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RESEARCH ARTICLE

Anticancer Drug Loading and Releasing Properties of Silica Coated Magnetic Nanoparticles of Controlled Thicknesses

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The stability of magnetite nanoparticles (MNPs) can be improved by coating them with biocompatible, inert and non-toxic materials. These coated nanoparticles have vast applications in drug delivery, magnetic bio-separation, cancer treatment and MRI. In the present study, the magnetite MNPs were prepared by hydrothermal method, while silica coated MNPs of various thicknesses were synthesized by absorption/adsorption method. The sodium silicate was used as a precursor material for silica and its concentration was taken in w/w with respect to MNPs. Silica was selected as a coating material due to its biocompatibility and nontoxicity in nature. The size and shape of magnetite and silica coated magnetite nanoparticles were analyzed by UV-visible spectroscopy, scanning electron microscopy (SEM), energy dispersive X-rays (EDX) spectroscopy, X-rays diffraction (XRD) and dynamic light scattering (DLS). Fourier-transform infrared (FTIR) spectroscopy was used to determine the surface functional groups. Finally, the anticancer curcumin drug loaded on the MNPs, and silica coated magnetite nanoparticles and the drug release was studied by dialysis method. The sustained and burst release of nanoparticles was studied. Silica coated magnetite nanoparticles show sustain release. Among all coatings, 10 times silica coated MNPs show more sustain drug release than others. This work describes the convenient method for drug delivery system.
Keywords: Hydrothermal method, Magnetite nanoparticles, Drug delivery system.

INTRODUCTION

Nanoscience is a branch of science that studies the structures of matter at the nanoscale (ADAMS 2007).According to the National Nanotechnology Initiative (NNI) nanotechnology is defined as the development of research and technology at nano level from 1 to 100 nm range. In the 21st century, Nanotechnology is the most populated area of research for the researchers. This operates the matter on atomic, molecular, and micro molecular level which leads to the structures at nano-meter ranges (1 to 100 nm) (McNeil, S. E., 2005). Nanotechnology is the development and research of different materials, devices and systems that exhibit the property of physical, chemical, and biological fields. Nanotechnology not only could improve existing technologies, but it also improves the efficacy of new applications (Feynman 1992). In the mid-twentieth century, automobiles, airplanes, colored televisions, and computers had an impact by nanotechnology (Gai, Roper et al. 2002) Particles having a small size range from 1 to 100 nanometers in one dimension are called nanoparticles. The nanoparticles (NPs) having small size, surface flexibility, solubility, and multi-functionality due to these nanoparticles (NPs) are widely used class (McNeil 2005)

Functionalized nanoparticles (FNPs) are capable of a very large number of applications in bio-separation, bio-catalysis, and bio-labeling. FNPs have been preferred over other due to high dispersion, reactivity, and easy separation. FNPs increase the properties of nanoparticles through their surface modification including conjugation of chemicals (Herranz, F., et al 2012). Magnetic nanoparticles having great importance around research including magnetic fluids (Chikazumi 1987), catalysis (Ricciardi 2015), biotechnology/biomedicine (Gupta, A. K., 2005), magnetic resonance imaging (Mornet, S., et al 2006), data storage

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Magnetic nanoparticles having great importance around research including magnetic fluid catalysis biotechnology/biomedicine (Gupta, A. K., 2005), magnetic resonance imaging (Mornet, S., et al 2006), data storage (Hyeon, T., 2003), and environmental remediation (Takafuji, M., 2004). Many techniques and methods have been used for the preparation of magnetic nanoparticles of different composition, due to large several applications of magnetic nanoparticles: depending upon the stability and size of nanoparticles. Magnetic nanoparticles having various properties like narrow size, biocompatibility, high magnetic response, super paramagnetic behavior, specific surface modification and chemical stability (Haw, 2010).

Magnetite is the member of iron oxide groups, and it has also been named lodestone, which is one of the best magnetic and naturally occurring mineral (Koziol, K., et al 2010). Its color is dark brown or black and it can attract small iron pieces (Yoo, D., et al 2011). It contains the highest percentage of iron which is 75 % which is greater than other ores. Its chemical name is ferrous oxide and IUPAC name is iron (II, III) oxide. It is prepared by mixing iron (II) chloride and iron (III) chloride by different methods some are expensive and some of them are cheap (Lu, A. H., et al 2007).

There are two synthesis approaches for the preparation of MNPs. Both approaches have their own importance and characteristics. Two classes for the preparation of NPs. 1) Top-down synthesis: here larger molecules decompose to smaller suitable size (Iravani, S., 2011). 2) Bottom down synthesis: here simpler particles are added up and form larger NPs. It is also called building up synthesis (Iravani, S., 2011). Magnetite NPs are mainly prepared by top-down approaches. However, the focus of this article is on the hydrothermal method, which has several advantages over other MNPs preparation methods.

Drug loading ability depends upon the drug solubility in solid state to the matrix. Two techniques for the drug loading, first is absorbing the other is incorporating (Mohanraj, V. J., et al 2006). Different drug delivery methods are given in literature like rotavapor loading, fluid bed loading method, immersion loading method (Limnell, T., et al 2011), and coaxial electrospray. For silica coated MNPs, methods are melting process, solvent immersion, incipient wetness impregnation, loading using SCF technology (Li, Z., et al 2019), incubation method and electroporation etc. (Mehryab, F., et al 2020). Controlled DDS depends upon the size of NPs so that maintain the size to get better results. In which Successful drug release depends upon the drug solubility, surface desorption of drug, diffusion of drug particles on NPs matrix and degradation ability of NPs matrix. Diffusion rate, solubility and degradation of NPs matrix determine the drug release ability. Particles are strongly bonded to the NPs matrix then diffusion rate is larger and sustain drug release. The drug release mainly depends upon the diffusion (Magenheim 1993). Various methods for drug release are side by side diffusion method, dialysis method, reverse reported dialysis method, agitation include by centrifugation and ultrafiltration etc. (Mohanraj, V. J., 2006).

We discussed different methods for preparation of magnetite nanoparticles, also focused on different coating techniques and the best method for coating has also been discussed. Further importance of various techniques will be described for the synthesis of MNPs. Here also discussed the different methods for the drug load and release study. Then we will have an overview of general applications. Finally, we conclude our session with the best strategy from the above synthesis techniques, methods, aims and objective of this study.

Magnetite Nanoparticles (MNPs)

Magnetite is a dark brown mineral that has the strongest magnetism among the other metal oxides (Laurent, S., et al 2008). It has an inverse spinel crystal structure and close packed face centered cubic array crystal structure.

