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Research Article

pH-RESPONSIVE CARBOXYMETHYL CELLULOSE CONJUGATED SUPERPARAMAGNETIC IRON OXIDE NANOCARRIERS

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ABSTRACT

In the present study, polyethyleneimine (PEI) coated superparamagnetic iron oxide nanoparticles (SPIONs) having the size of 15 nm in diameter with high magnetic saturation (60 emu/g) have been prepared by co-precipitation method. The synthesized PEI-Fe3O4 nanoparticles have been fully characterized by transmission electron microscope (TEM), dynamic light scattering (DLS), Fourier transform infrared (FTIR) spectroscopy, X-ray photoelectron spectroscopy (XPS) and X-ray diffraction (XRD) techniques. The free amine groups on the PEI-Fe3O4 surface has been covalently functionalized with carboxymethyl cellulose (CMC) by the catalysis of N,N'-Dicyclohexylcarbodiimide (DCC) and N, N'-Dimethylpyridin-4-amine (DMAP) coupling to produce CMC-Fe3O4 nanocarriers. The prepared CMC-Fe3O4 nanocarriers have been loaded with a well-known anti-tumor drug doxorubicin (Dox) and investigated its loading and releasing profiles from the nanocarrier. The CMC acted as an excellent nanocarrier for Dox with a loading efficiency ≈ 86%. The drug releasing profile has been studied at different pH values (3.5; 5.5; and 7.4). When the pH of the release medium (phosphate buffer solution) was changed from 7.4 to 5.5 or 3.6, the drug release has been increased which indicates that the drug releasing is pH dependent.

Keywords: *Superparamagnetic iron oxide, carboxymethyl cellulose, doxorubicin, pH, drug release*

1. INTRODUCTION

Nanotechnology has been become a fast growing research field in worldwide. The reason of its fast growing dramatically is that the nanotechnology has the potential to profoundly *improve* the *quality* of our health and our lives. Nanostructured materials

(nanoparticles, nanotubes, nanowires, thin films, nanocomposites) exhibit new physical, chemical and biological properties relative to bulk materials [1]. Due to the large surface area/volume ratio of the nano-sized materials, they can easily functionalize with ligands or coating agents. As a result of this property, the new nanomaterial can gain new properties which can be applied in many industries such as electric&electronics, biomedical, medical, food, agriculture, textile and cosmetics [2].

Nanomaterials can be classified into four categories: (i) carbon based, (ii) inorganic based, (iii) organic based, and (iv) composite based nanomaterials [3]. Magnetic iron oxide nanoparticles (IONPs) are in the class of inorganic nanomaterial and generally used in lithium ion batteries, supercapacitors, catalysis, releasing therapeutic agents, labelling the cells and separation of biochemical products [4]. Due to their low cytotoxicity and superparamagnetic properties (Fe_3O_4 and γ-Fe_2O_3), they can also be used as magnetic resonance imaging (MRI) and thermal therapy agent in the biomedical field [5].

IONPs composed of different magnetic properties and chemical ingredients. The main compounds of iron oxides are hematite (α-Fe_2O_3), magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3). Each of these three iron oxides has unique biochemical, magnetic, catalytic, and other properties which provide suitability for specific technical and biomedical applications. Even magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) have the same physical properties, maghemite has less magnetic than the magnetite [4].

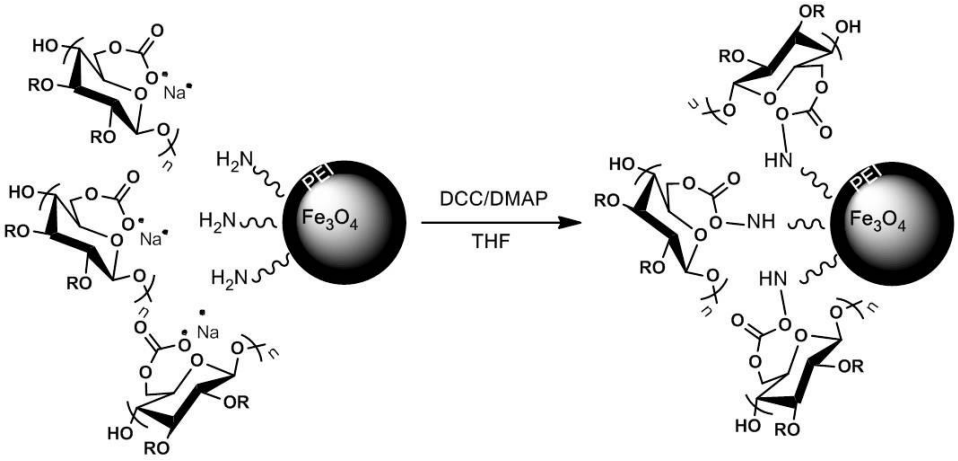
In order to synthesize these IONPs, a variety of synthetic methods such as co-precipitation, thermal decomposition, hydrothermal and solvothermal syntheses, sol-gel synthesis, microemulsion, ultrasound irradiation and biological synthesis can be carried out [6]. The bare magnetic nanoparticles have the problems about aggregation and surface oxidation which limits their therapeutic usage. Therefore, they need to be surface engineered in order to improve on their dispersibility, stability, and biocompatibility. For this reason, the surface of IONPs should be further functionalized with silica or polymeric coatings such as polyethylene glycol-PEG, dextran, polyethyleneimine-PEI, polyacrylic acid and/or chitosan depending on the biomedical applications [7]. As a result of the surface modification with these polymeric materials, the agglomeration can be inhibited and the superparamagnetic properties can be protected due to high surface energies of IONPs. In addition, the surface modification also offers the functional groups for further functionalization by anchoring drug molecules, antibodies or peptides.

