RESEARCH ARTICLE

Drug release rate and kinetic investigation of composite polymeric nanofibers

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ARTICLE INFO

Article History:
Received 10 August 2016
Accepted 28 September 2016
Published 07 October 2016

Keywords:
Drug release
Electrospinning
Kinetic investigation
PEO
Tetracycline

ABSTRACT

Objective(s): In this work, electrospun nanofibers were explored as drug delivery vehicles using tetracycline as a model drug. Nanocomposite fibers including chitosan (CS)/poly (ethylene oxide) (PEO) and antibiotic were successfully prepared using electrospinning. CS blended with PEO considering a weight ratio of (90/10), and then, nanofibrous samples were successfully electrospun from their aqueous solutions. Afterwards, tetracycline was added to these samples for producing wound dressing materials.

Methods: Scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR) were used for the evaluation of morphology and biodegradability studies of CS/PEO blend nanofibrous. The kinetic and drug release mechanism of drug-loaded electrospun samples were also investigated by ultraviolet-visible spectrophotometry (UV-Vis) and the appropriate model was proposed for prediction of drug release.

Results: The results have indicated that the addition of tetracycline as much as 0.4%wt brings about the best nanofiber. The results of stability study of composite nanofibrous showed that the samples containing the active ingredient of tetracycline have maintained their structure after 24 h in the vicinity of acetate buffer solution. The model of antibiotic release from the nanofiber was examined and it was found that the release mechanism can be described as Fickian diffusion model. According to this model, the kinetic degree of the drug release is around 0.41.

Conclusions: The study of drug release from this nanofiber showed that the liberation level is relatively high during the early hours and over time, high amounts of the drug diffuse from the inside of nanofiber into the aqueous environment.

How to cite this article:
Sadri M, Mohammadi A, Hosseini H. Drug release rate and kinetic investigation of composite polymeric nanofibers. Nanomed Res J, 2016; 1(2):112-121. DOI: 10.7508/nmrj.2016.02.008

INTRODUCTION

Every year, thousands of people need to repair and/or graft their skin because of some injuries due to burns or dermal wounds, heat and chemicals[1]. Skin is relatively soft and is the greatest organ in the integumentary system of the body and normally covers the interior parts and also, protects them against the outside environment[2]. The wound healing process is a complex procedure involving cells and biochemical phenomena in terms of inflammation, immigration and proliferation of the epithelial growth cells, formation of extracellular matrices (ECMs) of proteins, new and fresh vascular cells production, and etc.[3]. In recent years, electrospun nanofibers have shown a great promise for developing tissue-engineered scaffolds. These

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nanofibrous scaffolds have some unique properties such as high porosity, oxygen transmission capability, different pore size distribution, and high surface to volume ratio. Besides these interesting properties, the electrospun nanofibrous scaffolds have similar morphology with the biological tissue of the body that leads them to have good compatibility with extracellular matrix cells. Due to these special properties, biopolymer nanofibers have a great deal of mesenchymal stem cells proliferation, adhesion, and viability [4]. Different materials are used to make nanofibers. CS is a naturally occurring polysaccharide prepared by deacetylation of chitin, mainly obtained from crab and shrimp shells [5]. CS is a non-toxic, biocompatible, and biodegradable polymer that intrinsically has antibacterial features in nature [6]. This polymer has a huge potential in numerous fields such as anti-fungal and anti-viral effects, wound dressing and injuries [7-8], wound healing [9-11], drug delivery [12], and tissue engineering [13-14]. All of the advantages of CS-containing materials might contribute to faster wound healing processes, making them good candidates for wound dressing applications [15-16]. In addition, it has been shown in different studies that CS can prolong the residence time of drug-delivery systems at the drug absorption site [17-19]. In recent years, CS has widely been utilized in drug delivery and tissue engineering in the dentistry applications [20-22]. PEO is a synthetic polyether that is readily available in a range of molecular weights. These polymers are amphiphilic and soluble in water as well as in many organic solvents [23].

Tetracycline is an antibacterial medicine which is frequently used for wound healing [24-26]. Tetracycline works by interfering with the ability of bacteria to produce essential proteins. Without these proteins the bacteria cannot grow, multiply, and increase in numbers. Tetracycline is a broad-spectrum antibiotic that is active against a wide variety of bacteria [26]. In order to use polymer and antibiotic compounds, an efficient method should be chosen that can provide the most optimal state given time and cost constraints.

