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Original Research

# Core–shell drug carrier from folate conjugated chitosan obtained from prawn shell for targeted doxorubicin delivery

**Md. Sazedul Islam[1] · Papia Haque[1] · Taslim U. Rashid[1] · M. Nuruzzaman Khan[1] · Abul K. Mallik[1] · M. Nazrul I. Khan[2] · Mala Khan[3] · Mohammed Mizanur Rahman[1]**

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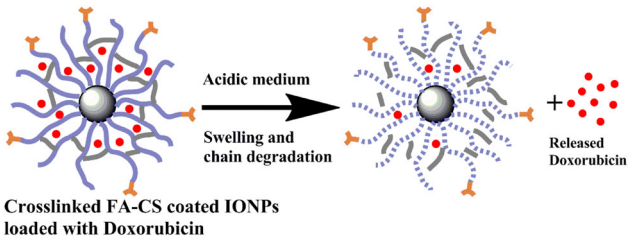
**Abstract** A multifunctional drug carrier with dual targeting (magnetic and folate-receptor) and pH sensitive core-shell hybrid nanomaterial has been developed to carry an anticancer drug doxorubicin.Superparamagnetic iron oxide nanoparticles (IONPs) were used as core of the carrier and cross-linked folate conjugated chitosan (FA-CS) was acted as shell in which doxorubicin was physically entrapped. Transmission electron microscopy (TEM) analysis confirmed the average particle size of IONPs and FA-CS coated IONPs 8.2 and 15.4 nm respectively. Magnetic measurement indicated that both the IONPs and FA-CS coated IONPs were superparamagnetic at room temperature with a magnetization value 57.72 and 37.44 emu/g respectively. At pH 5.8 (malignant tissue) showed a burst release of 30.05% of the doxorubicin in the first 4 h followed by a sustained release of 88.26% of drug over 72 h. From these results it is expected that doxorubicin loaded nanoparticles can be a promising drug carrier for the treatment of solid tumors with the ability to reduce toxic side effects of drugs by selective targeting and sustained release.

**Graphical abstract**




## 1 Introduction

The efficacy of many drugs especially anticancer drugs is often limited by their potential to reach the site of therapeutic action. Depending upon the physicochemical properties of the drug, only small amount of the administrated dose may reach the target site while the remaining amount distributes in the body which affects the normal tissues and gives rise to side effects [1]. Doxorubicin, an anticancer drug, is widely used in the treatment of numerous cancers including breast, ovarian, bladder, lung, thyroid, and stomach cancers etc. but they are highly toxic especially toxic to the heart and the kidneys, which limits its therapeutic applications [2, 3]. Moreover the way of its delivery (intravenous) into the body promotes the toxic action. Hence, novel drug delivery systems are urgently needed. Nanoparticles based targeted drug delivery system is a promising alternative to overcome the aforementioned limitations of classical chemotherapy. In an ideal targeted drug delivery system carrier nanoparticles would be directed to the tumour tissue and selectively release

✉ Papia Haque
papiahq@yahoo.com

✉ Mohammed Mizanur Rahman
mizanur.rahman@du.ac.bd

[1] Department of Applied Chemistry and Chemical Engineering, Faculty of Engineering and Technology, University of Dhaka, Dhaka 1000, Bangladesh

[2] Material Science Division, Atomic Energy Centre, Bangladesh Atomic Energy Commission, Dhaka 1000, Bangladesh

[3] Designated Reference Institute for Chemical Measurements (DRICM), Bangladesh Council of Scientific and Industrial Research (BCSIR), Dr. Kudrat-e-Khoda Road, Dhaka 1205, Bangladesh

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therapeutic molecules. Delivering therapeutically adequate doses of the pharmaceutical agent to specific sites in the body promotes a drug action where required and limits its effects elsewhere, which potentially results in a significant decrease of side effect [4].

Magnetic nanoparticles e.g., superparamagnetic iron oxide nanoparticles (SPIONs) which can be targeted to tumour site by applying external magnetic field, have gained importance in targeted drug delivery systems in recent years [5]. The SPIONs can be coated with biocompatible polymers e.g., chitosan to give a core shell structure in which anti-cancer drugs can be loaded [6]. The physical entrapment of doxorubicin in this core-shell carrier might be a good alternative to such traditional forms of the drug-like liposomes and micelles [7, 8].

Chitosan has important structural and biological properties, which include the fiber like structure, cationic character, solubility in slightly acidic medium and presence of reactive primary amine groups to which targeting ligand e.g., folic acid can be covalently attached [9]. Folic acid is a low molecular weight vitamin and one of the most commonly used molecules for active targeting of nanocarriers as an anticancer strategy because of its high binding affinity to folate receptors (FR) which are frequently over-expressed in human cancer cells [10]. Previous studies demonstrated that nanoparticles conjugated with folic acid were capable of improving chemotherapeutic efficacy and avoiding side effects on normal tissues due to their specific binding to FR-positive tumors and efficient cellular internalization through FR-mediated endocytosis [11, 12]. Since chitosan is soluble in slightly acidic medium [13] and it was reported that the pH of the malignant tissues is slightly acidic [14], so a pH responsive drug release will result.

