Nanomed Res J 3(1): 31-36, Winter 2018

ORIGINAL RESEARCH ARTICLE

Design and performance investigation of electrospun PVA nanofibers containing core-shell nanostructures for anticancer drug delivery

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ARTICLE INFO

Article History:
Received 6 December 2017
Accepted 3 February 2018
Published 15 February 2018

Keywords:
Core-Shell Nanostructure
Daunorubicin
Drug Release
Electrospun Nanofibers
Magneticnanocarrier

ABSTRACT

Objective: The purpose of this work was design and performance investigation of a nanocarrier based on magnetic nanofibers containing core-shell nanostructuresfor anticancerdrug delivery of daunorubicin (DAN) by measuring their drug release at different pH values.

Methods: Fe_3O_4 nanoparticles and Fe_3O_4@SiO_2core-shell nanostructures were synthesized through coprecipitation and Stöber methodrespectively. The composite nanofibers of polyvinyl alcohol containing core-shell nanostructures and anticancer drug of daunorubicinwere fabricated by electrospinning method. The nanostructures were characterized bySEM, XRD,VSM and FTIR techniques. The drug release was investigated by UV-Vis spectrophotometer at different pHs.

Results: The results is shown that in vitro drug release at pH= 6.0 is promisingly more and faster than drug release at pH= 7.4. The fitted equation of release curves is corresponded to Peppas model.

Conclusions: It can be concluded that the proposed nanocarrier is capable of responding to pH changes, that is an advantage in the targeted delivery of the drug. Also, this method has the advantages of magnetic sensitivity, high drug loading capacity and sustained release.

How to cite this article
Kavyanifar S, Shamspur T, Fathirad F, Mostafavi A. Design and performance investigation of electrospun PVA nanofibers containing core-shell nanostructures for anticancer drug delivery. Nanomed Res J, 2018; 3(1): 31-36.
DOI: 10.22034/nmrj.2018.01.005

INTRODUCTION

Today, Cancer is on the rise. So, striking effort has created for improvement of the cancer treatments. Chemotherapy and radiotherapy are the basic clinical treatment method [1-4]. The drugs of chemotherapy have high cytotoxicity and oral and intravenous administration lead to damage in human body [5,6]. Drug delivery systems are useful strategies for administering more performance and safe treatments in real scenarios [7,8]. Different approach is available for this. But targeted drug delivery in the presence of magnetic nanostructures is proposed as an efficient method [9]. This is due to good biosafety, affordability of needed materials and ability of targeted delivery of interest drugs [10,11]. The core-shell type nanostructure consistsa core (inner material) and a shell (outer layer material) [12]. Each core and shell can have properties such as metal conductivity, semiconductivity, magnetism, etc. Core-shell nanostructures are important from economic point of view, because valuable materials can be covered by a cheap material and reduce its consumption[13].Coating on the core in core-shell structures can increase surface levels, improve surface properties, increase performance and

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reduce the cost of consuming expensive materials. Creating an appropriate organic or inorganic coating on the surface of the magnetic core increases the lifespan of these particles for drug delivery [14].Drug loaded nanofibers based on a biocampatible polymer can be constructed by co-dissolving solutions [15,16].

In this work, we designed and prepared a biocompatible nanocarrier based on electrospun nanofibers containing magnetic core-shell nanostructures. The nanocarrier performance for DAN delivery and drug releasetoward cancer cells was evaluated at two different pHs. At last, the kinetic of drug release was investigated by different methods and equations.

MATERIALS AND METHODS

A Sonorex RK255 ultrasonic water bath was used for Fe_3O_4 synthesis. The electrospinning system was purchased from Fanavaran Nano Meghyas (Fnm-ES1000, Tehran, Iran).A Shimadzu system FT-IR 8400 spectrophotometer using KBr pellets was used to record spectra.Product XRD data was recorded by a Rigaku D-max C III, X-ray diffractometer using Ni-filtered Cu K_α radiation (Tokyo, Japan). Magnetic properties of the products were examined using a vibrating sample magnetometer (VSM) at room temperature. A Varian scanning spectrophotometer (CARY 50 Conc) was employed (Agilent, American). The samples were characterized with SEM (Hitachi S-9220) with gold coating.