Electrospinning offers a unique way to produce submicron and nanofibers [26-28]. Nanocomposite fibers including CS/PEO and antibiotic were successfully prepared using electrospinning [28]. The antimicrobial properties of nanofibers were also enhanced by the incorporation of small amounts of the antibiotic [29]. The electrospinning of CS /PEO would be useful in fabrication of biomedical scaffolds such as wound healing and tissue engineering. Electrospun nanofiber mats offer advantages due to their sorption/release properties. If loaded with drugs, release properties can be tailored to a specific release rate. The characteristics of electrospun nanofibers of CS/PEO such as high specific surface area and small pores are very favorable for the adsorption of liquids and preventing penetration of bacteria, thus provide good conditions for wound healing. There are several publications related to the design of CS/PEO-based nanofibers with antibacterial properties and good biocompatibility [9,28,31]. Under the same electrospinning conditions, average diameter of nanofibers was more than 100 nm, while the electrospinning of CS/PEO/tetracycline solution led to fibers with average fiber diameter of 86 nm. This diameter is lower than the other CS/PEO/antibiotic drug nanofibers reported in studies. Such thin nanofibers have good advantages such as better interaction with cells, more control of the humidity wound, more ability for loading the drugs in pores and finally, higher antibacterial properties. Combination of the advantageous properties of PEO, the antibacterial features of CS and antibiotic drug is a promising strategy for fabricating novel nanofibrous materials employed beneficially for wound dressing applications. The novelty of this research was the addition of tetracycline antibiotic for increasing the antibacterial activity.

In order to investigate the effects of the drug on human body, the conditions should be close to the human body as much as possible [30]. Suwei Jiang *et al.* evaluated the release behavior of tetracycline hydrochloride loaded CS/poly (lactic acid) (tetracycline–CS/PLA) antimicrobial nanofibrous membranes fabricated via electrospinning technique. They found that tetracycline–CS/PLA nanofibrous membrane had a slight initial burst within the first 4 h before a gradual increase in cumulative release, and the release percentage increased with increasing tetracycline contents [31]. The main purpose of this work has been to systematically study and evaluate the CS/PEO blend nanofibrous mats containing tetracycline for the acceleration of wound healing. Also, studies on drug release kinetics provide important information about the function of material systems. To elucidate the detailed transport mechanism and the structure-function relationship of a material system, it is critical to bridge the gap between the

macroscopic data and the transport behavior at the molecular level. Understanding the structure-function relationship of the material system is key to the successful design of a delivery system for a particular application. Moreover, developing complex polymeric matrices requires more robust mathematical models to elucidate the solute transport mechanisms. It is believed that the mechanism of tetracycline release from electrospun fibers is related to Fickian diffusion and some useful information along with interesting results and their interpretations are critically discussed.

MATERIALS AND METHODS

CS medium molecular weight (104000 $g.mol^{-1}$, degree of deacetylation: 75–85%, viscosity:200–800 CP) and PEO (average viscosity molecular weight:103 kDa, viscosity:400–800 CP) were purchased from Across organic, Belgium. Acetic acid and Polyoxyethylene (20) sorbitan monooleate (Tween 80) were purchased from Merck. Tetracycline was purchased from Abureihan pharmaceuticals. All the other chemicals were analytical reagent grade and used without further purification.

Electrospinning process was performed with a Fanavaran Nano- meghyas Co. of Iran (model ES1000) elctrospinning apparatus. A scanning electron microscope (Camscan SEM, model MV2300, of Czech & England) was employed to study the surface morphology of prepared nanofibers. FTIR model Magna-IR-550 was used to record IR spectrum of prepared nanofibers, UV-Vis spectrometer was used to study the drug delivery template of tetracycline from nanofiber scaffold. Sample stirring and heating was carried out with a heating magnetic stirrer, model IKA-RCT-B.

Electrospinning of CS/PEO /tetracycline solutions

In order to prepare CS / PEO /tetracycline solution, first it is required to dissolve CS and PEO in acetic acid 50% (v/v) individually. Next, the prepared solutions were mixed with each other. For preparation of CS 3%wt solution, first 0.3 g of CS powder was weighed, then poured inside a beaker, to which acetic acid 50% (v/v) was added. The solution was exposed to ambient temperature under stirring at 300 rpm for 12 h. The rate and manner of stirring were somehow important in preparation of the sample for obtaining a clear and transparent solution. The procedure of preparing poly(ethylene oxide) solution 3wt% has been similar to that of CS, where first 0.3 g of poly(ethylene oxide) powder was weighed, then poured inside a beaker, to which acetic acid 50% (v/v)was added. In order to prepare a homogeneous solution, the sample is exposed to ambient temperature under 300 rpm stirring for 4-5 h. After preparing 90-to-10 solution of CS/PEO, tetracycline has been added gradually with weight percentages of 0.4, 0.6, and 0.8 to the mixture. When a homogeneous solution of both systems was obtained, a syringe containing 90/10 CS/PEO/ tetracycline was used for the fabrication of a nanofibrous sample. Since the drug-contained systems were utilized for the electrospinning process, there was no interaction between the chemical structures of the drugs after evaporating the solvents and collecting the nanofibers in the form of a solid on the collector. The operation conditions of the electrospinning device for the preparation of the samples were as follows: the solution flow rate was 0.4-0.6mL/h^{-1}, applied voltage was adjusted to be 20 kV, and the distance between the syringe needle tip and collector was selected to be 10 cm. To reach fully-dried electrospun nanofibrous samples, they were removed from the aluminium foil and dried at room temperature for 48 h.