MNPs are ferromagnetic at below temperature of 858 K. MNPs can be prepared by best technique of easiest and less expensive is hydrothermal method. In this method iron salt with ammonia solution and HCl are used. MNPs are nanocrystals ranging from 10 to 100 nm. When these NPs aged for longer time, tend to agglomerate, and oxidize. By this it loses its specific properties. MNPs are highly reactive, they easily react with air. To overcome this problem MNPs are coated with specific material which has high melting point and hydrophobic (M Bulte, J. W., et al 2004).

Various synthesis techniques of MNPs

MNPs can be synthesized by many methods. Every method has its own importance and applications. Some of them are mentioned below.

Sol-gel process

Sol-gel process usually has solid NPs which are dispersed in solution and agglomeration occurs for the three-dimensional liquid phase called gel. Usually, hydrolysis and condensation reactions of alkoxides occur. The metal alkoxides tend to react as alkoxysilanes. Alkoxysilanes like tetramethoxysilane (TMOS) and tetraethoxysilane (TEOS) are commonly used metal alkoxides. Addition of water hydrolyzes the process to the silane solution with acidic, neutral and basic conditions. Sol-gel process does not require special conditions and can be done in a beaker with acidic nature catalyst. Sometimes, for improved quality, also use metalloids (Brinker, C. J., et al 1992). This is a cheap and low temperature process. Ceramics processing uses such techniques and casting materials, or as a means of producing very thin film of oxides of metal for various purposes. Sol-gel derived materials have diverse applications in energy-space, medicine, controlled drug, reactive material separation and chromatography technology (Sciancalepore, C., et al 2015).

Co-precipitation process

Controlled co-precipitation process is used to synthesize many kinds of NPs. This is widely used and easy to handle. In this method two salt species are used. However, the major obstacle is the occurrence of agglomeration of colloidal particles. In this method NPs are formed in the form of precipitates. Here sodium silicate is used to control the pH. By changing the concentration of sodium silicate control the size and diameter. When pH is constant the size of NPs is directly proportional to the alkali concentration (Mukhtar, M., et al 2012). Hence smaller size NPs are got at higher pH and lower alkali concentration. This technique also gets at a small range of temperature from 60 to 90 ^{0}C (Nkurikiyimfura, I. et al., 2020).

Microemulsion process

The microemulsion process involves the thermodynamic dispersion of two immiscible water and oil phases, with surfactant molecules forming a layer at the oil-water interface by dissolving hydrophobic groups in the aqueous form. It may be formed in binary systems of the water/surfactant or oil/surfactant systems. In this process the nano-droplets (ND) water containing reagents have a function of nano-reactor (NR) which allows the mixing to form precipitation reaction and the agglomeration occurs during the synthesis of MNPs (Asab, G., et al 2020). Microemulsion occurs with three different types:

1. Oil in water microemulsion
2. Bi-continuous microemulsion
3. Water in oil microemulsion

Reverse micelle process

In reverse micelle, NPs are synthesized in mild temperature conditions of about 100 ^{0}C. Here surfactant immobilized system is used for the synthesis of very small size about less than 5nm is produced. The prepared MNPs show poor crystallinity due to less temperature (Pileni, M. P., 2003). By this method MNPs are synthesized by the reaction of iron (III) stearate with oleylamine, F127, xylene (reverse micelle reactants) and added DI water and heated less than 90 ^{0}C temperature. Size of MNPs is controlled by controlling the carboxylate ions. This method has many biomedical applications (Jung, E., et al 2019).

γ-ray irradiation process

By using γ-ray irradiation synthesis get ultrafine MNPs than other synthesis. This is a new method for the preparation of MNPs. This process is done at room temperature and encircling pressure, in product no reducing agent. This process involves two steps: (1) preparation of $Fe(OH)_3$ sols (2) γ-irradiation of sols. By adding the ammonia solution to the ferric salt with continuous stirring the sol is produced. This sol has brown, red color. For the hydroxyl radical's isopropanol is added. After that radiated the sol with ^{60}Co γ-ray source and precipitates of MNPs are formed. These are separated and washed with DI water carefully and dried at 60 ^{0}C temperatures (Marić, I., et al 2020).

Solvothermal process

Solvothermal process is a popular process to produce monodispersed and crystalline MNPs. If vary the reaction conditions like time, amount of iron and temperature we can change the shape and structure of MNPs (Qi, M., et al 2016). Sodium acetate trihydrate (NaAc•3H2O) is used as a surfactant to produce MNPs. Here we obtained the particle size from 15 to 190 nm by using SDS (sodium dodecyl sulphate) as a protecting agent. In this method optimum temperature and pressure is mainly used. The maximum amount of MNPs can be obtained by conventional solvothermal process. By this process we obtained stable, monodispersed and control shape MNPs (Sani, S., et al 2021).

Hydrothermal process

It can be defined as a process of synthesis for producing single crystals which depends on the solubility of minerals in hot water at high pressure. The crystal growth is done under an apparatus consisting of steel blanket with pressure vessel called autoclave, in which we have materials along with water. In this process salts of iron are mixed to gather and ammonia solution and HCl also added in these salts. HCl is highly concentrated which prevents it from oxidation. In this article we discussed this process for the preparation of MNPs. This method has many advantages over others like targeted results, homogeneity, controlled crystal size, low agglomeration, virtuous, inexpensive, high limpidness (clearness), high purity, low temperatures (about 180 ^{0}C), simple equipment, good quality of crystals and environment friendly (Dem'yanets, L. N., & Lyutin, V. I., 2008). In this process we get large quality of crystals with controlled composition and specification and highly hydrophilic MNPs are obtained (Yang, X., et al 2012). Figure 4 represents the procedure formation of MNPs.

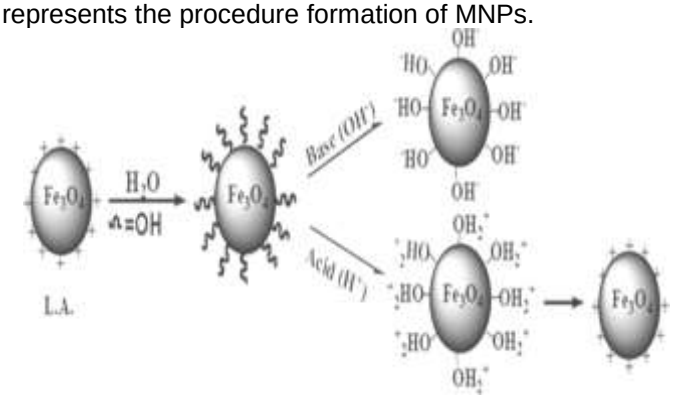


Figure 1: Procedure of MNPs reacted with acid or base (Yang, X., et al 2012).