Iron (III) chloride hexahydrate ($FeCl_3.6H_2O$), iron (II) sulfate dihydrate ($FeSO_4.2H_2O$) and TEOSwere purchased from Sigma-Aldrich. PVA and ammonium hydroxide (NH_4OH) were purchased from Merck. Anticancer drug of daunorubicin was prepared from Pharmacia Italia S.P.A.

Preparation of core-shell nanostructure

Magnetic nanoparticles as core were synthesized according to our previous work [17].$FeCl_3.6H_2O$ and $FeSO_4.2H_2O$were dissolved in distilled water under N_2 atmosphere. Then, NH_3 20% was added to the solution under ultrasonic waves.The precipitate was collected using a magnet and washed several times with distilled water and ethanoland was dried. The Fe_3O_4@SiO_2nanoparticles were synthesized through the Stöber method[18].Ethanol solution containing Fe_3O_4powder was ultrasound for half an hour. Then, 5 mL of ammonia was added to the solution. 20 mL of diluted TEOS in ethanol was dropwise added to the previous step solution and the resulting mixture was stirred at room temperature. The magnetic Fe_3O_4@SiO_2nanoparticles were collected by magnetic separation and washed with water and ethanol and were dried at 24C for 48 h.

Design and preparation of DAN-loaded nanocarrier

The polymer solutions for electrospinning process were prepared by dispersing 10mg Fe_3O_4@SiO_2 nanostructures in 5 mL DAN. After sonication for 15 min, the suspension was added to the various concentration of PVA water solution (5-14 %w/v)at the room temperature. These solutions were electrospuned according to our previous work [19].The composite solutions with different concentrations were placed in a 5 mL syringe attached to a needle with 18 gauge (0.216 mm) diameter. The syringe was fixed in 15 cm distance of the collector which was covered with aluminum foil. The voltage of 20±0.1 and solution flow of 0.5 mL min-1 was applied for fibers preparation on the foil.

Investigation of drug release from the DAN-loaded nanocarrier

For investigation of targeting based on pH, the releasing of DAN from targeted nanofibers was tested at pH of 7.4 and 6.0 (equal blood and tumor environment) at 37±0.5°C. The DAN-loaded nanocarrier was transferred to a dialysis bag and placed in 20 mL of PBS. In each of the selected time intervals, 3.0 mL from the solution was removed and subjected to UV-Vis assay at 480 nm to determine the daunorubicin content, and the amount of released drug was calculated.

RESULTS AND DISCUSSION

Nanostructures Characterization

Fig. 1 compares the FTIR spectra of Fe_3O_4 nanoparticles with Fe_3O_4@SiO_2 nanostructures. The characteristic band of Fe-O at573 cm^{-1} in Fig.1a was indicative of Fe_3O_4synthesis. The peaks at1618 and 3389 cm^{-1} were the characteristic of the bending andstretching vibration of OH.The existence of a characteristic band ofSi-O and bonding group of Fe-O in Fig. 1b confirmedthe formation ofcore-shell nanostructure.

Also, the Fe_3O_4@SiO_2 nanostructurewas characterized by XRD for the investigation of crystalline structure. As shown in Fig. 2, the position and relative intensity of the reflection peaks at (220), (311), (400), (422), (511), (440) and (533) demonstrate the cubic structure of Fe_3O_4 (ICSD

CARD # 01-072-2303).The coating of the magnetic nanoparticles with the amorphous silica phase does not create any new peak in the XRD pattern.

The Magnetic properties of the $Fe_3O_4$and Fe_3O_4@SiO_2nanostructures were investigated using VSM at room temperature. Fig. 3 shows that the magnetization (Ms) values of Fe_3O_4@$SiO_2$was lower than Fe_3O_4, because the magnet core was subsequently coated with a SiO_2layer, which result in the decrease of magnetism.The Ms value of Fe_3O_4@SiO_2isabout 55 emu g^{-1}that is sufficient for targeted delivery.

