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Synthesis, Characterization and Application of Chitosan-Coated Magnetite Nanoparticles in Drug Delivery

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Abstract: ***Magnetite nanoparticles were used extensively for various applications. In the present study, magnetite nanoparticles were synthesized and characterized by atomic force microscopy (AFM). AFM images showed that the obtained particles were perfectly spherical. Functionality is afforded to these magnetite nanoparticles by adding biocompatible polymer chitosan during the synthesis. AFM phase image clearly showed that the magnetite core is encapsulated with the polymeric shell. Fourier-transform infrared spectroscopy (FTIR) study showed the chitosan absorption on Fe_2O_3 nanoparticle surface. The drug sulphamethoxazole was loaded over magnetite nanoparticles and the encapsulation efficiency of drug was calculated at different concentrations of magnetite. The encapsulation efficiency increases with increase in the concentration of magnetite. Thus, an attempt was made in synthesizing drug loaded biopolymer magnetite nanoparticles suitable for targeted drug delivery.***

Keywords: Nanoparticle: Chitosan; AFM; Coating; Polymer

I. INTRODUCTION

Magnetic oxide nanoparticles were extensively investigated due to their vast applications. Due to their better magnetic properties and lower toxicity, magnetite nanoparticles are mostly preferred for the drug delivery system. Magnetite nanoparticles are widely used in the biomedical applications because of their smaller size, larger surface, and enhanced solubility. The biomedical applications of magnetite nanoparticles include: drug delivery, chemotherapy, magnetofection, hyperthermia, scaffold-based tissue engineering, MRI contrast agents, organ/tissue imaging, theranostic platforms, in vitro bioseparation, bioanalysis, and immunoassays [1-3]. Due to the multifunctional properties of the magnetite nanoparticles, they are able to interact with complex cellular functions. This rapidly growing field requires cross-disciplinary research and provides opportunities to develop multifunctional devices to treat cancer. In order to reduce drug doses, coats associated with drug treatment, and potential side effects, the magnetite nanoparticles are attached to the drugs. Generally, oxides of iron are short blood half-life and their primary application of oxides of iron is for imaging of liver. However, the surface modification of nanoprticles leads to long blood circulation times. Hence, the surface modified nanoparticles are highly useful for imaging of the vascular compartment and specific target. The syntheses of uniform iron nanoparticles are reported very little. The synthesis of iron nanoparticles by sonochemical decomposition of iron pentacarbonyl in the presence of polyvinylpyrrolidone (PVP) has been reported. The sonochemical decomposition method was used to synthesize various nanostructured materials. The inability to control particle size is one of the drawbacks in the synthesis of nanoparticles by sonochemical decomposition method [4-6]. The thermal decomposition method was also recently used to synthesize iron oxide nanoparticles from iron pentacarbonyl in the presence of oleic acid at 100 °C [7-11]. Monosized iron nanoparticles were also synthesized at 300 °C from iron-oleic acid metal complex. Magnetite nanoparticles are particularly desirable because it displays a strong magnetic behavior, and is less sensitive to oxidation than magnetic transition metals such as cobalt, iron, and nickel. For *in-vivo* applications, it is important that well-defined organic coatings surround the magnetite particles. It is rationalized that this will prevent any aggregation of the nanoparticles *in-vivo*, and may also enable efficient excretion and protection of the body from toxicity [12-16]. In this work, it is aimed to develop drug loaded biopolymer magnetite nanoparticles for biomedical application. The main objective is to synthesize and characterize magnetite (Fe_3O_4) nanoparticles and to afford functionality to the Fe_3O_4 nanoparticles by addition of biocompatible polymer chitosan. It is also aimed to load the drug sulphamethoxazole to the magnetite nanoparticles and to estimate the encapsulation efficiency of drug at different concentrations of magnetite.