Stability of composite nanofibers

After preparing the acetate buffer solution with pH 5.5 (simulation of human skin) the stability of composite nanofibers was investigated and the degree of water absorption (inflation) of the nanofibrous scaffold was measured. Therefore, the prepared composite nanofibers were placed in the refrigerator, and then exposed to a temperature of 37°C before the consumption. In order to examine the stability of the electrospun nanofibrous scaffolds, first the prepared nanofibrous scaffold samples were cut into 4 x 4 cm^2 dimensions and then immersed in the acetate buffer solution with pH 5.5 at 37°C for 24 h. Following this, the samples were removed from the buffer solution and allowed to be dried in the ambient temperature. The changes in their structure and morphology before and after immersion in acetate buffer solution have been studied through SEM.

FE-SEM studies

The study of the morphology and fiber diameters of the electrospun samples was carried out using SEM. For this purpose, first an aluminum foil containing collected nanofibers was cut into 1 x 1

cm pieces. The samples were gold-coated using ion coating device (model E5200) by exerting a voltage of 1 kV for 5 min. Thereafter, the nanofiber has been prepared by exerting a voltage of 19-20 kV. The diameter of the nanofiber has been measured out of 50 different points in the SEM image, and then the nanofiber diameters distribution was separately calculated and plotted for each sample.

FT-IR spectroscopy

The compositional and chemical characteristics of the electrospun nanofibrous scaffold have been investigated using FTIR analysis. In this method, the samples have been prepared with a press device in the form of clear plates with a thickness of 0.25 mm mixed with potassium bromide (KBr). Thereafter, the spectra have been recorded using FTIR device.

UV-Vis spectroscopy

For studies of drug release of a system in human skin-like conditions , first 30 mg of the composite nanofibrous scaffold was placed inside a dialysis bag. Inside the dialysis bag has been filled with 5 mL of acetate buffer solution (pH 5.5, 37°C). Next, the dialysis bag containing nanofibers has been hanged inside a beaker which contained 20 mL of the same buffer. The solution was kept under continuous stirring with a constant rate of around 200 rpm using a magnet inside the beaker. A thermometer was used inside the beaker to check the temperature. Within certain time intervals from 1 to 48 h, 3 mL of the solution inside the beaker was removed and stored as stock for measuring the absorption. After removing the sample, 3 mL of the same buffer was added to the solution inside the beaker with a temperature of 37°C in order to reach the initial volume of 20 mL. The absorption of the samples has also been studied with UV-Vis spectrophotometer at the wavelength of 529 nm. In order to measure the absorption of the stock samples, the standard curve was plotted. The only difference was that instead of standard solutions, stock solution has been used. In the next step, the degree of release has been estimated using standard curve. In order to carry out the release studies (the release of the active ingredient), the degree of the release of the active ingredient from the analysis bag method was calculated after plotting the standard curve.

The release kinetics of CS/PEO/tetracycline can be described using Korsmeyer–Peppas based on the results obtained from all the samples [32].

$$\frac{M_t}{M_\infty} = Kt^n$$

Where, M_t is the cumulative amount of drug released at time t, M_∞ is the initial drug loading, K is a constant characteristic of the drug-polymer system, and n is the diffusion exponent suggesting the nature of release mechanism.

RESULTS AND DISCUSSION

Morphology studies

The morphology of the electrospun CS/PEO (90/10) blend nanofibrous mats, the two of polymers, and electrospun nanofibers was studied. It is believed that the variation of their diameters depends on the type of the polymers solution combination. Figs. 1-2 shows the FE-SEM micrographs of electrospun CS/PEO (90/10) nanofibrous sample without and with tetracycline, respectively. It is obvious that the sample containing tetracycline 0.4%wt has uniform and smooth nanofibers. The resulting information from Fig. 3 shows that maximum peaks of diameter curves distribution for the optimized CS/PEO (90/10) containing tetracycline 0.4%wt nanofibers are about 86 nm.