Effects of concentration on nanofibers morphology were investigated in the concentration range of 5-14%w/v PVA solutions. On the concentration of lower and higher than 5 and 14 w/v%, no acceptable fibers were obtained. Fig. 4 shows the SEM images of PVA nanofibers in concentration of 6 %w/v containing 2 %wt. nanostructures and 3.4 %wt. DANrespect to polymer on aluminum foil. As shown, in concentration of 6 w/v%, obtained nanofibers have a smooth and grainy structures and average diameter of 60 nm.

Fig. 5 (a,b) shows the UV-Vis spectra ofa) daunorubicin and b) nanofibers containing daunorubicin. The UV spectrum of pure danurubicin shows maximum absorption at a wavelength of 480 nm, while the UV spectrum of composite nanofibers containing DAN shows a 20 nm shift at maximum absorption, indicating a covalent bond of drug to the surface of the nanocarrier and the hydrogen bonding of the NH_2 group in drug with the OH group of PVA.

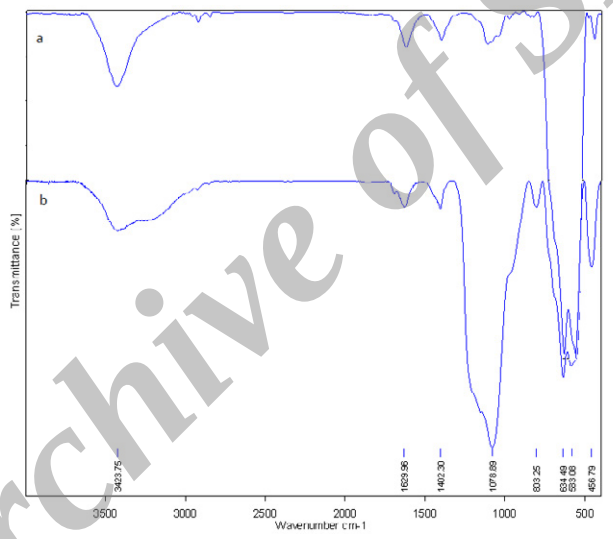

Fig. 1. FTIR spectra (a) Fe_3O_4 nanoparticles, (b) Fe_3O_4@SiO_2

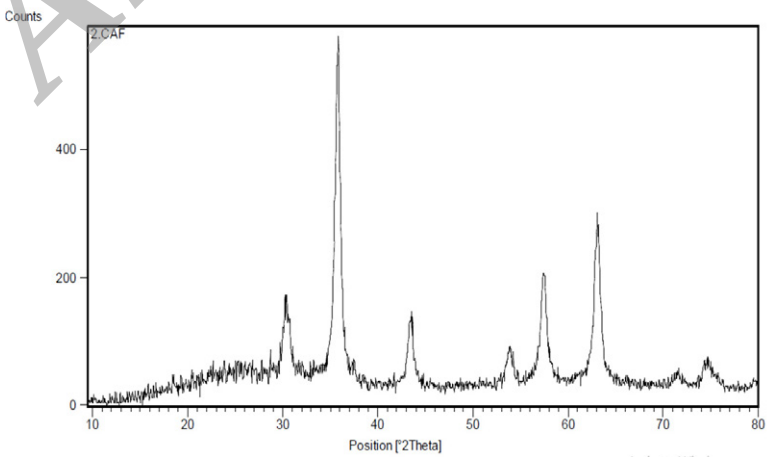

Fig. 2. XRD pattern of Fe_3O_4@SiO_2nanostructure

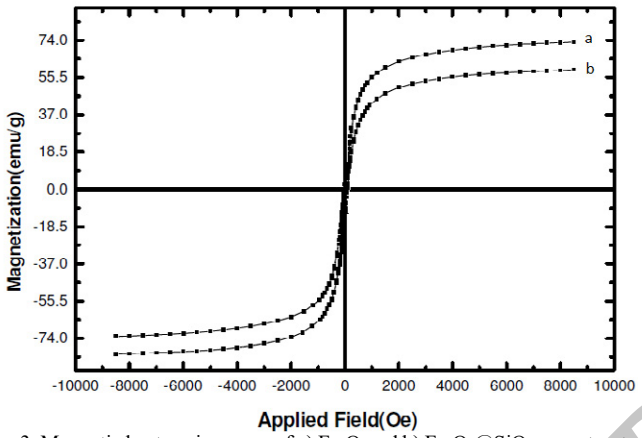

Fig. 3. Magnetic hysteresis curves of a) $Fe_3O_4$and b) Fe_3O_4@SiO_2 nanostructures