Coating techniques

Different coating techniques are present in literature. Every technique has its own properties and applications. Different materials are used to coat the MNPs to prevent the MNPs from agglomeration and oxidation. Some of them are given.

Chemical Coating Method

In this method interaction of the coating material with the MNPs is done by adsorption method where chemical reaction takes place. Here some coupling agents are used and about 92 % moisture of MNPs is removed. By this method small coating, strong binding force and thin layer of coating material is formed which reduce moisture maximum. But in this method coating materials mass ratio cannot be determined and coupling agent have low molecular weight. This is a time taking process (Wen, Y., 2003).

Encapsulation Methods

Micro-Arc Oxidation (MAO) Coating

This is a flexible process of coating. In this method to generate the micro-arc used anode and cathode with huge voltage difference. When arc hits the NPs, it melts some portion of NPs depending on the strength of arc. Simultaneously pressure emit from the plasma channels and coating material start deposit on the surface of NPs. Its advantage over other is high flexibility between the NPs and coating material, give porous structure, high hardness, and corrosion resistance. In this coating technique mainly Al, Mg, Ti and their alloys are mostly used (Nie, X., et al 2000). But this method is not used for valve metals like Al, Mg, Ti, Zr, Nb, and Ta (Pan, Y. K., et al 2014).

Electrodeposition Coating

In this type of coating, metallic ions are deposited on the surface of NPs. In this process anode and cathode having different potential difference and ions are transfer on the surface of NPs. Electrodeposition coating has vast area, and many metals coating is done by this type. This method improves the corrosion properties of the NPs that serve as the substrate. This coating type has two categories 1) electrolytic deposition (ELD) 2) electrophoretic deposition (EPD). By these methods uniform thicknesses of coating was done on the substrate NPs. In ELD ions are used and deposited on the surface with medium surface charge and EPD solid materials are deposited on the surface of NPs with high surface charge (Fashu, S., et al 2018).

Drug delivery system

Target drug delivery is done by using proper size NPs and fine coating done on them. Two methods are used for DDS; one is conventional which is not used because it has many disadvantages like unsustainable and nonspecific bio-distribution. Another is targeted method where we study sustained drug load and release. Different methods for drug loading and release are discussed below.

Drug loading methods

Melt process.

In this process heated the mesoporous system above the melting point of drug. Using this process mainly thermal stability and viscosity of drug is studied. In this process the temperature of the system is mainly 5 to 10 ^{0}C of drug. In this method coating is disturbed due to this problem this process is not commonly used (Li, Z., et al 2019).

Solvent immersion

In this method adsorption of drug is usually studied by using centrifugation. By this also recovered the drug loaded particles by filtration. This method is used for both types of hydrophobic or hydrophilic drug. In hydrophilic

type drug is added into PBS (phosphate buffer saline) and then NPs are added (Xie, X., et al 2016). By this process the drug is loaded. If large concentration of drug added then the pores of NPs adsorb drug particles and pores are blocked, in this way surface area decrease. This method is least applicable due to its limitations (McCarthy, C. A., et al 2016).

Loading using SCF technology.

In this method supercritical CO_2 ($SCCO_2$) is used to load the drug into the coated NPs. Drug is dissolved into supercritical CO_2. $SCCO_2$ is a superior solvent, inflammable, demonstrates solubility, nontoxic, and demonstrates solubility easily available and its critical temperature (31 °C) and pressure (7.38 MPa) is easily attainable. In this solvent system, drug is loaded without using any other solvent as a co-solvent. SCF technology is a non-residual solvent technique (Bouledjouidja, A., et al 2016).

Absorption/Adsorption method

This method applied after the formation of MNPs. In this method concentrated solution of drug is used and drug absorption /adsorption ability depends upon the drug solubility (Singh, R., 2009). In this method if the drug is polar, it favors the hydrophilic MNPs and if it reverses hydrophobic for polar drug particle is not facilitated. Production performance is determined by the following formula given in equation 1 (Zamani, M., et al 2013).

$$PP= \frac{\text{curcumin}-\text{Loaded NPs obtained (mg)}}{\text{Sum of all the material used in the elaboration of NPs (mg)}}\times 100 \quad (1)$$

The encapsulation efficiency (E.E) can be calculated by the following formula given in equation 2.

$$\%\ E.E= Q_{curcumin}/\ Q_{total}\ \times 100 \quad (2)$$

Where $Q_{curcumin}$ is the encapsulated quantity of drug and Q_{total} is the total quantity of drug which is used. The absorption/adsorption method is very simple, adoptive and effective method (Waseem, M., et al 2019). In this method a substantial quantity of drug is loaded on the MNPs. In this technique, no expensive instruments are used.

Drug release methods

Some important drug release methods are given which are commercially preferable over others simple methods.

Side by side diffusion method

In this method two chambers of equal volume are used one is donor and other is receiver which are separated by semi permeable membrane. In donor chamber, micron-sized emulsions while in receiver chamber, continuous phase are placed. The drug is analyzed in the receiver chamber. Surface area of membrane is smaller than the donor compartment and restricted the transport of free drug solution into the receiver chamber. The rate of drug released is measured by the following formula given in equation 3.

$$K= AD/h \quad (3)$$

In this equation the K is release rate constant, A is the membrane surface area, D is coefficient of diffusion and h is the thickness of membrane (Chidambaram, N., et al 1999).

Reverse dialysis method

In this method dialysis bag has two portions i.e., one is receiver which has continuous phase suspended in flask and second is the donor phase having dilute emulsion. This system is done by continuously stirring. This method is used to overcome the problem of side-by-side diffusion method. In reverse dialysis method small amount solution is used and having large surface area. In this method also control the sink violation conditions and stabilize the emulsion during separation of drug from the NPs. This method is mainly used because it is less step method and gives increased efficiency than other methods (Chidambaram, N., et al 1999).

Dialysis method for drug release

The dialysis method is commonly used for the study of kinetics of drug release. This method has advantages over others because in this method the drug release from NPs was monitored at various time intervals. The other methods have problem like equilibrium disturbance and incomplete drug release. By dialysis sustains drug release which having advantages like reduces the intake ability, reduction of the side effect and uniform release of drug ultimately (Modi, S., et al 2013). In this method the coated NPs are put into the sealed dialysis bag and placed into a beaker which contains buffer solution. Into the outer sink of dialysis bag the diffusion rate of drug increases by agitation of content present in the beaker. The dialysis method is in vitro method and here small sized NPs are preferred. It is an easy method, less step mechanism and physical separation of NPs done (D'Souza, S. S., et al 2006).