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II. EXPERIMENTAL METHODS

2.1 Materials

Ferric chloride ($FeCl_3$.$6H_2O$, 98%), Ferrous sulphate ($FeSO_4$, 98%), NH_4OH, CH_3COOH were obtained from Sigma Aldrich. Ethyl alcohol was purchased from Hong yang corpn, China. Chitosan, less molecular weight (<6000Mn), was obtained from Sigma Aldrich.

Sulphamethoxazole was purchased from Hi Media Laboratories, Mumbai. Analytical grade reagents were used without any purification.

2.2 Synthesis of Magnetite Nanoparticles

0.1 M KOH solution was mixed with the solution of 0.05 M $FeSO_4$ in a three neck flask. 0.2 M of KNO_3 was added into the solution and the solution mixture was kept at 90°C for 24 h with constant stirring. Ethanol and deionized water were used to wash the resultant black precipitate. Then, the dispersion of nanoparticles took place in ethyl alcohol.

2.3 Coating of Chitosan over Magnetite Nanoparticles

Chitosan solution was prepared by dissolving chitosan in 1% acetic acid. Fe_3O_4 nanoparticles were purified by centrifugation before adding to chitosan solution (0.4mg/ml). Magnetite nanoparticles were mixed with chitosan solution to form chitosan coated magnetite nanoparticles. The mixture was stirred at room temperature for 6 hours. The colloidal solution of Fe_3O_4 nanoparticles was centrifuged for 10 min (8,000 rpm). The chitosan coated magnetite nanoparticles was then washed with deionized water and dispersed in ethyl alcohol.

The coating duration was varied for 4, 6 and 8 hours. Then, the colloidal solution of chitosan coated magnetite nanoparticles was obtained after centrifuging for 10 min at 10000 rpm. Then, the particles were analyzed using AFM and FTIR studies. The effect of coating thickness with respect to coating time was also studied.

2.4 Loading of drug and polymer to magnetite nanoparticles

The drug sulphamethoxazole and the polymer chitosan were loaded to magnetite nanoparticles by adding 2 mg of drug to 50 µl of magnetite and then 950 µl of ethanol was added to the solution. Then, the mixture was sonicated for 3 minutes. Again, the solution was sonicated for 10 minutes, while sonicating, the chitosan solution (1% acetic acid) of 1 ml was added drop by drop to the mixture. The mixture was then stirred at room temperature until the ethanol evaporated. Then, 2 ml of distilled water was added to the sediment powder. Then the colloidal solution of sulphamethoxazole/chitosan/magnetite nanoparticles was centrifuged for 15 minutes at 3000 rpm. The procedure was repeated for various concentrations of magnetite viz. 25 µl and 15 µl.

2.5 UV-Vis Analysis of Drug, Polymer loaded Magnetite Nanoparticles

The drug, polymer loaded magnetite nanoparticles with different concentration of magnetite (viz.50, 25 and 15 µl) were analyzed using UV Spectroscopy. Initially, 100 µl of the drug, polymer loaded magnetite nanoparticle sample was taken in the cuvette and 3 ml of ethanol was used as a solvent to characterize the sample. The absorbance values of all the three samples were noted.

2.6 Characterization of Magnetite/Polymer Nanoparticles

AFM was done to obtain the morphology of the magnetite/chitosan nanocomposite. The samples were analyzed using atomic force microscopy (Veeco CP II) in non-contact mode. The phase image for chitosan coated magnetite nanoparticles was recorded. This phase image reveals the information about coating over magnetite nanoparticles.

FTIR Spectroscopy is an appropriate technique to understand chemical adsorption or functionalization of Fe_3O_4 nanoparticles with polymers. The samples of magnetite and chitosan modified magnetite particles were ground with KBr and the mixture was compressed in to a pellet. FTIR (**Thermo Nicolet, AVATAR 330, Mid IR,**) was used with scanning range of 400-4000cm^{-1} to characterize the chitosan coated-Fe_3O_4 nanoparticles.