To this end, we synthesized a novel dual targeting core–shell drug carrier with magnetic targeting, pH sensitivity and folate receptor (FR) targeting to deliver doxorubicin. Superparamagnetic IONPs was synthesized by co-precipitation method and used as the core of the carrier. Folic acid was covalently attached to chitosan by a carbodiimide-mediated coupling to the reactive amino group of chitosan and this folate–chitosan conjugate was used to coat the SPIONs core followed by cross-linking with sodium tripolyphosphate (TPP) to give the final core-shell structure of the carrier. An anticancer drug doxorubicin was physically entrapped in the shell of the drug with good loading efficiency. The drug release profile was also investigated which showed a pH responsive and sustained release behaviour. The novelty of this work is imparting a dual targeting character in the drug delivery system along with pH responsive release of drug which will significantly reduce toxic side effects by selective targeting and sustained release.

## 2 Experimental

### 2.1 Materials

All the chemicals used were of the highest quality available and used without further purification. Ferric chloride ($FeCl_3.6H_2O$, >98%) was purchased from Daejung Chemicals and Metal Co., Ltd, (Gyeonggi-do, Korea). Ferrous chloride ($FeCl_2.4H_2O$, >98%), Folic acid (>98%), and Dimethylsulfoxide (DMSO, >99%) were purchased from Loba Chemie Pvt. Ltd., (Mumbai, India). N-hydroxysuccinimide (NHS, >98%), N,N′-Dicyclohexylcarbodiimide (DCC, >99%), and Triethylamine (TEA, >99%) were purchased from Sigma-Aldrich (St Louis, USA). Sodium tripolyphosphate was purchased from E. Merck, (Darmstadt, F.R. Germany). Diethylether (>98%) was purchased from BDH (England). Doxorubicin hydrochloride was purchased from Beacon pharmaceuticals limited (Mymensingh, Bangladesh). Chitosan was extracted from prawn shell. Prawn shells were purchased from local prawn hatchery (Satkhira, Bangladesh).

### 2.2 Synthesis of superparamagnetic iron oxide nanoparticles

IONPs were synthesised by co-precipitation method after consulting the literature described by Maria Cristina Mascolo et al. with slight modification [15]. 0.01 mol of $FeCl_2 \bullet 4H_2O$ and 0.02 mol of $FeCl_3 \bullet 6H_2O$ were dissolved in 100 mL degassed deionized water and added into a 250 mL three-neck flask, which was immersed in a water bath at 25 °C. 0.1 moles of NaOH were dissolved in 100 mL degassed deionized water. The reaction solution was mechanically stirred at 800 rpm while nitrogen gas flowed into the flask to avoid the oxidation of precipitated magnetite ($Fe_3O_4$) into maghemite ($\gamma$-$Fe_2O_3$). Then 100 mL of 1M NaOH was chargedinto the reactor and stirred for 3 h upto crystal growth. The nanoparticles were then separated magnetically and the solution was decanted, allowing the particles to be washed with degassed deionized water. This procedure was repeated until the pH of the solution reached 7, and then the particles were separated by a permanent magnet and dried in a vacuum desiccator.

### 2.3 Extraction of chitosan from prawn shell

Chitosan was extracted from prawn shell using a modified method of Rashid et al. [16]. The prawn shells were first washed with distilled water for 1 h at 50–60 °C and then dried in an oven at 100 °C followed by crushing in a milling machine. The crushed shells were treated with 4% (w/w) NaOH in 1:16 ratio (w/w) at 70–90 °C for 3 h to remove the proteins. The mixture was washed with distilled water and

placed in an oven at 105 °C for 24 h. The dried sample was treated with 1N HCl at a ratio of 1:16 (w/w) with constant stirring for 3 h. The mixture was washed with distilled water and again dried in oven at105 °C for 24 h and thus chitin was obtained. The chitin was then treated with 50% NaOH solution at a ratio of 1:20 (w/w) at 90–100 °C for 4 h, washed with distilled water to make it neutral and dried in an oven under vacuum to get the product, chitosan.

### 2.4 Conjugation of folic acid with chitosan

The folate–chitosan conjugate was prepared by a two-step method described by Yuangang Zu et al. with slight modification [17, 18]. In the first step the folic acid was activated by reacting it with N-hydroxysuccinimide (NHS) to form N-hydroxysuccinimide ester of folic acid (NHS-FA) and in the second step NHS-FA reacted with chitosan to form folate–chitosan conjugate as shown in Scheme 1.

3 g of folic acid was dissolved in 60 mL Dimethyl sulfoxide (DMSO) containing 1.5 mL Triethylamine (TEA); then 2.82 g N,N′-Dicyclohexylcarbodiimide (DCC) and 1.56 g NHS were added in the mixture. The mixture was stirred for 12 h at room temperature. After the removal of insoluble side product dicyclohexylurea by filtration, the filtrate was poured into an ice-cold anhydrous ether solution containing 30% acetone, centrifuged, and washed twice. Finally, after vacuum drying NHS-FA, a delicate light yellow solid powder, was obtained.

To prepare folate–chitosan conjugate, NHS-FA (1.50 g) was dissolved in DMSO (150 mL) in an ultrasonication bath. Thereafter, chitosan (CS) (1.00 g) was added into the solution, and stirred for 4 h at 60 °C. The folate–chitosan conjugate was deposited after centrifuging (6000 rpm, 15 min) at room temperature, and free NHS-FA was washed off by DMSO. Finally, the product was washed with deionized water for several times to remove residual DMSO and FA-CS was obtained by freeze-drying.