IONPs can also be modified with a pH responsive polymer in order to apply to a pH dependent drug delivery systems [8]. The microenvironment of the tumor tissue has low pH values (5.8) and even lower at endosomes (pH 5.0-6.0) and lysosomes (pH 4.0-5.0) which emphasize the importance of pH parameter on cancer [9]. In recent years, many pH-responsive IONPs have been developed. Among these studies, IONPs have been coated with imidazole modified PEG-polypeptide (mPEG-poly(L-asparagine) [10], bovine serum albumin [11], alginate [12],

β-cyclodextrin [13], poly (N-isopropylacrylamide) [14], polyethyleneglycol (PEG) [15] and hydroxyapatite [16] to obtain core-shell iron oxide structures. These core-shell structures have been loaded with an anti-tumour drug, doxorubicin and investigated their pH dependent releasing profiles. According to the studies mentioned above, the drug delivery in acidic buffer media (pH 5.5) is higher than that of physiological medium pH 7.4. The advantage of using iron oxide nanoparticles is that they can be directed through the cancer side via the guide of external magnetic field. By the carrying of these nanoparticles to the targeted cancer side, Dox delivers through the surface of magnetic nanocarrier due to the acidity of the microenvironment of the cancer tissue.

In the current study, PEI has been coated to the surface of Fe_3O_4 nanoparticles *in situ* and further functionalized with CMC by using DCC/DMAP coupling to produce CMC-Fe_3O_4 nanocarriers (Fig.1). For the surface functionalization, a cellulose based coating agent has been chosen due to its sustainability, biodegradability and biosafety. Additionally, cellulose has a well-documented history of successful use in U.S. Food and Drug Administration approved drugs/products [17].

Figure-1. The binding of carboxymethyl cellulose (CMC) to the PEI coated Fe_3O_4 nanoparticles covalently.



In some recent studies, CMC nanoparticles has been mixed with zein [18], graphene oxide [19] or resin [20] to produce CMC based nanocomposites as pH-responsive drug delivery nanocarriers. With the light of these studies, among many polymeric nanocarrier systems, cellulose based nanocarriers are seem to be ideal candidates for drug loading and pH-dependent drug delivery.

There is also a few study based on CMC based IONPs for pH-responsive drug delivery applications. Lang and co-workers prepared 5-Fluorouracil, an anti-cancer drug, loaded CMC-IONPs nanocarriers and investigated their drug release profiles at different pH values (5.5 and 7.4) [21]. In the preparation method of these nanocarriers, firstly CMC has been prepared as nanoparticles, then IONPs have been synthesized, and the synthesized IONPs were embedded to CMC nanoparticles. The drug loading efficiency was 89% and more than 85% of the encapsulated drug was released in a period of 60 h. in pH 5.5 buffer, whereas 74% of the drug was released in pH 7.4 buffer. The saturation magnetization was found as $8x10^{-5}$ Wb m/kg for CMC-IONPs.

Movagharnezhad and co-workers prepared a core-shell CMC-magnetic nanoparticles (MNP) by the covalent bonding of hexamethylenediamine modified CMC with hexamethylenediisocyanate grafted MNP [22]. The prepared CMC-MNP has been loaded with Dox molecules with ≈57.5% drug loading efficiency. The drug release studies showed that at pH 5.0, 65% of Dox was released within 5 hours, whereas only 50% of the Dox was released at pH 7.4 within this time interval.