MATERIALS AND METHODS

Chemical Utilized

All the chemicals used in this study were of analytical grade. Deionized (DI) water was obtained from the Nano lab of COMSATS University Islamabad. Iron (II) chloride (FeCl2. 4H2O) and Iron (III) chloride (FeCl3. 6H2O), Sodium Silicate (Na2SiO3) solution, ammonia (NH3) solution and HCl were obtained from Sigma Aldrich. All the glassware was washed three times with aqua regia and DI water before use.

Magnetite nanoparticles (MNPs) synthesis

MNPs were synthesized by hydrothermal method. FeCl2.4H2O and FeCl3.6H2O were prepared in 1:2 molar

ratios in 119.05 mL of DI water and stirred for 15 minutes at room temperature. To this mixture, 10.95 mL of HCl was added and stirred for 5 minutes. Then 20 mL of NH3 solution was added into it and stirred for a further 5 minutes. The prepared solution was black in color. This solution was then transferred to Teflon coated autoclave and kept it into the oven at 180 0C for two hours. Afterward, the contents were transferred to beaker and washed three times with DI water properly. Finally, the solution was put it into petri dishes and dried overnight at 110 0C temperature. Then the weight of the MNPs thus obtained was about 0.14 g. A complete synthesis setup is shown in figure 5.

Figure 2: Preparation of MNPs hydrothermal setup and dried sample obtained at 110 ^{0}C.

Various thicknesses coating of silica on MNPs

To avoid the loss of the magnetic properties, MNPs were coated two times, five times and ten times by taking sodium silicate (Na_2SiO_3) 1.32, 3.33- and 6.66-mM ratios respectively. The pre calculated amount of Na_2SiO_3 was added in 100 mL of DI water already having 0.015 g of MNPs which was stirred for 20 minutes vigorously at room temperature. After this 20 mL of NH_3 solution was added into it drop wise and carefully and stirred for further 10 minutes. Then 10 mL of 0.1 M solution of HCl was added drop wise and stirred it further for 10 minutes. At last, 20 mL of NH_3 solution was added in a drop wise manner. After that, the solution was poured into Petri dishes and dried in oven overnight at 110 °C. Similar procedure was adopted for all coating systems. After drying, the weight of the coated material thus obtained was 0.024 g, 0.072 g and 0.132 g for 2-, 5- and 10-times silica coated MNPs respectively.

Characterization Techniques

We have examined the particle behavior, surface morphology, internal structure, and a variety of other characteristics by using characterization techniques. Here, in UV-Vis spectroscopy, XRD, Zetasizer, FTIR, SEM, EDX and vibrating-sample magnetometer (VSM) were used as characterization tools.

UV-Vis spectroscopy

UV-Vis is used as a non-invasive method to study the materials' properties. It is used to identify and analyze the materials which are prepared in the laboratory. Here mainly study the interactions of electromagnetic radiation with matter. Here two regions first are ultraviolet which ranges from 10-380 nm wavelengths and other is visible region which ranges from 380-750 nm wavelengths. Its main function is to excite the outermost electrons of an atom. This technique performed reflectance, photoluminescence, and transmittance. In this technique study the different electronic transitions and absorption bands. Two types of orbitals are formed bonding molecular orbital (BMO) and antibonding molecular orbital (AMBO). Bonding molecular orbitals (BMO) are σ and π and antibonding molecular orbitals (AMBO) σ* and π* is given in equation 5.

$$\Delta E = E_2 - E_1 = h\ v \rightarrow h\ v = hc\bar{\nu} = hc/\lambda \quad (5)$$

ΔE is difference between two energies, E_2 is final energy, E_1 is the initial energy, h is Planck's constant its value is 6.62×10^{-34} Js, c is speed of light its value is 3×10^8 ms^{-1}, v is frequency, $\bar{\nu}$ is wave number and λ is wavelength (Picollo, M., et al 2019).

X-ray diffraction (XRD)

Through X-ray diffraction (XRD) identify the crystalline and amorphous phases. Crystalline phase shows characteristic peaks with different intensity levels according to material whereas amorphous phase does not give any peak only give noise in results (Epp, J., 2016). By using XRD explore the structure of crystalline materials. The diffraction occurs when X-rays strike a crystalline substance. The direction and intensity of the diffracted beams depends upon the orientation of the crystal lattice with respect to the incident beam (Jenila, P. A., et al 2011).Fourier Transform Infrared (FTIR)

FTIR is a powerful instrument for the identification of functional groups and chemical bonds between the materials which are examined. FTIR is used to describe both quantitative and qualitative analysis. FTIR ranges

from 400-4000 cm^{-1}. The fingerprint region of FTIR is from 400 to 1500 cm^{-1}. This technique is mainly used for quality assurance. FTIR mainly used absorption, emission and Raman scattering of gases, solids, and liquids (Sindhu, R., et al 2015).

Scanning Electron Microscope (SEM)

To find out sample's morphology and topographic information, SEM is used to scan by focusing electron beam. Therefore, the physical features of a particle size and shape can be monitored by using this technique. The working principle of SEM is to focus beam of electron on sample/specimen and display on screen after raster scan to produce different signals that contain information about surface topology and composition of particles.

Energy Dispersive X-rays (EDX)

It is a parallel technique coupled with SEM and is useful to determine the elemental composition of sample under study. Every element has a different atomic structure which allows a specific set of peaks upon falling of electromagnetic emission spectrum. Usually, the graph we will obtain will be discrete energy versus intensities coordinates. For characteristic X-rays from a sample, a high energy beam of X-rays is focused onto the sample at rest or ground state for creating discrete energy levels in a nucleus. The difference in energy between the higher to lower shell occurs in the form of X-ray. **Zetasizer**

Zetasizer is used to measure the particles size in a dispersed system. Diameter is measured from nanometer to several micrometers. Its measuring range is from 0.3 nm to 10 µm. In Zetasizer uses the technique of Dynamic Light Scattering (DLS).The particle size distribution of MNPs and silica coated MNPs is measured by Zetasizer Nano ZS Malvern (UK). The solid MNPs are dispersed in 50 mL of DI water and sonicated for 30 minutes. After that, a small amount of suspension was taken in the cell and analyzed for the size distribution. Here also analyze the charge and mobility of particles. It is widely applicable and independent of materials. It has several applications in research and industries like industrial minerals, pharmaceuticals, microemulsions, polymers, colloids, and many others.