### 2.5 Coating of iron oxide nanoparticles by folate conjugated chitosan

The IONPs were coated by folate–chitosan conjugate according to the method described by Chia-Hung Kuo et al. with some modification [20]. 0.5 g of folate conjugated chitosan was dissolved in 50 ml of 1% (v/v) acetic acid. 1 g of IONPs were added into the solution and mixed with ultrasonicator for 10 min. Then 12.5 ml of 1 mg/ml sodium tripolyphosphate solution was added into the mixture as a crosslinker to enhance colloidal stability and stirred vigorously by mechanical stirrer for 30 min to ensure the uniform coating of the folate conjugated chitosan onto the nanoparticles. 25 ml of 1 N NaOH was added slowly to the suspension to precipitate the coated nanoparticles. The resulting FA-CS coated IONPs were recovered from the suspension by applying a magnet followed by washing with deionized water for several times until the pH reached 7.0 and then the final core–shell FA-CS coated IONPs were obtained by freeze-drying.

### 2.6 Loading of doxorubicin on FA-CS coated IONPs

Doxorubicin was loaded on FA-CS coated IONPsby the method described by Gozde Unsoy et al. [21]. 5 mg of FA-CS coated IONPs were dispersed in 5 mL aqueous doxorubicin solution of different concentrations (100, 200, 300, 400, 500, 600 and 1000 µg/mL) in order to obtain the highest loading efficiency. The mixture of FA-CS coated IONPs in doxorubicin was shaken in an orbital shaker at 90 rpm for 24 h at room temperature to facilitate doxorubicin uptake. Then, Doxorubicin loaded nanoparticles were separated by magnetic decantation. The loading efficiency was quantified by measuring the absorbance values of unloaded drug in the supernatant with a UV-spectrophotometer at 481 nm. The percentage of loading efficiency was calculated by the following equation [22].

$$\text{Loading efficiency } \% = \frac{\textbf{Initial drug conc.} - \textbf{Drug conc. in supernatant}}{\textbf{Initial drug conc.}} \times 100\%$$

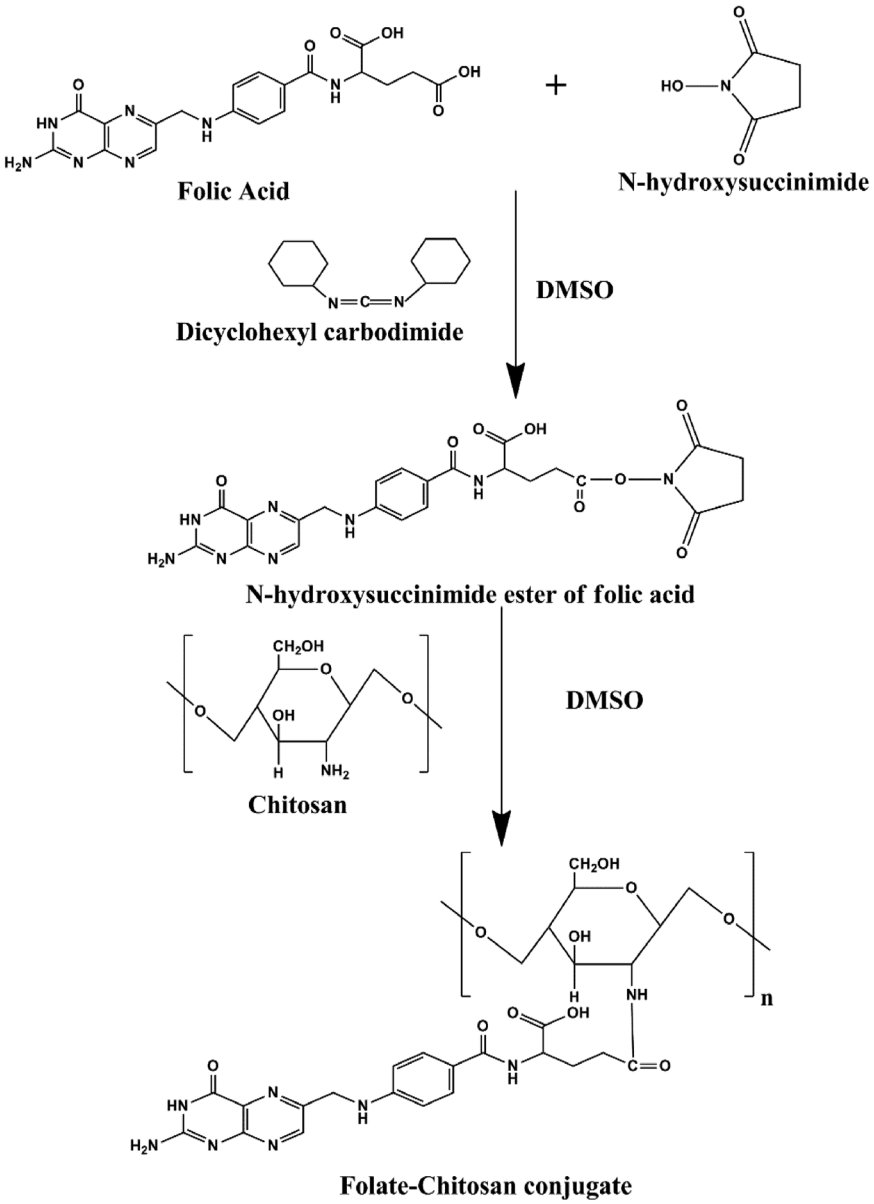
### 2.7 In vitro drug release study

The doxorubicin release profile was determined by the most widely used ‘Sample and Separate’ method described by Jadhav et al. [23]. The drug release responses of the doxorubicin loaded FA-CS coated IONPs carrier were studied in phosphate buffer solution at the physiological temperature of 37 °C and at pH 5.8 (malignant tissue) and 7.4 (blood) [14]. 10 mg of drug loaded nanomaterial was placed in the test vessel containing the dissolution medium (900 ml of phosphate buffer) maintained at 37 °C and 100 rpm. Aliquots, 5 ml were withdrawn every time up to 72 h and the amount of Doxorubicin in the buffer solution was quantified using UV–Vis spectrophotometry. The same amount of fresh phosphate buffer was used to replace the amount withdrawn from the dissolution media.