In another study, Kanagarajan and co-workers developed CMC-$MnFe_2O_4$ magnetic nanocarriers for an anticancer hydrophobic drug, curcumin [23]. The preparation technique of these nanocarriers includes firstly the synthesis of magnetic $MnFe_2O_4$ nanoparticles, then coating with CMC and then with glutaraldehyde for crosslinking the polymer matrix. The resultant nanocarrier has ≈40% drug loading efficiency and pH-dependent drug release studies show that 46% of the drug has been released from the nanocarrier at pH 5.5 during 120 h,

whereas 42% of the drug has been released at pH 7.4 during 120 h. The saturation magnetization of the CMC-$MnFe_2O_4$ nanoparticles were also found to be 36.1 emu/g.

The originality of our study is the covalently functionalization of CMC polymer having carboxylic acid functional group with PEI-Fe_3O_4 nanoparticles having the free amine group on the surface. As a result, the resultant nanocarriers provides a higher saturation magnetization (58 emu/g) compared to the related to the studies mentioned above. Additionally, in literature, after the introduction of CMC to the IONPs, the saturation magnetization has been decreased significantly [21-23], whereas in our study, the saturation magnetization was slightly decreased after CMC functionalization.

2. MATERIALS AND METHODS

2.1. Materials

Raw materials used during the synthesis, including iron(III) chloride hexahydrate ($FeCl_3 \cdot 6H_2O$), iron(II) chloride hexahydrate ($FeCl_2 \cdot 4H_2O$), polyethylenimine (PEI), carboxymethyl cellulose (CMC), *N,N′*-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), sodium hydroxide (NaOH), dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich with minimum purity of 99%. Ammonium hydroxide (NH_4OH) with 25% purity was purchased from Merck. Doxorubicin HCl salt used as model drug was purchased from Toronto Research Chemicals. Dialysis tubing, 12,000 Da MWCO, 25 mm flat-width, from Sigma-Aldrich was used for drug loading studies. Deionized water and anhydrous ethanol were used in the experiments and purification processes.

2.2. Methods

2.2.1. Synthesis of PEI coated superparamagnetic Fe_3O_4 nanoparticles

$FeCl_3.6H_2O$ (2.36 g, 8.73 mmol) and $FeCl_2.4H_2O$ (0.86 g, 4.32 mmol) were transferred into three-necked flask and 40 mL of deionized water including PEI solution (2g/50 mL). The resulting solution was stirred and heated to 80°C under nitrogen atmosphere. Subsequently, NH_4OH (5 mL, 25%) was added into the flask and stirred for further one hour. After one hour, the reaction mixture was cooled to room temperature and the obtained Fe_3O_4 nanoparticles were separated from the mixture by means of a magnet. After washing three times with deionized water and ethanol, the nanoparticles were filtered and dried in a vacuum oven at 40°C [24].

2.2.2. Synthesis of CMC-Fe_3O_4 by covalent bonding of PEI-Fe_3O_4 with CMC

PEI coated Fe_3O_4 nanoparticles (20 mg) were dispersed in DMSO (15 mL). DMAP (10 mg) and DCC (10 mg) were added to the nanoparticle solution and stirred under nitrogen atmosphere for 10 minutes. Then, CMC (200 mg) was added into the above reaction mixture and stirred at room temperature overnight. The resulting CMC-Fe_3O_4 NP's were collected by centrifugation at 7500 rpm, washed 3 times with THF (50 mL), then washed twice with ethanol (50 mL). Finally, the CMC-Fe_3O_4 nanoparticles were dried in a vacuum oven at 40°C.

2.2.3. Preparation of Dox loaded CMC-Fe_3O_4 nanoparticles

For drug loading studies, doxorubicin (Dox), an anticancer drug, was selected as a model drug. To prepare the drug loaded CMC-Fe_3O_4 NPs, doxorubicin HCl (2.5 mg, 4.6 μmol) was dissolved in deionized water (20 mL). After adding CMC-Fe_3O_4 nanoparticles (150 mg) into this solution, the solution was transferred to a dialysis tube (MWCO: 12000 g/mol, diameter: 25 mm) and placed in the beaker containing deionized water (500 mL). It was kept at room temperature under stirring at 200 rpm for 24 hours for loading of the drug into the CMC-Fe_3O_4 nanoparticles. At the end of this period, the drug loaded nanoparticles were separated from the loading medium by centrifugation (7500 rpm). Drug concentrations loaded to CMC-Fe_3O_4

nanoparticles were determined by using Perkin Elmer, Lambda 650 UV-Visible spectrophotometer. The loading efficiency (LE%) and loading capacity (LC%) of Dox into the NPs were calculated using Equations (1) and (2), respectively.