III. RESULTS AND DISCUSSION

3.1 Atomic Force Microscopy (AFM)

The magnetite nanoparticles were analyzed by AFM with respect to their size and their size-distribution. Fig. 1 depicts the AFM images of the magnetite nanoparticles. The spherical shape of magnetic nanoparticles was obtained and its diameters were found to be in the range 5-50 nm. The average particle size was found to be around 10 nm.

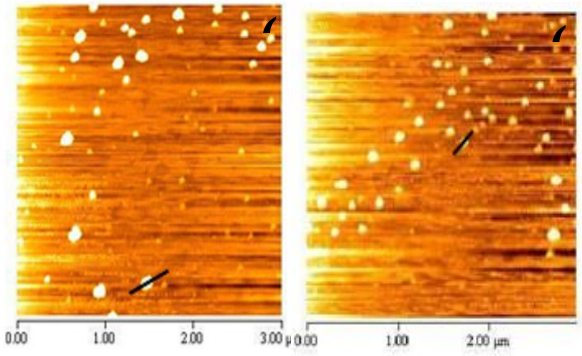


Figure 1 (a) & (b) AFM images of magnetite nanoparticles.

Fig. 2 shows the AFM images of magnetite nanoparticles after chitosan surface modification.The coating duration was 4 hours. The particle size is found to be around 83 nm and the coating thickness is around 35 nm.

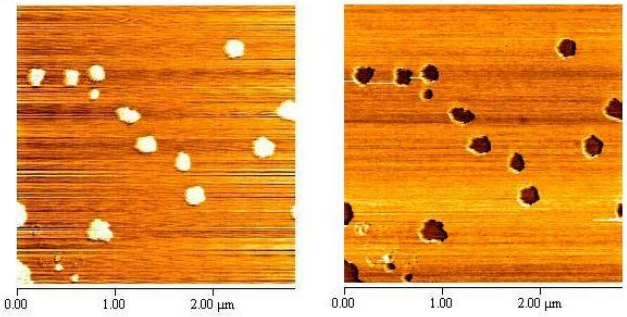


Figure 2 (a) Topography and (b) phase images of scan size 3 µm of magnetite nanoparticles coated with chitosan for a coating duration of 4 hours

Fig. 3 shows the AFM images of the magnetite nanoparticles coated with chitosan for a coating duration of 6 hours. The magnetite-polymer core shell particle size was found to be around 14 nm and coating thickness of around 13 nm and 10 nm. Fig. 4 depicts the phase image of magnetite nanoparticles coated with chitosan for a coating duration of 6 hours.

The phase image confirmed that the chitosan was nicely coated over magnetite nanoparticles. The nanocomposite remained perfect spherical and most of the particles are uniform in size. The particle size is around 14 nm and the coating thickness is around 13 nm and 10 nm.

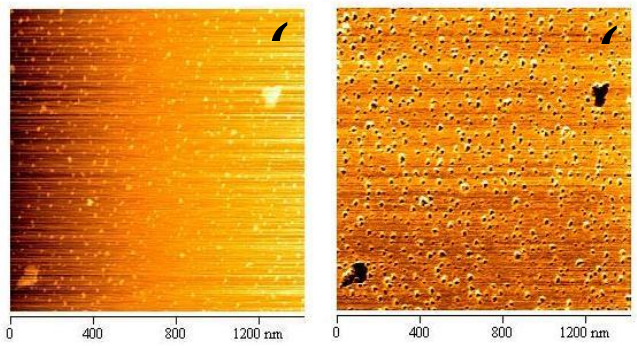


Figure 3 (a) Topography and (b) Phase images of scan size 1400 nm of the magnetite nanoparticles coated with chitosan for a coating duration of 6 hours