### 2.8 Characterization

Fourier transform infrared (FT-IR) spectra of the samples dispersed in KBr pellets were obtained using a FT-IR spectrophotometer (Model 8400S, Shimadzu Corporation, Japan) in the range of 4000–400 $cm^{-1}$, resolution: 4 $cm^{-1}$; no. of scans: 30 times. The thermal properties of materials were

**Scheme 1** Synthesis of folic acid conjugated chitosan [19]




investigated by thermo gravimetric analysis (TGA). TGA was performed in alumina cell under nitrogen atmosphere from room temperature to 800 °C at a rate of 10 °C/min with a TGA-50 instrument (Shimadzu Corporation, Japan). X-ray powder diffraction (XRD) analysis was carried out in Rigaku Ultima IV X-ray diffractometer (Rigaku Americas Corporation, Japan.) using Cu-Kα radiation with a scan speed of 5°/min ranging from 20° to 80°.

Magnetic measurements were carried out at room temperature using a vibrating sample magnetometer (VSM) VSM02 (Hirst Magnetic Instruments Ltd., U.K.).

The JEOL JSM-7600F field emission scanning electron microscope (JEOL Ltd. Tokyo, Japan) was used to observe the surface morphology of prepared nanoparticles with 100,000× magnification and 5 KV accelerating voltage. The particle size and their distribution was analysed by field emission transmission electron microscope HF-3300 (Hitachi, Ltd., Tokyo, Japan.) operating at 300 kV. Samples were prepared by placing a drop of well dispersed particle solution onto the carbon-coated copper grid and allowing it to dry at room temperature.

For the study of drug release profile from the drug loaded nanomaterial, a United States Pharmacopeia (USP) Type-I (basket) dissolution tester DIS 8000 (Copley Scientific, United Kingdom) was used. The UV-1800 (Shimadzu Corporation, Japan) spectrometer was used for the determination of drug concentration in solution. A wavelength of 481 nm was used for the drug doxorubicin.

## 3 Results

### 3.1 Characterization of chitosan, IONPs and FA-CS coated IONPs

The degree of deacetylation as determined by FTIR spectrum [24] and the viscosity average molecular weight of chitosan was found to be 86.16% from 155.245 KDa respectively which is sufficiently low to be used in biomedical application especially in drug delivery.

Figure 1 shows the FTIR spectra of (a) IONPs, (b) folate conjugated chitosan, (c) chitosan, and (d) FA-CS coated IONPs. The two distinct absorption peaks observed in the FTIR spectrum of IONPs (Fig. 1a) at 464.8 and 570.9 $cm^{-1}$ were attributed to the stretching vibration of Fe–O bonds in the octahedral and tetrahedral sites [25]. In case of IR spectrum of chitosan (Fig. 1c), the absorption peaks in 1654.9 and 1595.1 $cm^{-1}$ belong to the C=O stretching vibration of amide I and N–H bending of primary amines respectively, and the wide absorption band in 3452.5 $cm^{-1}$ is O–H stretching overlapping the N–H stretching of primary amine; the strong absorption peaks in 1089.7 $cm^{-1}$ belongs to the vibration of C–O–C bridge stretching. Significant difference is observed between the IR spectra of chitosan and Folic acid conjugated chitosan (Fig. 1b). The absorption in 1595.1 $cm^{-1}$ disappears as $-NH_2$ group of chitosan reacts with COOH group of folic acid and two new peaks appear in 1631.1 $cm^{-1}$ (overlapped with the shifted absorption peak 1654.9 $cm^{-1}$ of chitosan) and 1018.4 $cm^{-1}$, which belong to the vibration of newly formed C–N [19]. The new absorption peak at 1481.3 $cm^{-1}$ is due to the pteridine ring stretching of folic which also confirms the binding of folic acid to chitosan.

IONPs were also characterized by XRD for structural determination and estimation of crystallite size. All the peaks of XRD patterns (Fig. 2) were analysed and indexed after comparing with magnetite standards (JCPDS card no. 19-0629) [26]. The peaks indexed at $2\theta = 30.30°$, 35.40°, 43.21°, 53.44°, 57.03°, 62.52° as planes (220), (311), (400), (422), (511) and (440) corresponded to a cubic unit cell, characteristic of a cubic spinel structure [27]. Crystallite size measurements were determined from the full-width at half maximum (FWHM) of the strongest reflection of the (311) peak, using the Scherrer approximation [15] the crystallite size of pure $Fe_3O_4$ and FA-CS coated IONPs were found to be 7.79 and 7.07 nm, respectively.

Magnetic properties of IONPS and FA-CS coated IONPs were characterized by vibrating sample magnetometer (VSM). The magnetic hysteresis curves are shown in Fig. 3a uncoated IONPs and (b) FA-CS coated IONPs. The saturation magnetization of the uncoated IONPs was 57.72 emu/g but in case of FA-CS coated IONPs it was 37.44 emu/g. This decrease in saturation magnetization was due to the existence of the large amount of diamagnetic chitosan in the FA-CS coated IONPs [28].