$$LE\% = \frac{\text{Total amount of Dox (mg)} - \text{The amount of Dox released from dialysis membrane (mg)}}{\text{Total amount of Dox (mg)}} x100 \qquad \text{Eq-(1)}$$

$$LC\% = \frac{\text{Total amount of Dox (mg)} - \text{The amount of Dox released from dialysis membrane (mg)}}{\text{The weight of NPs (mg)}} x100 \qquad \text{Eq-(2)}$$

2.2.4. Dox release from CMC-Fe_3O_4 NPs

Dox release from nanoparticles was analyzed using a UV-Visible spectrophotometer (Perkin Elmer, Lambda 650). The calibration curve was constructed by analysing five different concentrations of Dox standard solutions in the concentration range of 5-50 ppm. Absorption spectra of Dox was measured in the range of 200-800 nm wavelength and the wavelength of maximum absorption of Dox was determined as 480 nm. The calibration curve was constructed by analysing five different concentrations of Dox standard solutions in the concentration range of 5-50 ppm. Molar absorptivity coefficient (ε) was calculated by using Lambert-Beer equation given in Equation (3) (Skoog et al. 1998).

$$A = l.\varepsilon.C \qquad \text{Eq-(3)}$$

Here, A is the absorbance of the solution; I is the length of the cuvette and C is the concentration of the solution. Quartz cuvettes with 1 cm light path were used in the measurements.

Drug releases were performed with a dialysis method at three different *pH values.* For this purpose, Dox-loaded CMC-Fe_3O_4 NPs were divided into three equal parts by weighing. 2 mL of three different phosphate buffer solution (PBS) (pH = 3.5; pH = 5.5 and pH = 7.4) were added and each of the solutions were transferred into the dialysis membrane. Dialysis membranes were placed into the bottles containing 50 mL of buffer solution at three different pHs (3.5; 5.5 and 7.4) and allowed to stir at room temperature at a stirring rate of 200 rpm. At certain time intervals (2, 4, 6, 8, 24, 48, 72, 96, 120 and 144 hours), 1 mL solution was withdrawn from each release medium for analysis and after the measurement it was put back into the medium.

2.2.5. Characterization

The synthesized PEI-Fe_3O_4 and CMC-Fe_3O_4 nanoparticles were characterized by various techniques. Transmission electron microscopy (TEM) (ZEISS, LEO 906E) and dynamic light scattering (DLS) (Malvern, Nano ZS) analyses were performed to identify the surface morphology, particle size and particle size distributions of PEI-Fe_3O_4 and CMC-Fe_3O_4 in aqueous solutions. The Fourier transform infrared spectroscopy (FTIR) spectra were collected on a PerkinElmer L160000R FTIR spectrometer in order to confirm the functional groups of the polymers attached on the surface of Fe_3O_4 nanoparticles. Amount of polymer coating on the *Fe_3O_4 surface* was determined by using a Perkin Elmer, Pyris Series STA-8000 thermogravimetric analyzer (TGA) with a heating ramp of 10°C/min from 30 to 800°C under nitrogen purge (20 mL/min). The *in situ* functionalization of PEI to the Fe_3O_4 nanoparticles was further proved by X-ray photoelectron spectroscopy (XPS) (Thermo Scientific, K-Alpha-monochromated). Magnetic properties of the synthesized magnetic nanoparticles were

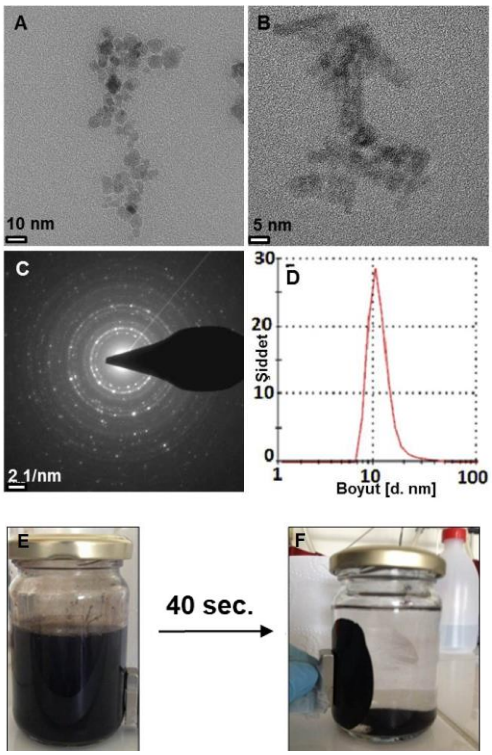
measured with vibrating sample magnetometer (VSM), (Cryogenic Limited PPMS). UV-Visible spectrophotometer (Perkin Elmer, Lambda 650) was used for drug release experiments.