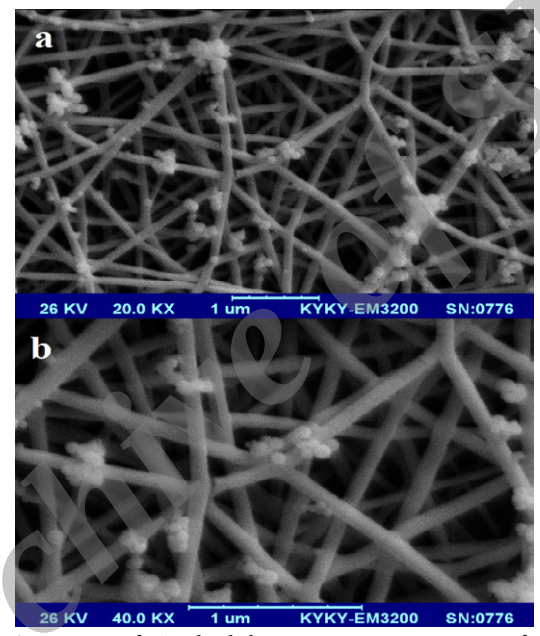

Fig. 4. SEM images of DAN-loaded nanocarrier in concentration of 6 %w/v

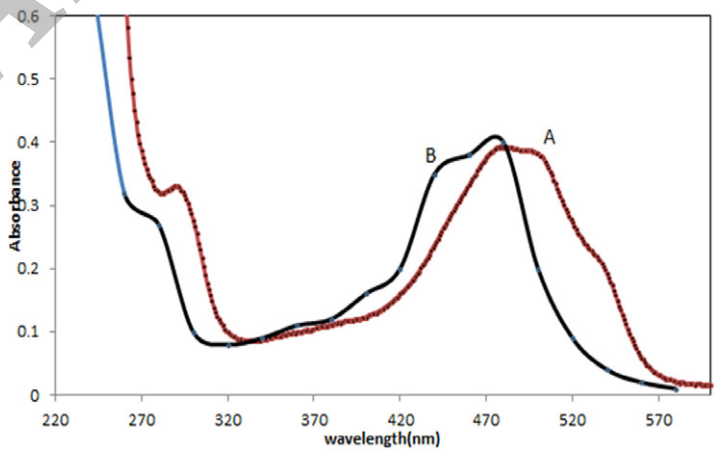

Fig. 5. UV-Vis spectra ofa)DAN and b)DAN- loaded nanocarrier

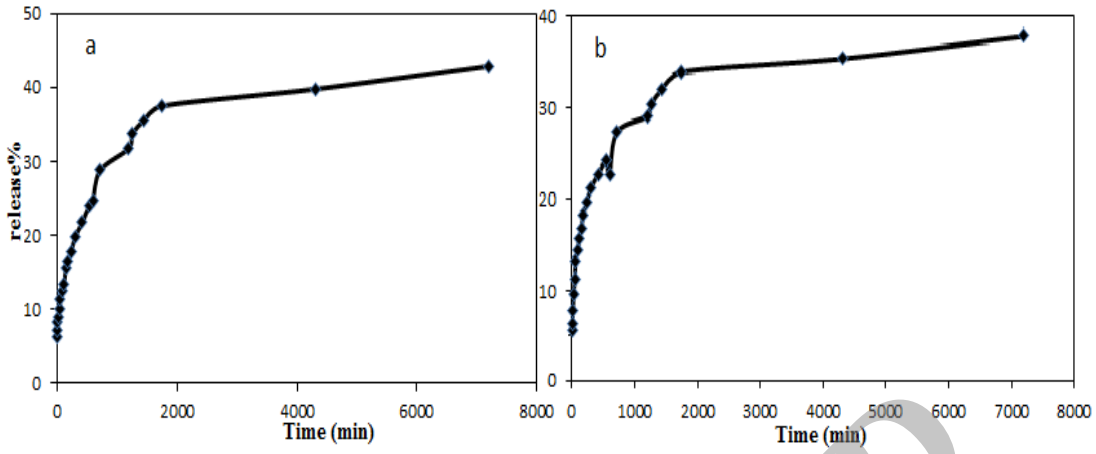

Fig. 6. Release profiles of DOX from nanocarrier in PBS at37˚C (a) pH=6, (b) pH=7.4

Table 1. Simulated equations and correlation coefficients of release curves for different kinetic models

Kinetic models	Correlation coefficients	Line equations
Zero-order	R^2 =0.90	Y=0.0298x+8.974
First-order	R^2 =0.88	Y=0.0018x+0.8884
Peppas	R^2 =0.99	Y=0.2665x+0.5926

In vitro release of DAN in pH=6.0 and 7.4

The release of the DAN-loaded nanocarrier investigated in PBS (pH 6 and 7) at 37 ◦C. As shown in Fig. 6a, in PBS (pH 6) an initial ascent of DAN release was observed at first and was followed by a slow release over 5 days. The initial ascent of DAN release from the nanocarrier was attributed to the DAN molecules absorbed onto the surface of the nanocarrier. Moreover, the total amount of DAN release from the nanocarrier was about 45% over a 120 h.Fig. 6b shows the release profiles of DAN from nanocarrier in PBS (pH 7.4) at 37 ◦C. The total release amount from DAN-loaded nanocarrier was about 35% after 120 h.

According to the results, the pH and time are an efficient parameters on the drug release. In pH=7.4, the release of drug is slow and stable respect to pH=6.0. At pH of 7.4, the most DAN remain in the nanocarrier for a long time. Therefore the side effects are decreased to the normal tissue. In pH=6.0, DAN is released faster and particularly lead to the improvement in cancer cells.

Drug release kinetics