Drug load and release study

The encapsulation efficiency of curcumin drug was calculated using a UV-visible spectrometer at 420 nm after it was loaded on silica coated MNPs and naked MNPs using the adsorption/absorption method. In this method, 1 μgmL^{-1} solution of curcumin was prepared in ethanol solvent. After this, magnetite nanoparticles 0.10 g was added into it. Then MNPs along with the drug solution were mechanically stirred for 30 min. After that, the nanoparticles separated, and concentration of curcumin drug was measured in the filtrate comparing it with the calibration curve. The following equation (6) was used to calculate the percent encapsulation efficiency of drug.

$$E = Q_{Curcumin} / Q_{total} \times 100 \quad (6)$$

Encapsulation efficiency is denoted by E, encapsulated drug quantity is denoted by $Q_{Curcumin}$ and drug's total quantity is represented by Q_{total}.

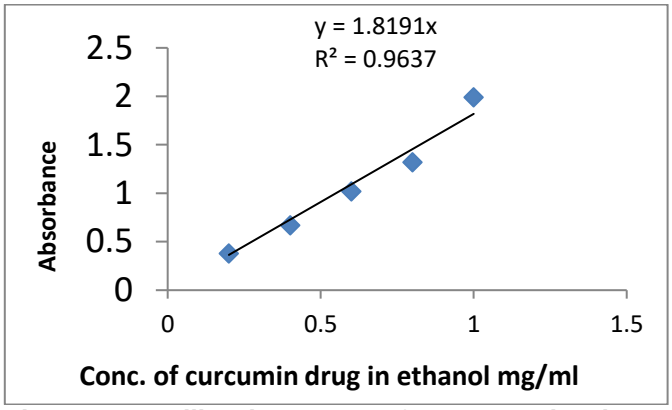


Figure 3: Calibration curve for curcumin drug in ethanol

Release study of curcumin was done by dialysis method. It is carried out at room temperature under dark conditions. In this method, dialysis tubes were filled with donor solution and dialyzed against 40 mL of buffer solution with pH of 7.4 which is the pH of blood as a receiver solution. The release of curcumin drug from the donor solution was measured at regular intervals of time by taking 2 mL from the receiver solution. By using UV-Visible spectrophotometer model Perkin Elmer UV/Vis Lambda 25 was used to record the absorbance (Waseem, M., et al 2019). Following figure 7 shows the different concentration solutions of curcumin drug, dialysis tubing system and dried MNPs and SMNPs.

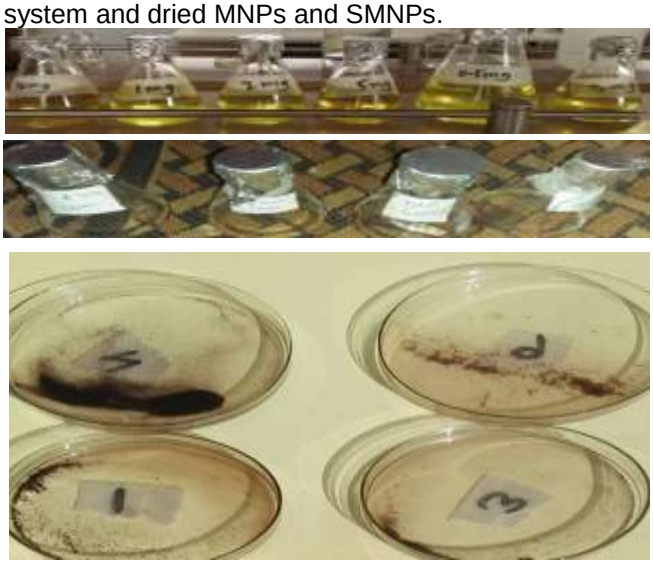


Figure 7: Various concentration of curcumin, dialysis tubing system and dried MNPs and silica coated MNPs

RESULTS

After successful synthesis, the magnetite nanoparticles were found to attract with the magnetic given in figure 8. Afterward, we have analyzed MNPs before and after silica coating by various analytical techniques such as UV-Vis spectroscopy, X-ray diffraction (XRD), Zetasizer, Fourier Transform Infrared (FTIR), Scanning Electron Microscope (SEM) and Energy Dispersive X-rays (EDX).

Figure 8: Attracted with magnet and without attracted MNPs.

UV-Vis spectroscopy

Prepared MNPs were sonicated with DI water for 30 minutes. MNPs were dispersed in the water and used the DI water as a reference in UV-Vis spectrometer. The absorbance of absorption spectrum peak was fall at the visible range (Chaki, S. H., et al 2015). The maximum absorbance at 300 nm was reported for the MNPs under investigation (Zheng, J., et al 2013) Shown in figure 9 (A). Using the tau plot the band gap of MNPs was calculated 2.8 eV given in figure 9 (B) Band gap energy (Eg) was calculated by using the following formula which is given in equation 7.

$$Eg = 1240/\lambda \quad (7)$$

Where Eg is band gap energy in electron volt and wavelength correspond to absorption.

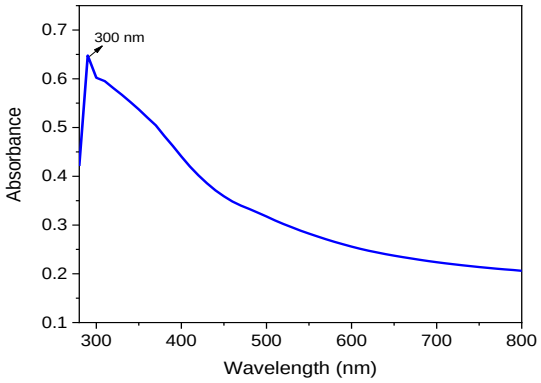


Figure 9: (A) UV-Vis spectra of MNPs

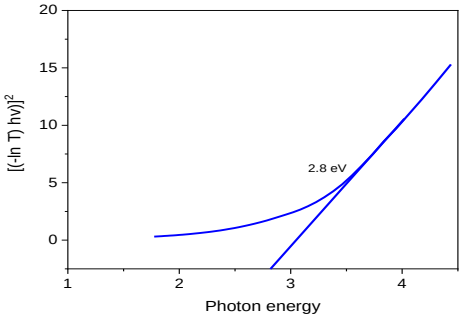


Figure 9: (B) Band gap of MNPs

X-ray diffraction (XRD)

To check the purity, XRD was applied. For MNPs the diffraction peaks were obtained at 30^0, 35.6^0, 43^0, 53.9^0, 57^0 and 62.8^0 which are given in the following figure 10 (A). These diffractions peaks are indexed to hkl plane (220), (311), (400), (422), (511) and (440). The diffraction peaks are like those reported by Loh, K. S., et al while working on, use of Fe_3O_4 nanoparticles for enhancement of biosensor response to the herbicide 2, 4-dichlorophenoxyacetic acid.