3. RESULTS AND DISCUSSION

3.1 Characterization studies of PEI-Fe_3O_4 and CMC-Fe_3O_4 nanocarriers

The surface morphology and particles sizes of both synthesized PEI-Fe_3O_4 and CMC-Fe_3O_4 nanoparticles have been determined by TEM and DLS techniques. The dilute solutions of the samples were dropped onto the carbon coated TEM grid and dried at room temperature for TEM measurements. According to the TEM measurements, PEI coated Fe_3O_4 nanoparticles have the size of 15 ± 5 nm in diameter with spherical shape (Fig 2A, 2D). After functionalization with CMC polymer, the sizes of the Fe_3O_4 nanoparticles have not been changed dramatically (Fig 2B), but their dispersibility in aqueous solution increased significantly. Electron diffraction pattern also indicates that the synthesized nanoparticles have highly crystalline structure. In Fig.2E, it can be clearly seen that the CMC-Fe_3O_4 nanoparticles are well dispersed in aqueous solution and did not precipitate over a week. When a magnet placed to one side of the bottle, CMC-Fe_3O_4 nanoparticles were collected in 40 seconds leading to a clear solution (Fig 2F).

Figure-2. TEM images of PEI-Fe_3O_4 nanoparticles (**A**),
CMC-Fe_3O_4 nanoparticles (**B**),
Electron diffraction pattern (**C**),
DLS of CMC-Fe_3O_4 nanoparticles in aqueous solution (1mg/mL) (**D**),
The well dispersed CMC-Fe3O4 nanoparticles in H2O (**E**),
with a neodymium magnet (**F**).



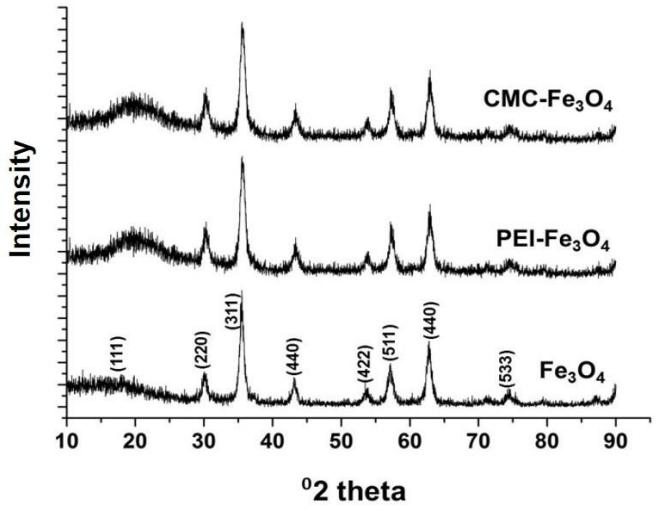
The crystal phase of the all synthesized nanoparticles have been determined by XRD measurements. Both the nanoparticles, as depicted in Fig. 3, bare Fe_3O_4, PEI-Fe_3O_4 and CMC-Fe_3O_4 nanoparticles have been exhibited strong diffraction peaks indexed as (111), (220), (311), (440), (422), (511), (440) and (533). These peaks were coherent with the reference of JCPDS card no-79-0417 and indicated that IONPs are in cubic phase. On the other hand, it should be

noted that the peak positions did not changed after the functionalization with CMC polymer, which indicated that the crystallinity of the IONPs was not affected by the polymer modification process.