The kinetic of drug release was investigated by fitting various standard models and mathematical equations of zero-order, first-order and Peppas equations were characterized [20]. Table 1 shows the results for calculation and comparison of equations and correlation coefficients. It was clearly observed that thedrug release from nanocarrier was better described using Peppas model where correlation coefficient was greater than 0.99.

CONCLUSIONS

In this study, electrospun composite nanofibers containing magnetic core-shell nanostructures were proposedas nanocarrier for the targeted drug delivery of an anticancer drug of daunorubicin. For this purpose, magnetic Fe_3O_4nanoparticles were coated with a silica shellusing the stober method and then polyvinyl alcohol composite nanofibers containing these nanoparticles and DAN drug were prepared by electrospining method.The DAN release study from proposed nanocarrier showed that the release rate of the drug at pH= 6 was higher than the release value at pH = 7.4 and the release kinetic was corresponded to the Peppas model. Therefore, it can be concluded that this nanocarrier is capable of responding to pH changes, that is an advantage in the targeted delivery of the drug. Also, this method has the advantages of magnetic sensitivity, high drug loading capacity (due to the hydrogen bonding between the drug groups and the silica layer surrounding the magnetite nanoparticles) and

sustained release. Due to the surface-to-volume ratio, nanofibers can interfere with the drug and, therefore, lower the rate of release.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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