The thermogravimetric analysis (TGA) of uncoated IONPs and FA-CS coated IONPs provide qualitative and

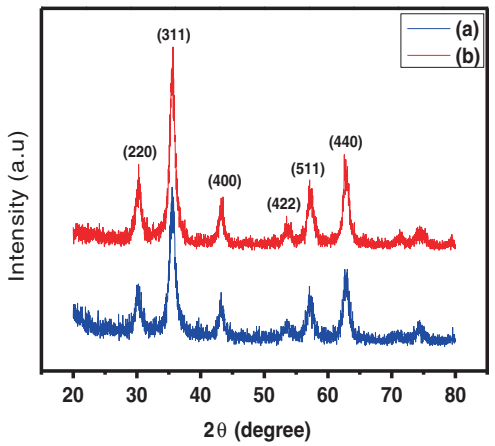



**Fig. 2** XRD pattern of **a** FA-CS coated IONPs and **b** IONPs

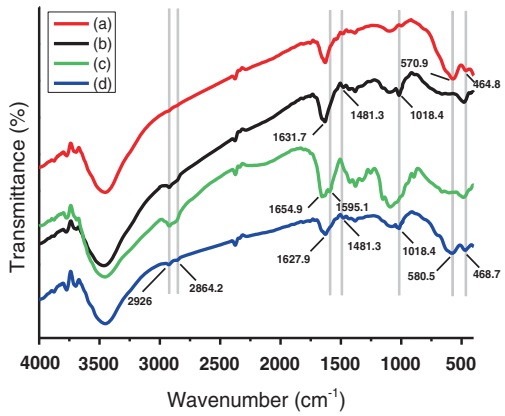



**Fig. 1** FTIR spectra of **a** IONPs, **b** folate conjugated chitosan, **c** chitosan, and **d** FA-CS coated IONPs

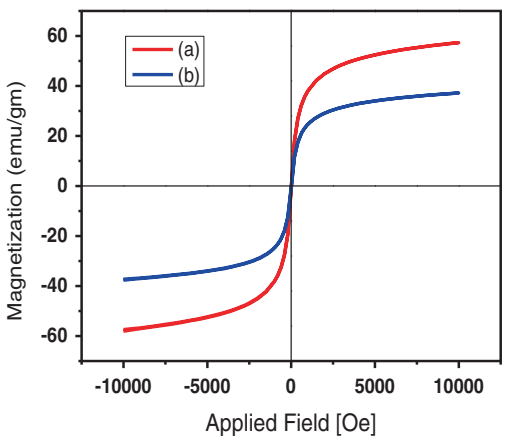



**Fig. 3** Magnetization curve of **a** IONPs and **b** FA-CS coated IONPs

quantitative information about the volatile components of the nanoparticles. The TGA curve (Fig. 4b) shows that the weight loss of uncoated IONPs over the temperature range from 28.33 to 800 °C is about 2.61%. This might be due to the loss of residual water in the sample [29]. From the TGA curve of FA-CS coated IONPs (Fig. 4a), it was found that the initial weight loss below 150 °C was due to the removal of physically and chemically adsorbed water [30]. The principle chains of folic acid conjugated chitosan began to degrade at about 230 °C and the final temperature of decomposition was around 500 °C. There was no significant weight change from 500 to 800 °C, implying the presence of only IONPs within the temperature range. From the percentage weight loss in the TGA curve, the average mass content of folic acid conjugated chitosan in nanoparticles by TGA was found to be about 34.08%.

In Fig. 5, the morphology and particle size of IONPs and FA-CS coated IONPs. The SEM image of IONPs (Fig. 5a) revealed the presence of nearly monodispersed particles with nearly spherical in shape. The image of FA-CS coated IONPs (Fig. 5b) clearly shows the coating of folic acid conjugated chitosan over iron oxide nanoparticles and the size also increased due touniform coating with nearly spherical shape and supports the final core–shell structure of the nanomaterial.TEM image of IONPs (Fig. 5c) reveals the parallel lattice fringes clearly visible at almost all the nanoparticles. The lattice spacing seen in the lattice fringe of the nanoparticles indicates the crystallinity and structural uniformity of the sample [31]. The average size of the IONPs was about 8.2 nm while the average size of FA-CS coated IONPs (Fig. 5d)was about 15.4 nm which was larger than uncoated IONPs. The enlargement of the nanoparticles size indicated the formation of the chitosan layer over IONPs.

### 3.2 Doxorubicin loading on FA-CS coated IONPs

In order to obtain the highest loading efficiency, FA-CS coated IONPs were dispersed in aqueous doxorubicin solution of different concentrations (100, 200, 300, 400, 500, 600 and 1000 µg/mL). The loading efficiency was quantified by measuring the absorbance values of unloaded drug in the supernatant by suitable dilution with a UV-spectrophotometer at 481 nm compared to the standard calibration curve of doxorubicin (Fig. 6a). The loading efficiencies of 100, 200, 300, 400, 500, 600 and 1000 µg/mL doxorubicin on core–shell nanomaterial were 97.88, 94.83, 93.32, 91.82, 76.56, 67.81, 44.56% (Table 1.). The optimum loading efficiency was 91.82% obtained with doxorubicin concentration of 400 µg/mL (Fig. 6b).