$$D = \frac{0.9\,\lambda}{\beta.\cos\theta} \qquad \text{Eq-(4)}$$

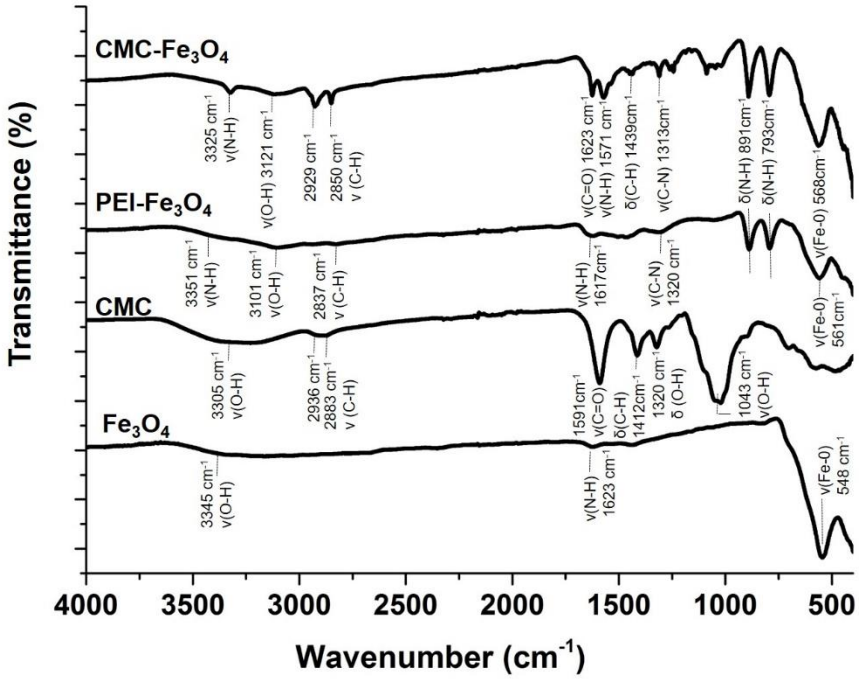
The size of the nanoparticles can also be calculated from the Debye-Scherrer's equation given in Eq-4, where D is the mean crystallite size, β is full width of half maximum intensity, θ is the Bragg's angle in degrees, and λ is the X-ray wavelength. The peak (311) at 2θ = 35.6° was used for the calculation because of its well resolution. The size of the PEI-Fe_3O_4 and CMC-Fe_3O_4 nanoparticles were calculated to be 19.8 nm and 25.04 nm, respectively which are coherent with the TEM data.

Figure-3. XRD spectra of bare Fe_3O_4, PEI-Fe_3O_4 and CMC-Fe_3O_4 nanoparticles



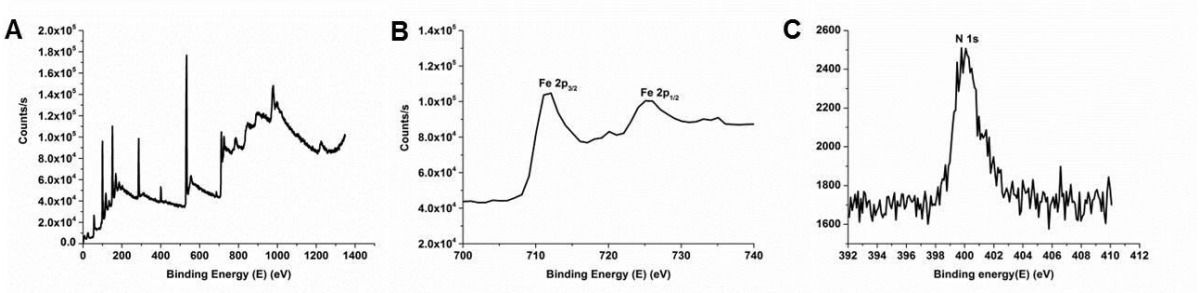
The existence of functional groups of PEI and CMC on the Fe_3O_4 nanoparticles have been proved with FTIR analysis (Fig. 4). In the FTIR spectrum of bare Fe_3O_4, the peaks at 3345 cm^{-1} and 1623 cm^{-1} represent the stretching of hydroxyl groups (–OH) and/or bending vibrations of adsorbed water molecules, respectively. In addition, the peak at 548 cm^{-1} is the characteristic absorption band of Fe-O stretching vibrations. By the modification of Fe_3O_4 with PEI, the peak 2837 cm^{-1} have been appeared due to the C-H stretching vibrations of the aliphatic chains. Additionally, N-H stretching, C-N stretching vibrations belonging to free amine groups (-NH_2) in the PEI were appeared at 3351cm^{-1}, 1617 cm^{-1} and 1320 cm^{-1}, respectively. Due to the modification with PEI, the stretching peak of Fe-O was shifted to 561 cm^{-1}. After the covalently bonding between PEI and CMC polymers, amide functional group (-NHCO-) has been formed which can be seen at 3325 cm^{-1} as stretching of N-H, 1623 cm^{-1} as stretching of carbonyl group (Amide-I band, C=O), 1571 cm^{-1} as the stretching of N-H (Amide-II band, N-H) and 1313 cm^{-1} as the stretching vibration of C-N (Amide-III band, C-N) [25]. These are the essential absorption bands of amide which was also proved that the CMC has been covalently bonded to the surface of PEI-Fe_3O_4.