These values showed that the structure of MNPs is face centered cubic (FCC). The crystallite size of MNPs was calculated from the most intense peak (311) by using Debye-Scherrer formula which is given in equation 8. The broad nature of peak shows small size of MNPs. The crystallite size of MNPs was 15 nm, which is like those reported by Lobato., et al while working on solvent extraction using magnetic nanoparticles functioning with oleic acid (Lobato, N. C. C., et al 2017).

$$D = k\lambda/B\cos\theta \quad (8)$$

Where D is crystallite size in nm, λ is wavelength θ is Bragg angle, B is line broadening and k is shape factor which is 0.9 for face center cubic (FCC). Lattice constant (a) of MNPs were calculated by using the formula given in equation 9. By applying this formula, the value of lattice constant is approximately 0.84 nm.

$$A = d\sqrt{h^2+k^2+L^2} \quad (9)$$

Figure 10 (B), (C) and (D) represent the diffraction pattern displayed by the MNPs with 2-, 5- and 10-time silica coating. It has been observed that all the characteristics diffraction peaks associated with magnetite were disappeared due to presence of amorphous silica around the MNPs.

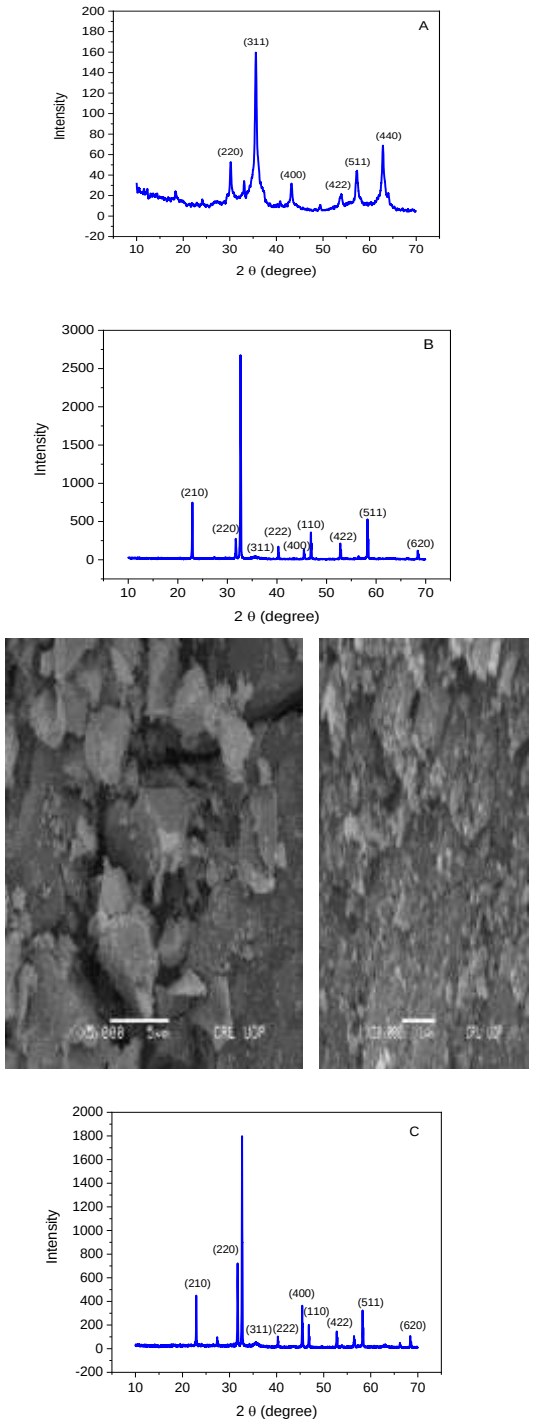


Figure 10: (A) XRD pattern for magnetite (Fe_3O_4) sample (B) XRD pattern for 2 times SiO_2 @ Fe_3O_4 (C) XRD pattern for 5 times SiO_2 @ Fe_3O_4 (D) XRD pattern for 10 times SiO_2@ Fe_3O_4.

SEM of Magnetite Nanoparticles

Before taking the scanning electron micrograph (SEM), the sample was deposited onto a double stick tape fixed on aluminum sample holder and were sputter coated with gold in sputter coater model SPI-Module (USA) for 90 sec at 30 mA. The SEM micrograph of MNPs is given in Figure 11 which shows that the particles are non-spherical in shape. The morphology of MNPs is homogenous and some clumps are also found due to agglomeration (Fahlepy, M. R., et al 2018).

Figure 11: SEM of Fe_3O_4.

SEM after coating

Figure 12 represents the micrograph where 2 times SiO_2@Fe_3O_4. Figure 13 represents the micrograph where 5 times SiO_2@Fe_3O_4. 10 times SiO_2@Fe_3O_4 micrograph is represented in Figure 14. It represented that coating is done on the MNPs homogenously to prevent the MNPs from agglomeration. The white contrast represents the successful coating.

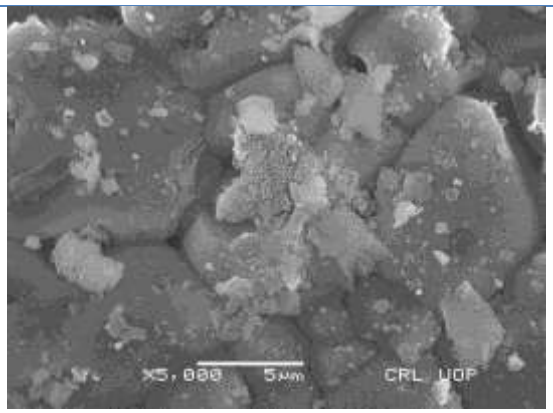


Figure 12: SEM of 2 times SiO_2@Fe_3O_4.

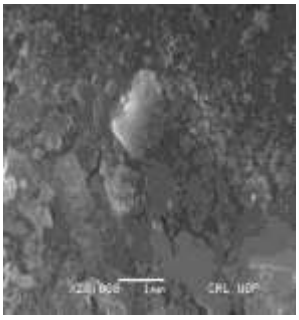


Figure 13: SEM of 5 times SiO_2@Fe_3O_4.

EDX of Magnetite nanoparticles

Energy dispersive X-ray (EDX) spectroscopy is an elemental analysis technique which provides a quantitative analysis of the sample very quickly. EDX of MNPs has been shown in Figure 15. The different energy levels of iron are due to the presence of energy sub levels. Table 1 shows the elemental data in the form of atomic and weight percent. In elemental analysis found that the weight percentage of Fe in Fe_3O_4 is 73.26 % and oxygen is 19.04 % (Hariani, P. L., et al 2013). Some amount of carbon was detected which is due to the use of carbon double stick tape used for the deposition of sample onto sample grid.