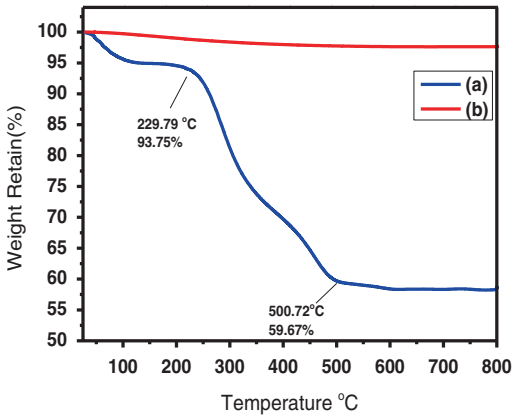



**Fig. 4** TGA of **a** FA-CS coated IONPs and **b** IONPs

### 3.3 In vitro drug release

In vitro drug release study of FA-CS coated IONPs demonstrated an initial burst release of Doxorubicin followed by a sustained release up to 72 h. The burst release was detected in the first 4 h as 30.05% for pH 5.8 and 28.92% for pH 7.4. After this initial burst effect, a slower and controlled release occurred throughout the incubation period of (Fig. 7). A maximum of 88.26% of adsorbed drug at pH 5.8 and 39.49% of adsorbed drug at pH 7.4 were released in 72 h from the core–shell which indicated pH responsive and sustained release of drug.

## 4 Discussion

The aim of this study was to develop a dual-targeting core–shell drug carrier having the ability of magnetic targeting, folate receptor (FR) targeting and pH sensitive sustained drug release.All characteristic peaks of IONPs and folate conjugated chitosan were present in the FTIR spectrum of FA-CS coated IONPs (Fig. 1d) proving that magnetite nanoparticles were successfully coated by folic acid conjugated chitosan. As there are no new peaks except those for IONPS and folate conjugated chitosan found in FTIR spectrum of FA-CS coated IONPs it can be assumed that the coating process was governed by electrostatic interaction between cationic chitosan and negatively charged IONPs.

After comparing with magnetite standards (JCPDS card no. 19-0629) [26], no diffraction peaks other than those of $Fe_3O_4$ were observed in the X-ray diffraction (XRD) pattern, indicating that highly phase-pure $Fe_3O_4$ particles were obtained. The peaks shown in the XRD pattern of the prepared sample are sharp and intense, indicating good crystallinity of $Fe_3O_4$. FA-CS conjugates are more likely to form amorphous rather than crystal structure [19]. All the

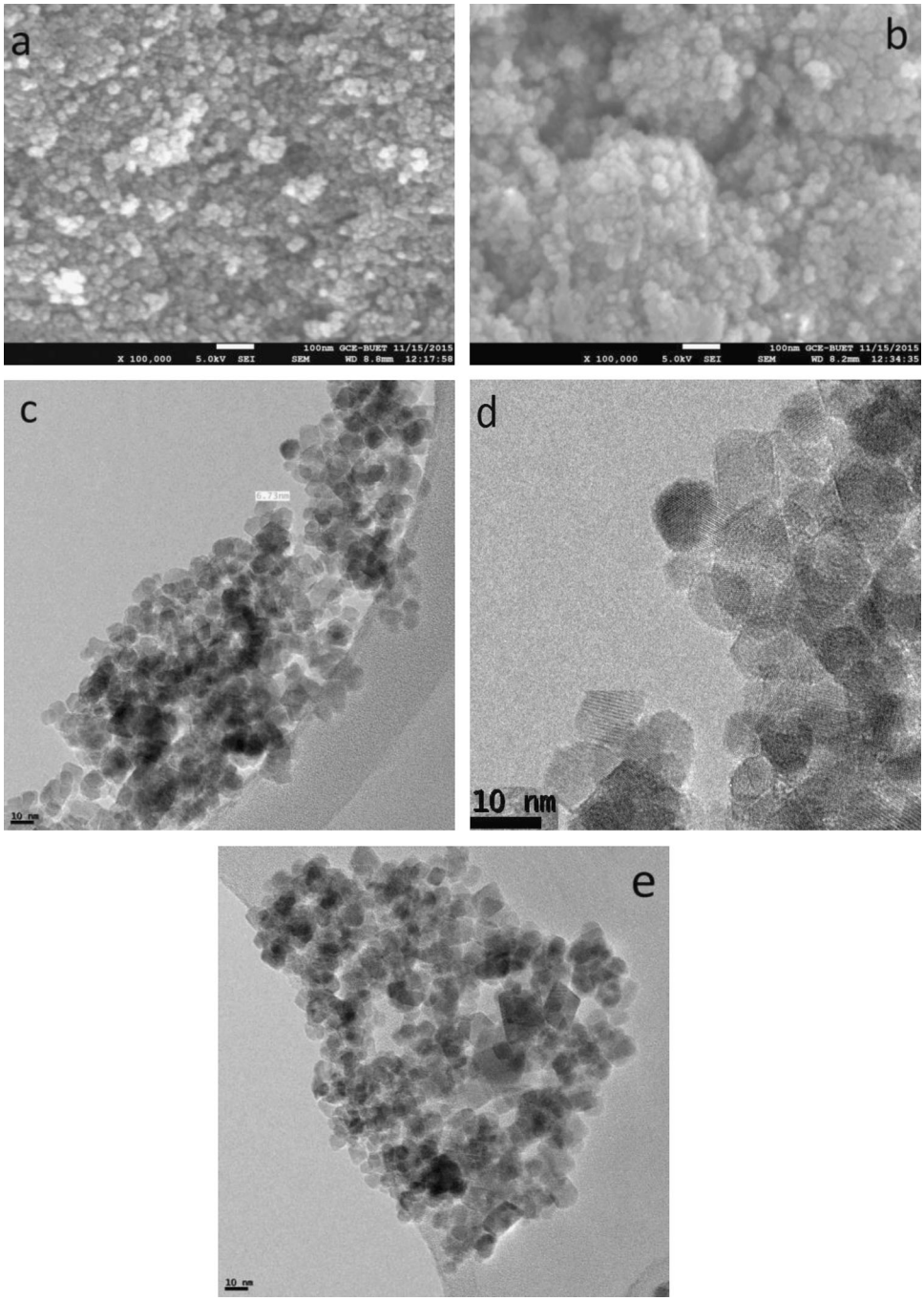



**Fig. 5** SEM image of **a** uncoated IONPs, **b** FA-CS coated IONPs and TEM image of (**c**), uncoated IONPs, **d** magnified image of uncoated IONPs and **e** FA-CS coated IONPs

characteristic peaks for $Fe_3O_4$ were observed in the FA-CS coated IONPs and these results indicated that the modification did not change the crystal structure of the $Fe_3O_4$ nanoparticles. The weaker diffraction lines of FA-CS coated IONPs compared with $Fe_3O_4$ nanoparticles indicated that the $Fe_3O_4$ nanoparticles were covered by amorphous folic acid conjugated chitosan polymer [32].