Figure-4. FTIR spectra of the bare Fe_3O_4, PEI-Fe_3O_4 and CMC-Fe_3O_4 nanoparticles



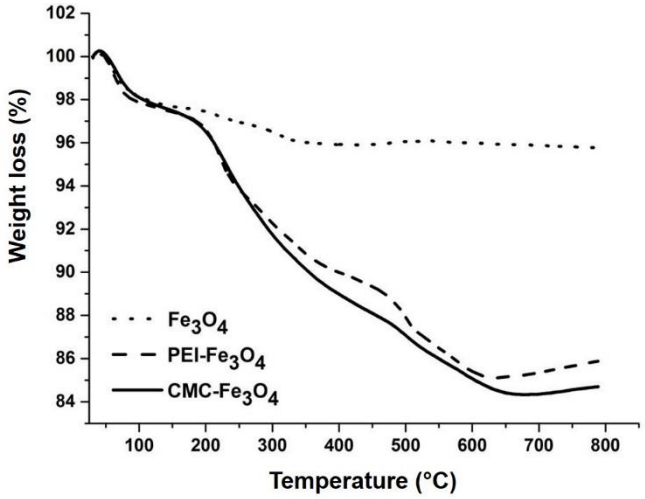
In addition, XPS spectrum confirms the existence of PEI on the magnetic nanoparticle surface Fig. 5A. The peak at 402 eV corresponds to N 1s which proves that the magnetic Fe_3O_4 nanoparticles coated with PEI (Fig. 5C). The peaks correspond to the binding energies at ~711 eV and ~725 eV are related to Fe 2p3/2 and Fe 2p1/2, respectively [26]. Also, the binding energy at 531 eV is attributed to O1s indicating O-Fe in magnetic phase (Fig. 5B).

Figure-5: XPS spectra of the PEI-Fe_3O_4 nanoparticles coated on a silicon wafer (**A**), binding energies of Fe 2p orbital at PEI-Fe_3O_4 nanoparticles (**B**), binding energy of N 1s orbital at PEI-Fe_3O_4 nanoparticles (**C**)



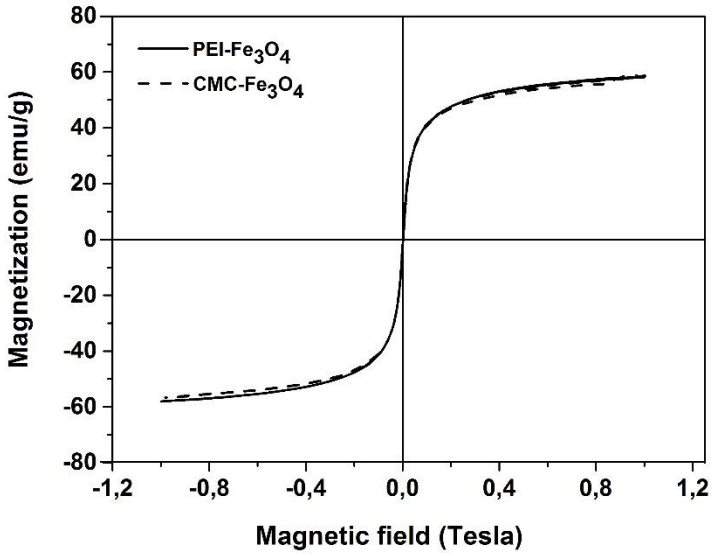
In order to determine the mass percentages of the PEI and CMC polymers on the Fe_3O_4 nanoparticles, thermal gravimetric analysis (TGA) has been carried out (Fig. 6). All samples were heated from 25ºC to 800 ºC at a heating rate of 5 ºC/min. under nitrogen atmosphere. First of all, for all samples there are 2.5 % weight loss due to the removal of residual moisture owing to the adsorbed water molecules. On the other hand, for PEI and CMC polymers, there are 14 % and 15 % weight loss in total, respectively due to the decomposition of the organic polymers. Also, the Fe_3O_4 nanoparticles were thermally stable up to 800°C which indicated the presence of Fe_3O_4 nanoparticles. The TGA results confirmed that the modification with CMC polymer has been done successfully.

Figure-6. TGA curves of bare Fe_3O_4, PEI-Fe_3O_4 and CMC-Fe_3O_4



A vibrating sample magnetometer (VSM) was used to study the magnetic properties of *in situ* synthesized PEI-Fe_3O_4 and CMC-Fe_3O_4 nanoparticles. The saturation magnetizations (Ms) were obtained 60 and 58 emu/g for PEI-Fe_3O_4 and CMC-Fe_3O_4 nanoparticles, respectively (Fig. 7). In addition, there was no hysteresis loop in the magnetization curve, demonstrated that the IONPs are superparamagnetic. It should be noted that, the saturation magnetization of IONPs was slightly decreased after the modification with CMC, which means that synthesized CMC-Fe_3O_4 nanocarriers were still superparamagnetic which makes them also a good candidate for T1 contrast agent for MRI.

