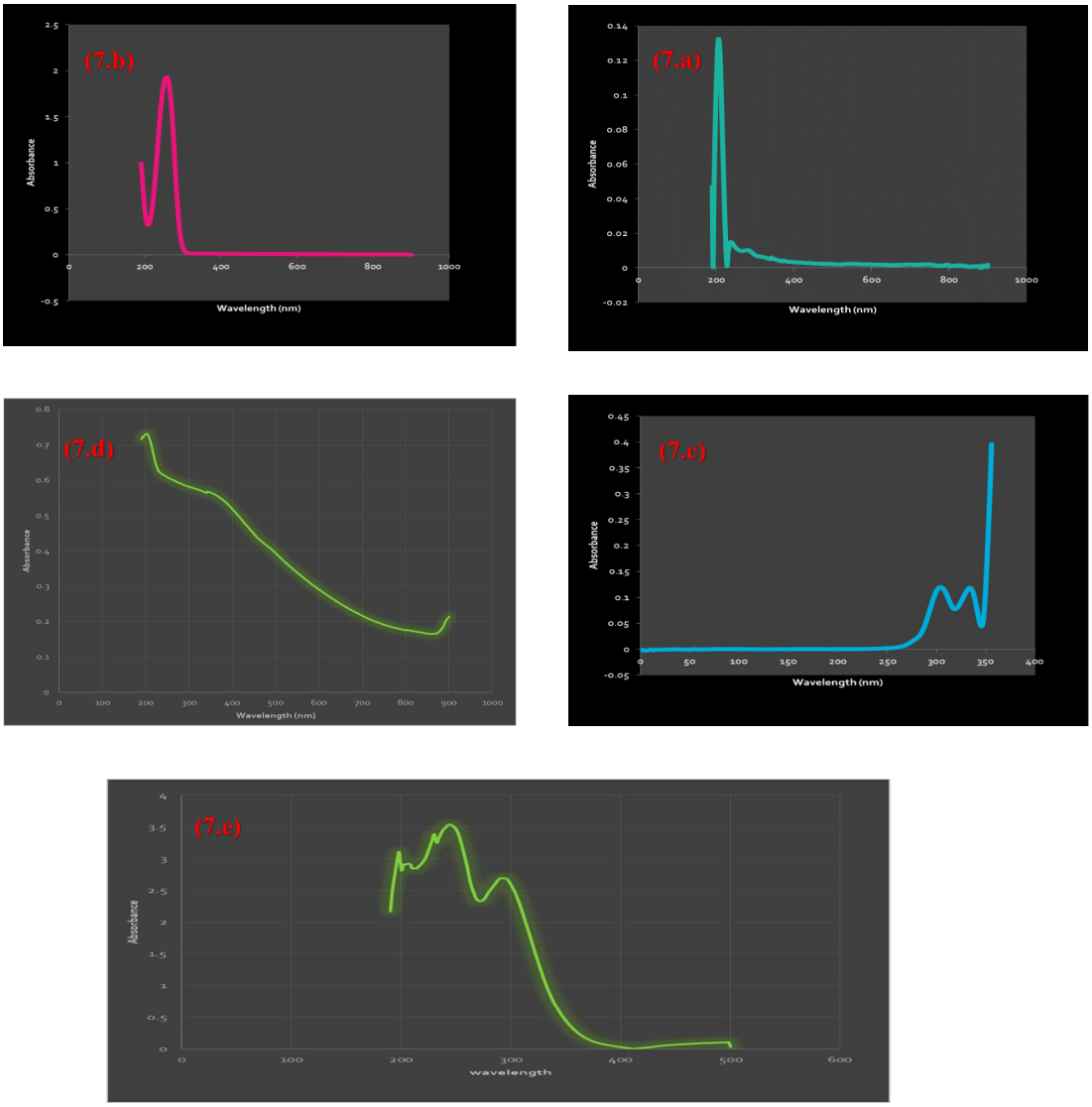

Fig. 7. UV–vis absorption spectra of) PVA b)Ascorbic acid (Vitamin C) c) PVA/Vitamin C composition d) $F_{e3}O_4$ nanoparticles e) Core-shell drug

was performed several times on samples with a different ratio in the amount of core-shell-drug, but the results were not suitable and acceptable. Fig. 8 show the UV–vis spectrum of release drug. Fig (8.a) is related to the experiment used for the amounts used: about 0.2 g of Fe_3O_4 NPs (wet), 0.4 g of PVA and 0.4 g of vitamin C were used. After drying, the weight of the product obtained in this section was 0.132 g, which was poured in 50 ml of deionized water and was stirred by mechanical stirrer. After 0.5 hours, the stirrer was turned off and 5 ml was removed from the solution to be sampled, and subsequent samples were taken after 1, 1.5, 2, 2.5, 3 hours. As shown in Fig. 8a, with increasing time and at different times, the Density in the Peak desired was not "regular". The resulting spectrum indicates that gradual drug release has not been achieved. Fig 8b refers to experiment that used about 0.2 g of Fe_3O_4 NPs (wet), 0.2 g of PVA and 0.4 g of vitamin C. After drying, the product weighed about 0.3g, which was poured into 50 ml of deionized water and was stirred by a mechanical stirrer, the first sample was taken after 1.5 hours, samples Next wastaken after 2, 4, 7 and 10 hours. In this experiment, at each sampling, 1 ml of the solution was removed and 9 ml of distilled water was added to make all the samples dilute to a similar degree. Regarding the shape, absorption peaks in the range of the wavelength range of 200 to 350 nm can be seen, and passing of time, peak intensity increases, indicating increased density and gradual release of the drug. Fig. 8c shows experiment that used about 0.2 g of Fe_3O_4 NPs (wet), 0.1 g of PVA and 0.5 g of vitamin C. After drying, the product weighed at about 0.419 g, which was poured into 60 ml of deionized water and was stirred by a mechanical stirrer, the first sample was taken after 1 hour, followed by samples after 1.5, 2, 2.5 and 3 hours. In this experiment, at each sampling, 1 ml of solution was removed and 9 ml of distilled water was added to make all the samples dilute