In the VSM data, no coercivity or remanence was observed in the magnetic hysteresis curves of the uncoated and coated IONPs suggesting the superparamagnetic properties of both samples. This can be ascribed to the small size of nanoparticles which were smaller than the superparamagnetic critical size (25 nm) [33]. This superparamagnetic property enables the drug carrier to be manipulated by external magnetic field to the desired place of drug delivery. The saturation magnetization of FA-CS coated IONPs was lower than uncoated IONPs which was due to the existence of the large amount of diamagnetic chitosan in the FA-CS coated IONPs [28].

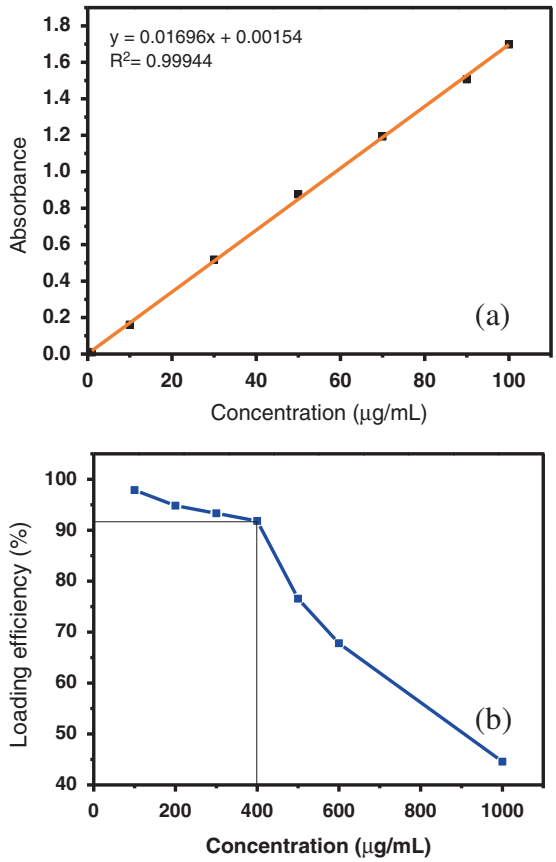



**Fig. 6** **a** Standard calibration curve of doxorubicin measured at 481 nm using UV–Visible spectroscopy and **b** Determination of optimum loading efficiency

One of the main findings in this study was that, anti-cancer drug doxorubicin can be successfully loaded into the folate conjugated chitosan matrix and in case of drug release it showed sustained and pH responsive release. Folate conjugated chitosan cross-linked with sodium tripolyphosphate provides some void spaces. The anticancer drug doxorubicin was physically entrapped in these void spaces (Fig. 8) [21]. Initially, with lower concentrations of drug, the doxorubicin was almost completely entrapped leading to higher loading efficiencies up to drug concentration of 400 µg/mL. Then a sharp fall in efficiency occurred which indicated the saturation of drug loading on the shell of the nanomaterial i.e. there were no more spaces in the chitosan structure to entrap drug. Drug release mechanisms of chitosan coated nanoparticles involve three consecutive steps i.e. (i) desorption, (ii) diffusion, and (iii) matrix degradation [34, 35]. The initial rapid release, characterized as "burst effect", occurs by desorption of Doxorubicin, localized on the surface of nanoparticles. After this initial rapid release, a slower and controlled release occurred throughout the incubation period of 72 h caused by diffusion of drug through the matrix and swelling and degradation of chitosan shell in the acidic medium.

**Table 1** Loading performance of FA-CS coated IONPs for doxorubicin at different concentrations (100–1000 µg/mL)

| Doxorubicin concentration (µg/mL) | Doxorubicin concentration (µg/mL) after 24 h | Loaded amount of doxorubicin (µg/mL) | Loading efficiency (%) |
|---|---|---|---|
| 100 | 2.12 | 97.88 | 97.88 |
| 200 | 10.34 | 189.66 | 94.83 |
| 300 | 20.04 | 279.96 | 93.32 |
| 400 | 32.73 | 367.27 | 91.82 |
| 500 | 117.18 | 382.82 | 76.56 |
| 600 | 193.16 | 406.84 | 67.81 |
| 1000 | 554.43 | 445.57 | 44.56 |