Figure-7. VSM of PEI-Fe_3O_4 and CMC-Fe_3O_4 nanoparticles

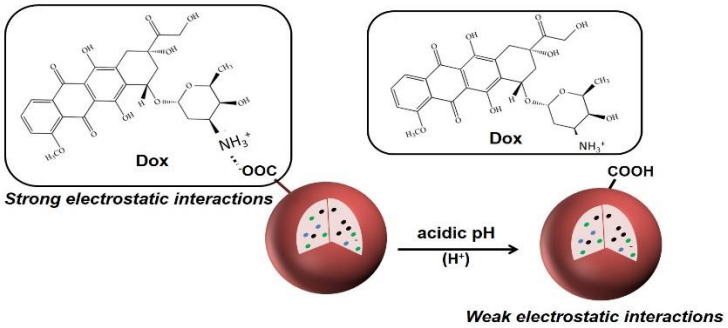


3.2 Drug loading efficiency and in vitro drug release studies

After the preparation of CMC-Fe_3O_4 nanocarriers, Dox molecules have been loaded via adsorption in buffer solution and studied their Dox releasing profiles in phosphate buffer solution (PBS) having different pH values (3.6, 5.5 and 7.4) [23]. The working principle of our system can be explained as follow: due to the chemical structure of CMC, it is interacted with Dox molecules via hydrogen bonds at neutral pH. With the decreasing of pH, CMC is

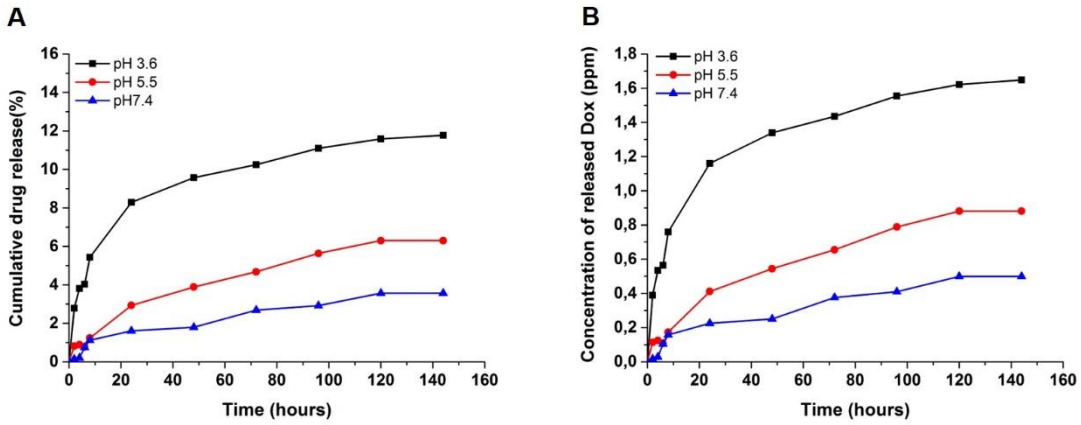
protonated and the interaction between Dox and CMC becomes weak, and then Dox molecules become free from the CMC polymer (Fig. 8).

Figure-8. The interaction mechanism between CMC-Fe_3O_4 nanocarrier and Dox molecule and releasing of Dox depending on pH



According to the adsorption studies of Dox molecules onto the CMC-Fe_3O_4 nanocarriers, the Dox loading efficiency and drug loading capacity has been calculated as 86.2% and 1.44%, respectively. On the other hand, *in vitro* drug release from Dox loaded CMC-Fe_3O_4 nanocarriers at three different pH values were done as shown in Fig. 9. At physiological pH 7.4, 3.24% drug released was observed for 144 h, which increased to 6.30% at pH 5.5 and 11.8% at pH 3.6 for 144 h (Fig. 9).

Figure-9. Drug release profiles of CMC-Fe_3O_4 nanocarriers at pH 3.6, 5.5 and 7.4



4. CONCLUSION

In this study, superparamagnetic CMC-Fe_3O_4 nanoparticles have been developed as a drug-delivery carrier. The resultant Dox loaded CMC-Fe_3O_4 nanocarriers were approximately 15 nm in diameter with a spherical shape and high encapsulation efficiency. *In vitro* studies of the drug release pattern showed a sustained release of Dox over a period of 144 hours at acidic, mild acidic and neutral conditions where the pHs 3.6, 5.5 and 7.4, respectively. Among these different pH values, the CMC-Fe_3O_4 nanocarriers exhibited higher Dox release profile at acidic medium (pH 3.6). On the other hand, due to the superparamagnetic property of the nanocarriers, they can be used as T1 contrast agent for MRI. As a result, dual function CMC-Fe_3O_4 nanocarriers with combined characteristics of MRI and controlled drug delivery could be of high clinical significance in the treatment of cancer.

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