ORIGINAL RESEARCH ARTICLE

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

Sakineh Kavyanifar¹, Tayebeh Shamspur¹, Fariba Fathirad², Ali Mostafavi¹

¹ Department of Chemistry, Faculty of Sciences, ShahidBahonar University of Kerman, Kerman, Iran ² Department of Nanotechnology, Graduate University of Advanced Technology, Kerman, Iran

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ABSTRACT

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Core-Shell Nanostructure Daunorubicin Drug Release Electrospun Nanofibers Magneticnanocarrier **Objective:** The purpose of this work was design and performance investigation of a nanocarrier based on magnetic nanofibers containing core-shell nanostructures for anticancerdrug delivery of daunorubicin (DAN) by measuring their drug release at different pH values.

Methods: Fe₃O₄ nanoparticles and Fe₃O₄@SiO₂core-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.

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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 consists 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

* Corresponding Author Email: *shamspur@gmail.com*

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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 Fe₃O₄ 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_a 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 (FeCl₃.6H₂O), iron (II) sulfate dihydrate (FeSO₄.2H₂O) and TEOSwere purchased from Sigma-Aldrich. PVA and ammonium hydroxide (NH₄OH) 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].FeCl₃.6H₂O and FeSO₄.2H₂Owere dissolved in distilled water under N₂ atmosphere. Then, NH₃ 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 Fe₃O₄@SiO₂nanoparticles were synthesized through the Stöber method[18]. Ethanol solution containing Fe₃O₄powder 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 Fe₃O₄@SiO₂nanoparticles 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 $10 \text{mg Fe}_{3}\text{O}_{4}$ @ SiO₂ 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 $37\pm0.5^{\circ}$ 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_4 synthesis. 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 confirmed the formation of core-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 @SiO₂nanostructures were investigated using VSM at room temperature. Fig. 3 shows that the magnetization (Ms) values of Fe_3O_4 @SiO₂was lower than Fe_3O_4 , because the magnet core was subsequently coated with a SiO₂layer, which result in the decrease of magnetism. The Ms value of Fe_3O_4 @SiO₂isabout 55 emu g⁻¹that 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 NH₂ group in drug with the OH group of PVA.



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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 Fe₂O₂nanoparticles 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 = 7.4and 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.

REFERENCES

- Kaur G, Verma N. Nature curing cancer review on structural modification studies with natural active compounds having anti-tumor efficiency. Biotechnology Reports. 2015;6:64-78.
- Petersen LJ. Anticoagulation therapy for prevention and treatment of venous thromboembolic events in cancer patients: A review of current guidelines. Cancer Treatment Reviews. 2009;35(8):754-64.
- Gupta P, Wright SE, Kim S-H, Srivastava SK. Phenethyl isothiocyanate: A comprehensive review of anti-cancer mechanisms. Biochimica et Biophysica Acta (BBA) -Reviews on Cancer. 2014;1846(2):405-24.
- Mamidi S, Höne S, Kirschfink M. The complement system in cancer: Ambivalence between tumour destruction and promotion. Immunobiology. 2017;222(1):45-54.
- Izzedine H, Perazella MA. Thrombotic Microangiopathy, Cancer, and Cancer Drugs. American Journal of Kidney Diseases. 2015;66(5):857-68.
- Regan D, Guth A, Coy J, Dow S. Cancer immunotherapy in veterinary medicine: Current options and new developments. The Veterinary Journal. 2016;207:20-8.
- Gu FX, Karnik R, Wang AZ, Alexis F, Levy-Nissenbaum E, Hong S, et al. Targeted nanoparticles for cancer therapy. Nano Today. 2007;2(3):14-21.
- Markman JL, Rekechenetskiy A, Holler E, Ljubimova JY. Nanomedicine therapeutic approaches to overcome cancer drug resistance. Advanced Drug Delivery Reviews. 2013;65(13-14):1866-79.
- 9. Yan S, Zhang X, Sun Y, Wang T, Chen X, Yin J. In situ preparation of magnetic Fe3O4 nanoparticles inside nanoporous poly(l-glutamic acid)/chitosan microcapsules for drug delivery. Colloids and Surfaces B: Biointerfaces. 2014;113:302-11.
- Chomoucka J, Drbohlavova J, Huska D, Adam V, Kizek R, Hubalek J. Magnetic nanoparticles and targeted drug

delivering. Pharmacological Research. 2010;62(2):144-9.

- Verma NK, Crosbie-Staunton K, Satti A, Gallagher S, Ryan KB, Doody T, et al. Magnetic core-shell nanoparticles for drug delivery by nebulization. Journal of Nanobiotechnology. 2013;11(1):1.
- ChaudhuriRG, PariaS. Core-shell nanoparticles: classes, properties, synthesis mechanisms, characterization, and applications.Chemical Reviews,2012;112:2373-2433.
- Girginova PI, Daniel-da-Silva AL, Lopes CB, Figueira P, Otero M, Amaral VS, et al. Silica coated magnetite particles for magnetic removal of Hg2+ from water. Journal of Colloid and Interface Science. 2010;345(2):234-40.
- 14. del Campo A, Sen T, Lellouche J-P, Bruce IJ. Multifunctional magnetite and silica-magnetite nanoparticles: Synthesis, surface activation and applications in life sciences. Journal of Magnetism and Magnetic Materials. 2005;293(1):33-40.
- Yu D-G, Chian W, Wang X, Li X-Y, Li Y, Liao Y-Z. Linear drug release membrane prepared by a modified coaxial electrospinning process. Journal of Membrane Science. 2013;428:150-6.
- 16. Taepaiboon P, Rungsardthong U, Supaphol P. Vitaminloaded electrospun cellulose acetate nanofiber mats as transdermal and dermal therapeutic agents of vitamin A acid and vitamin E. European Journal of Pharmaceutics and Biopharmaceutics. 2007;67(2):387-97.
- 17. ShamspurT,Fathirad F, GhanbariM, Esmaeili MahaniS. Synthesis and cytotoxicity evaluation of electrospun PVA magnetic nanofibers containing doxorubicin as targeted nanocarrier for drug delivery.Nanomedicine ResearchJournal, 2017; 2(4): 224-229.
- AlizadehA,KordestaniD, Biguanide-Functionalized Fe₃O₄/SiO₂ Magnetic Nanoparticles:An Efficient Heterogeneous Organosuperbase Catalyst for Various OrganicTransformations in Aqueous Media.Journal of Materials Chemistry, 2012; 33: 38-42.
- MehrabiF,ShamspurT,MostafaviA,SaljooqiA, FathiradF. Synthesis of cellulose acetate nanofibers and its application in therelease of some drugs. Nanomedicine Research Journal,2017; 2(3): 199-207.
- 20. Ghanbari M, Shamspur T, Fathirad F. In Situ Preparation of Magnetic Fe3 O4 Nanoparticles in Presence of PLGA and PVA as Magnetite Nanocarrier for Targeted Drug Delivery. Journal of Pharmaceutics & Drug Delivery Research. 2017;06(02).