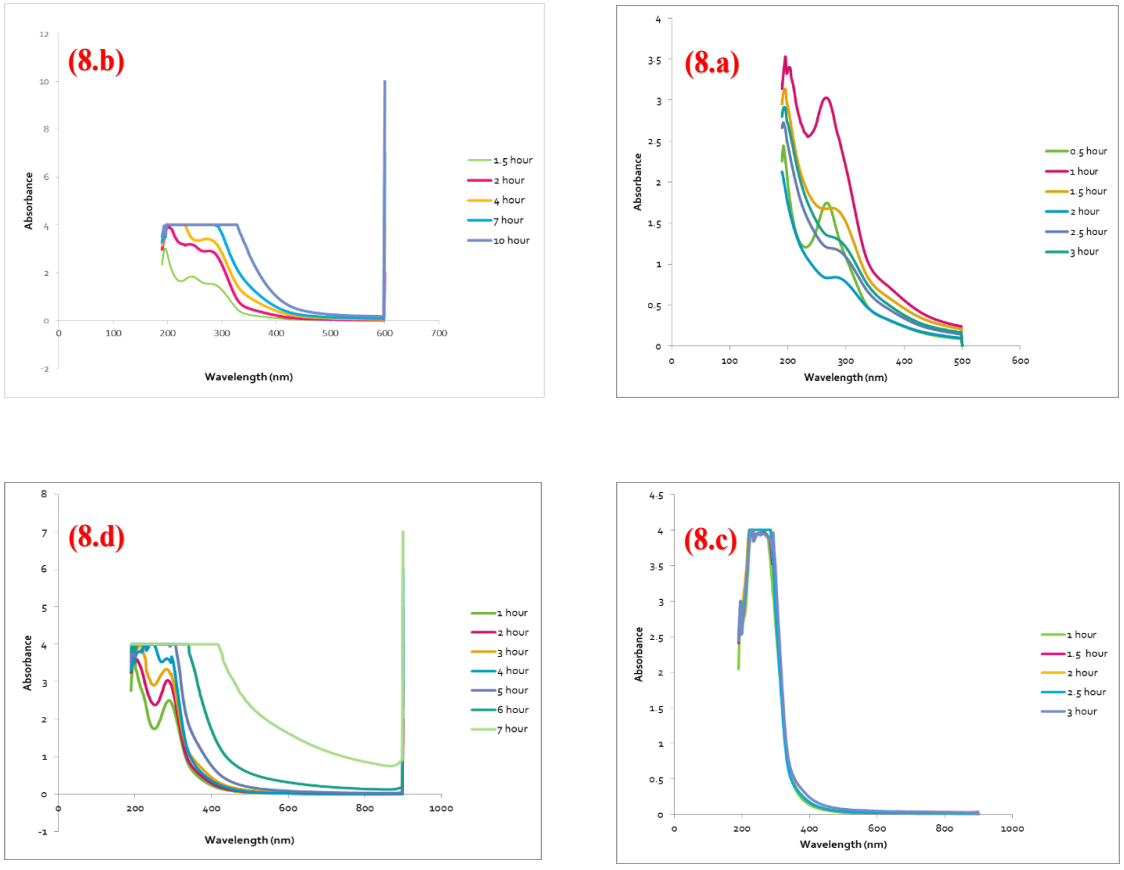

Fig. 8. UV–vis spectra of gradual drug a) Release (1) b) Release (2) c) Release (3) d) Release (4).

to a similar degree. According to the shape, the intensity of the absorption peaks at all hours is the same and the expected peaks in this result are not observed. in the final study, the results of previous trials were considered. In this experiment, about 0.2 g of Fe_3O_4 NPs (wet), 0.2 g of PVA and 0.4 g of vitamin C were used. After drying, the product weight was about 0.223 g. Initially,the amount of 2 drops of HCl was added to 40 ml of deionized water to water to make the acidified (approximately the mount of the pH stomach) and then the combination of core-shell-drug was added and was stirred by mechanical stirrer. The first sample was taken after 1 hour, followed by samples after 2, 3, 4, 5, 6 and 7 hours. In this experiment, at each sampling, 1 ml of the solution was removed and 9 ml of distilled water was added to make all the samples dilute to a similar degree. Fig. 8d shows that the expected absorption peaks (in the range of the wavelength range of 200 to 350 nm) are seen, and peak intensity increases with increasing time. Gradual release of the drug with passing of time is evident. The results of this phase of other stages of drug release are better and accepted.

CONCLUSION

In this study, magnetic nanoparticles were prepared by chemical precipitation, hydrothermal, microwave and under magnetic field methods. The microwave method is a very fast way to make nanoparticles, also in the preparation of polymeric base nanocomposites, core-shell structure, core-shell -drug. The analysis showed that the nanoparticles were spherical and homogeneous and their size were less than 20 nm and due to the Scherrer relationship, the crystallite size in this method was lower than the other methods. By vibrating sample magnetometer, the superparamagnetic behavior of the magnetite nanoparticles was determined and by analyzing the polymer nanocomposite, it was concluded that the magnetization decreased due to the presence of polyvinyl alcohol polymer but its magnetization did not disappear. Finally, ultraviolet-visible spectroscopy was used to evaluate the gradual release of the drug, in an experiment in which the amount of ferrite, polymer and drug was the same and the solution was acidified with HCl, the results of gradual release were successful.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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