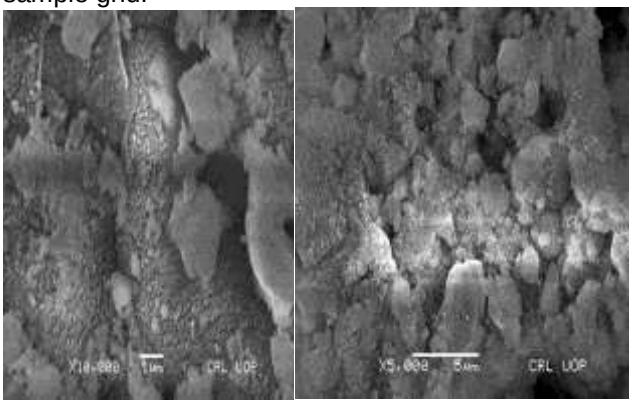


Figure 14:SEM 10 times SiO2@Fe3O4.

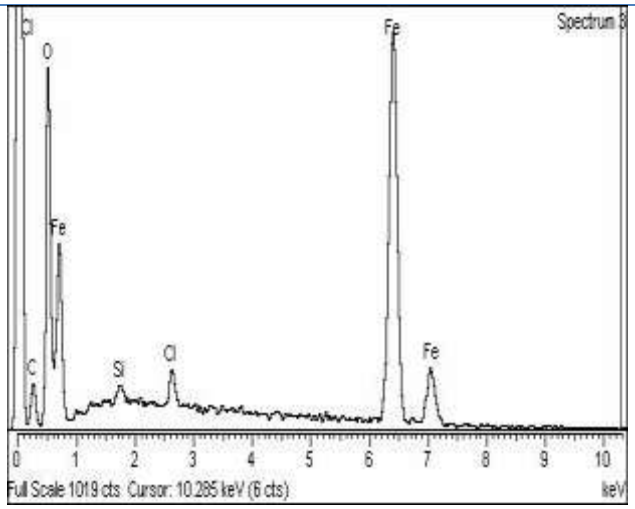
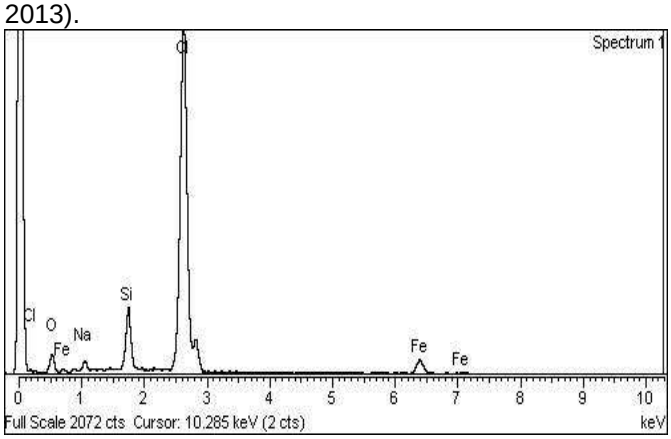


Figure 15:EDX micrograph of Fe_3O_4

Table 1:Elemental analysis of MNPs EDX of silica coated MNPs

Element	Weight %	Atomic %
C	5.51	15.16
O	19.04	39.32
Si	0.60	0.71
Cl	1.58	1.48
Fe	73.26	43.33
Total	100	

The EDX data of silica @ Fe_3O_4 of 2, 5 and 10 spectra are shown in figure 16 (A, B and C) respectively. The peak height of Si atom increases with the increase of silica concentration and Fe atom peak decreases which confirmed the increased silica thicknesses around magnetite. The weight percent of Fe is 12.46, 3.97 and 3.77 and Si weight percent is 7.89, 25.67 and 29.71 for 2, 5 and 10 times coated SMNPs respectively. The Si percent is like those reported by Emadi, M., et al while working on Removal of zinc from aqueous solutions by magnetite silica core-shell nanoparticles (Emadi, M., et al 2013).



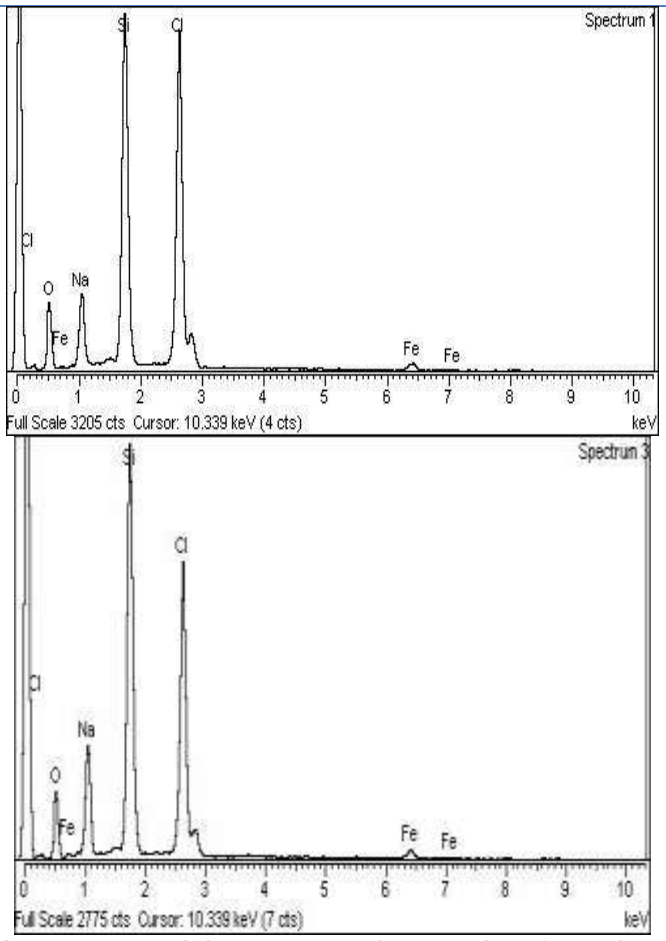
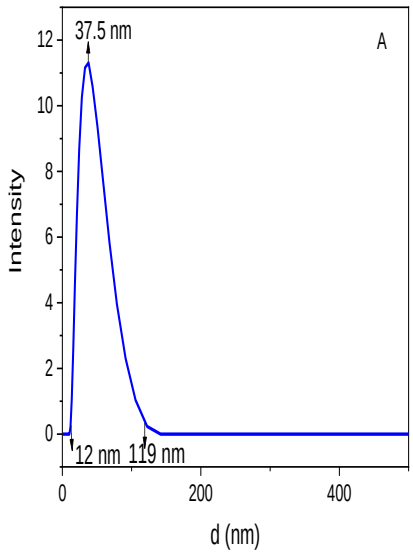