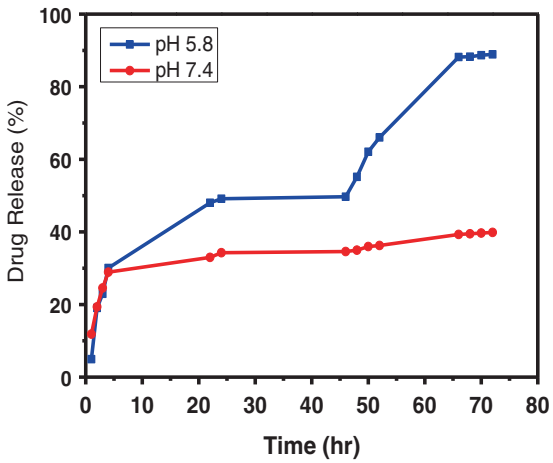



**Fig. 7** Drug release profile of doxorubicin from drug carrier in phosphate buffer solution at pH 5.8 and pH 7.4

## 5 Conclusion

In the present study, we developed a novel core-shell drug carrier to carry an anti-cancer drug, doxorubicin. The core of the nanomaterial was superparamagnetic iron oxide nanoparticles and the shell was composed of folic acid conjugated chitosan. Folate-chitosan coating around the magnetic nanoparticles reduces the agglomeration, provides internal cavities for loading of doxorubicin and imparts FR-targeting specificity. TGA results indicated that the folate–chitosan content of the coated nanoparticles was about 34.08%. The drug carrier showed good loading efficiency of doxorubicin and the optimum loading efficiency obtained was 91.82% with drug concentration of 400 µg/mL. The release profile of doxorubicin from this drug carrier at pH 5.8 (malignant tissue) shows a burst release in the first 4 h followed by a sustained release

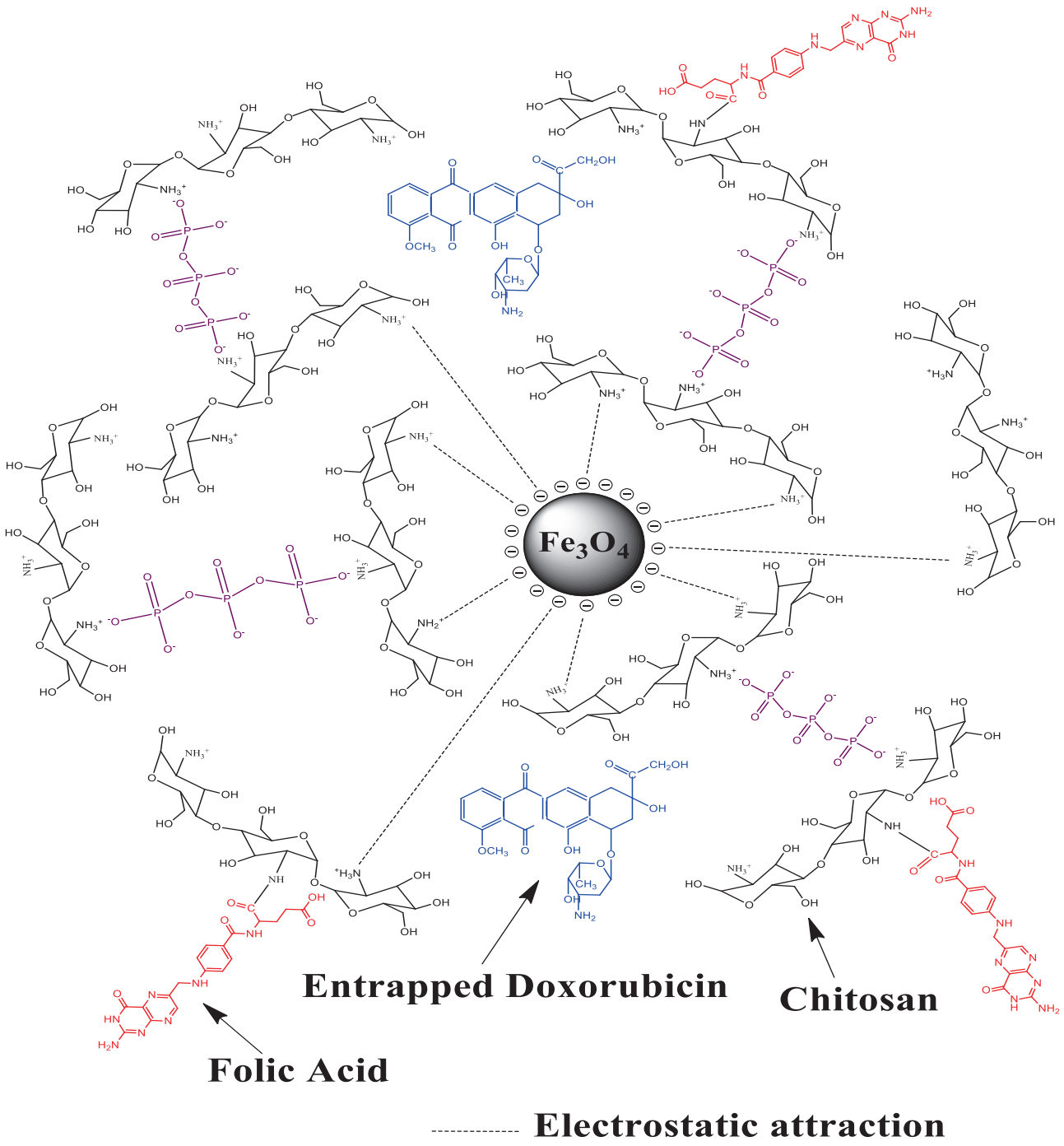



**Fig. 8** Schematic illustration of core-shell nanomaterial loaded with drug

over 72 h. The drug carrier can be directed to the desired place by applying external magnetic field followed by selective binding with the folate receptors. It can be envisioned that this core–shell drug carrier may also be used to encapsulate other anticancer drugs (such as Paclitaxel) to obtain synergistic effects from multidrug therapy. This willopenup new possibilities for anticancer therapy of solid tumors.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no competing interest.

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