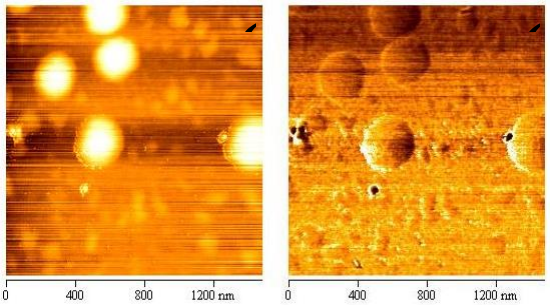


Figure 4 (a) Topography and (b) Phase images of scan size 1300 nm of drug, polymer loaded magnetite nanoparticles (concentration of magnetite is 50 µl)

Fig. 5 presents the AFM image of sulphamethoxazole, magnetite nanoparticles coated with chitosan. The concentration of magnetite used was 50 µl. The particle size is 36.5 nm and the coating thickness is 17.8 nm. The magnetite-polymer, drug core shell particle with particle size of 36.5 nm and coating thickness of 17.8 nm and 16.9 nm. Fig. 6 shows the AFM image of sulphamethoxazole, chitosan coated magnetite nanoparticles for the concentration of 25 µl of magnetite. The particle size is 18.4 nm and the coating thickness was 13.4 nm. The magnetite-polymer core shell particle with particle size of 18.4 nm and coating thickness 13.4 nm.

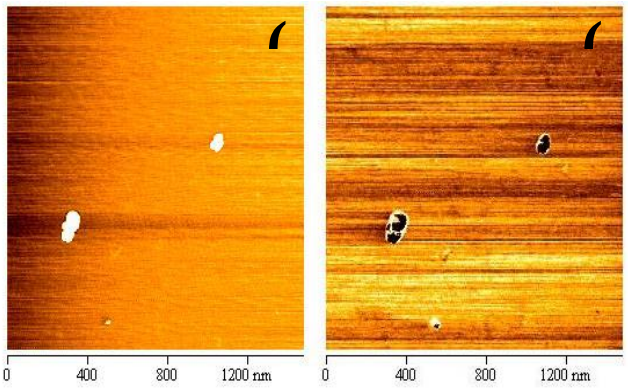


Figure 5 (a) Topography and (b) Phase images of scan size 1300 nm of drug, polymer loaded magnetite nanoparticles (concentration of magnetite is 25 µl)

3.2 Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of the magnetite nanoparticles coated with chitosan was shown in Fig. 6. The magnetite nanoparticles coated with chitosan possessed the characteristic peaks of chitosan. The absorption peak at 3434 cm^{-1} is corresponded to the hydroxyl (OH^-) group and the peak at 1635 cm^{-1} is corresponded to the amine group ($-NH_2$). The absorption peak at 1015 cm^{-1} corrsponds to C-C and C-O stretching modes of polysaccharides backbone, and the bending vibration of $–CH_2$ group is at 1389 cm^{-1}. The characteristic peak at 572 cm^{-1} corresponds to the magnetite nanoparticles which is also observed in the spectra of the magnetite nanoparticles coated with chitosan. Hence, this spectrum is confirmed that the magnetite nanoparticles are coated with chitosan

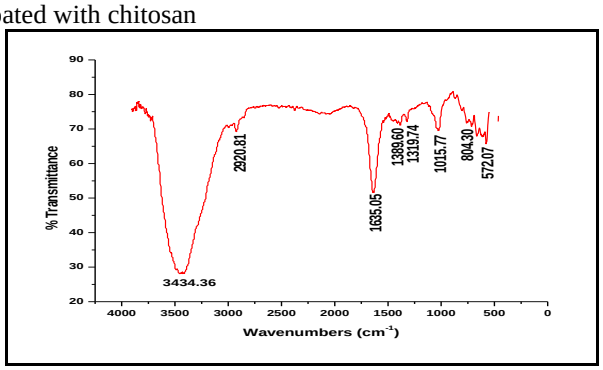
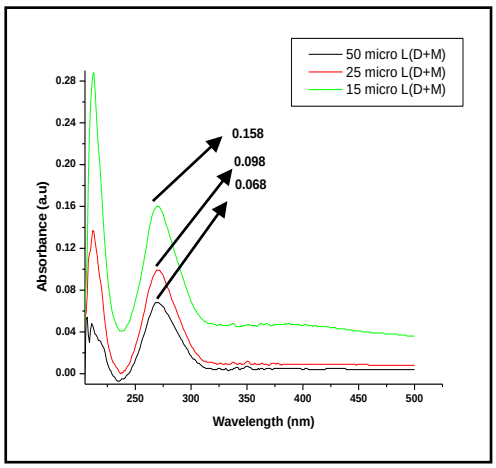