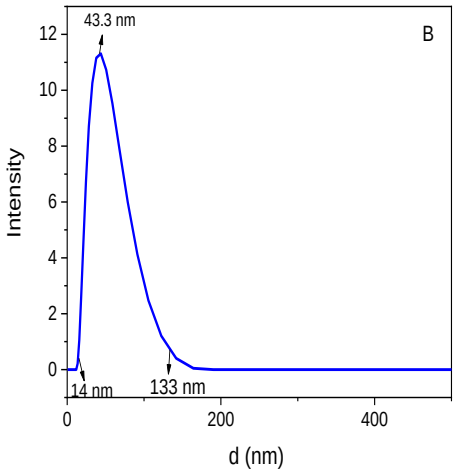
Figure 16: (A) EDX micrograph of 2 times SiO_2 @ Fe_3O_4, (B) EDX micrograph of 5 times SiO_2 @ Fe_3O_4 and (C) EDX micrograph of 10 times SiO_2 @ Fe_3O_4

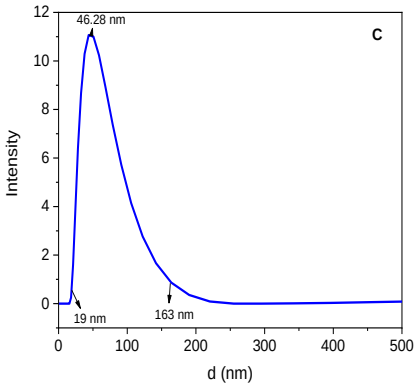
Zetasizer

Zetasizer is a technique to measure the size of particles. In our preparation the magnetite nanoparticles (MNPs) size is range from 12 to 119 nm mainly and mean of particle size is 37 nm as shown in figure 17 (A). After coating the NPs, the size increases. In two coatings of SiO_2 on MNPs, the size of particles was found in the range 14 to 133 nm whereas the mean particle size was 43.3 nm shown in figure 17 B. In five times coating of SiO_2 on MNPs, the particle size was found to increase further, and it was ranges from 19 to 163 nm whereas the mean particle size was 46.28 nm shown in figure 17 C. In ten times coating of SiO_2 the size of MNPs further increases ranging from 23 to 316 nm and mean of the particle size was 84.8 nm shown in figure 17 D.

In literature the size of precursors was related to the size of the MNPs (Daou, T. J., et al 2006). Silica coated MNPs size was found larger than bare MNPs (Ranjbakhsh, E., et al 2012). The particle size in present study was found to be less than the reported in literature (Hassan, K., 2013). The difference in size may be due to use of pulse current electrochemical method. The hydrothermal method was therefore found to be preferred over pulse current electrochemical method (Ranjbakhsh, E., et al 2012).







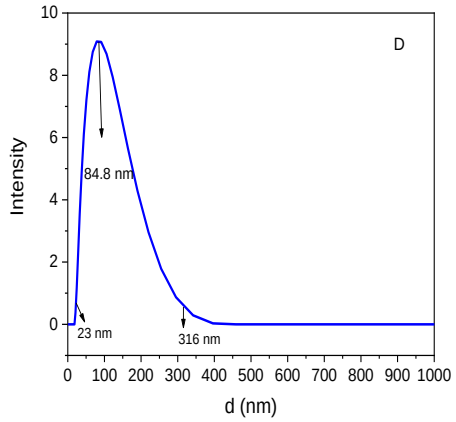


Figure 17: (A) DLS of MNPs (B) DLS of 2 times SiO2 @ Fe_3O_4 (C) DLS of 5 times SiO_2 @ Fe_3O_4 (D) DLS of 10 timesSiO_2 @ Fe_3O_4.

Figure 18 represents the effect of silica on MNPs, with the increasing of silica content size of MNPs also increased. The increment of size with respect to increase silica content is given in table 2.

Table 2:Effect of silica coating on the size of MNPs

Sample	Amount of silica (mM)	Size of MNPs (nm)
MNPs	0	37
2 times SiO_2 @ MNPs	1.32	43.3
5 times SiO_2 @ MNPs	3.33	46.28
10 times SiO_2 @ MNPs	6.66	84.8

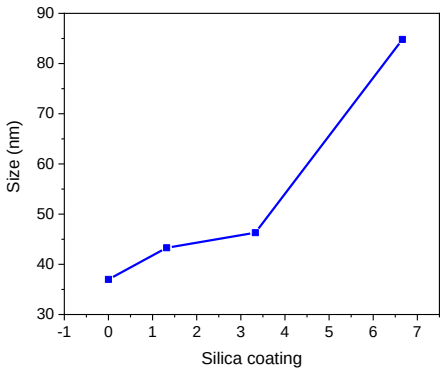


Figure 18: Effect of silica coating on the size of MNPs

After successful synthesis, the magnetite nanoparticles were found to attract with the magnetic given in figure 8. Afterward, we have analyzed MNPs before and after silica coating by various analytical techniques such as UV-Vis spectroscopy, X-ray diffraction (XRD), Zetasizer, Fourier Transform Infrared (FTIR), Scanning Electron Microscope (SEM) and Energy Dispersive X-rays (EDX).

CONCLUSION

Spherical shaped MNPs were prepared by hydrothermal method. Sodium silicate was used as a precursor for silica to coat the MNPs. After coating the silica on MNPs the diffraction peaks of MNPs disappeared. The broadness of the diffraction peak in XRD is decreased which shows that the size of MNPs increases with the increase of silica content. XRD says that the size of synthesized MNPs was 15 nm. The absorption band at 1120 cm^{-1} increases with the increase of silica content which confirms the increasing of the thicknesses of MNPs. EDX says that the weight percent of iron is 73.26 % and oxygen is 19.04 % in MNPs and the silica coated MNPs shows a trend in the increase of thicknesses. Weight percent of silica increased with the increase of silica content. SEM tells the morphology of MNPs. MNPs were homogenous and spherical in shape. Drug load is also studied, maximum drug loaded on 10 times silica coated MNPs. Drug release is studied by dialysis method, the MNPs show burst release and the silica coated MNPs show sustained drug release. However, 10 times coated MNPs showed more sustained drug release than others silica coated MNPs.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

ACKNOWLEGEMENT

Abdul Shakoor and Muhammad Ali contributed equally so both of these two authors share 1st author position

AUTHOR CONTRIBUTIONS

AS, MA designed and performed the experiments and also wrote the manuscript. MK, AM, and MN performed data analysis. AS and MS and ZA designed experiments and reviewed the manuscript. All authors read and approved the final version.

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