Figure 6 FTIR spectra of Chitosan coated Magnetite Nanoparticles

3.3 UV-Vis spectroscopy

Fig. 7 displays the UV-Vis spectra of the absorbance of polymer, drug loaded Magnetite at different concentrations of magnetite versus Wavelength. It is concluded that the absorbance increases as the concentration of magnetite increases. The encapsulation efficiency also increases as the concentration of magnetite increases. The encapsulation efficiency is 99.80 % when the concentration of magnetite is 15 µl. However, the encapsulation efficiency is found to be 99.82 % with the magnetite concentration of 25 µl. Therefore, it is concluded that the encapsulation efficiency is not significantly different in the presence of polymer.



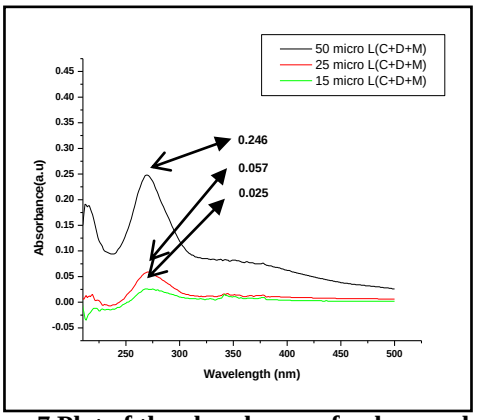


Figure 7 Plot of the absorbance of polymer, drug loaded Magnetite at different concentrations of Magnetite versus Wavelength

IV. CONCLUSION

Atomic force microscopic (AFM) was used to characterize the magnetite nanoparticles as well as magnetite nanoparticles coated with chitosan. Ferric chloride and ferrous sulphate were used as the precursor for synthesizing the magnetite nanoparticles and analysed by AFM techniques in order to ascertain the size and shape using non-contact AFM. It was observed from the AFM analysis that the AFM images showed the spherical shape of the nanoparticles with 5-50 nm height. The average particle size was found to be 10 nm.

Chitosan was coated over the magnetite nanoparticles for varying duration of coating time. AFM phase images showed that individual Fe_3O_4 particles were nicely coated with the polymer. The polymeric nanoparticles have a core-shell structure with magnetite core and polymeric shell. The magnetite-polymer core shell has a typical particle size of around 14 nm and average coating thickness of around 11.5 nm.

The drug sulphamethoxazole was loaded over magnetite nanoparticles using solvent evaporation method. AFM phase images of the drug-loaded magnetite nanoparticles showed that the magnetite nanoparticles were coated with sulphamethoxazole. The drug, polymer loaded magnetite nanoparticles have a typical particle size of 36.5 nm and average coating thickness of around 17.4 nm.

The drug loaded magnetite nanoparticles and drug/polymer loaded magnetite nanoparticles were also analyzed using UV-Vis spectroscopy. The encapsulation efficiency was calculated for the drug loaded magnetite nanoparticles and the polymer/drug loaded magnetite nanoparticles at different concentration of magnetite. It was found that the absorbance increases as the concentration of magnetite increases. It was found that the encapsulation efficiency is not significantly different in the presence of polymer.

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