Stability of nanofibers

Fig.4 shows the SEM images of samples containing 0.4%wt tetracycline. As can be seen, these samples have retained their structure after 24 hours in the presence of buffer acetate solution. In this case, the water molecules scarcely penetrated into the scaffold matrix. Based on the results, CS/PEO/ tetracycline (0.4%wt) is a suitable choice as

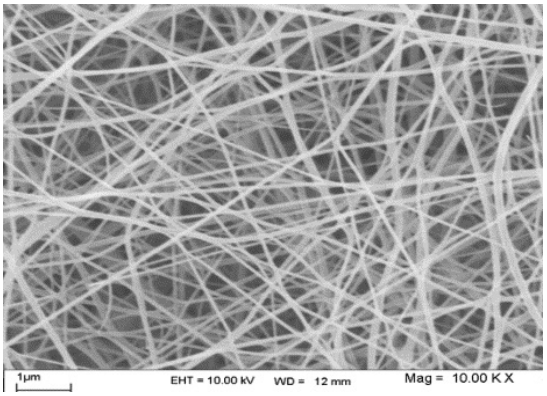


Fig. 1. SEM micrograph of electrospun CS/PEO (90/10) nanofibrous samples

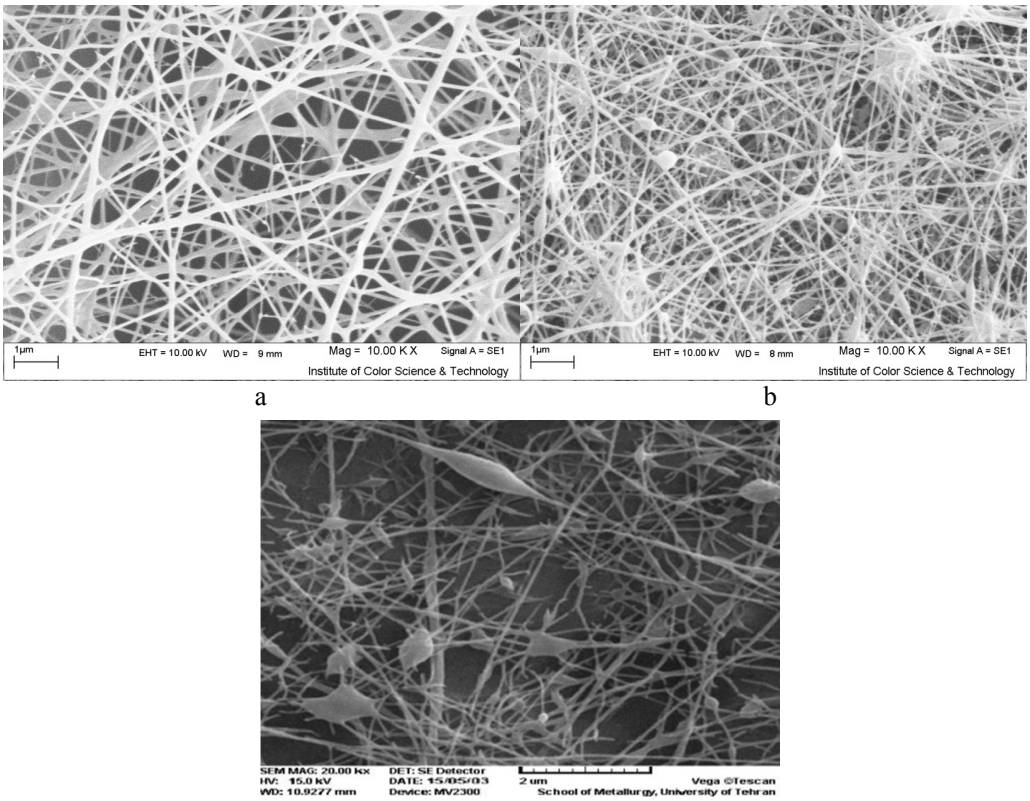


Fig. 2. SEM micrographs of electrospun CS/PEO (90/10) a) 0.4%wt tetracycline, b) 0.6%wt tetracycline, c) 0.8%wt tetracycline nanofibrous samples

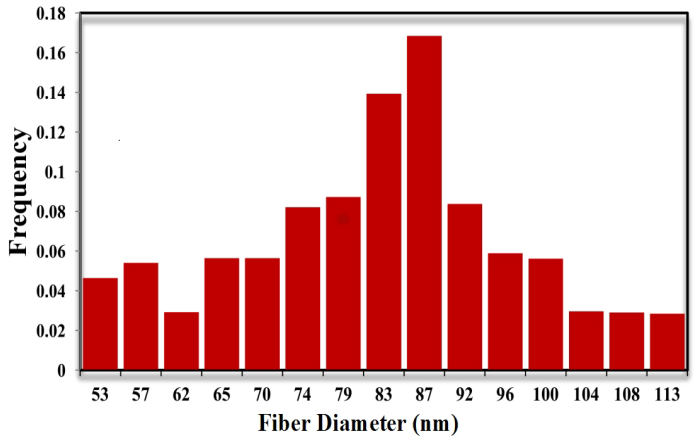
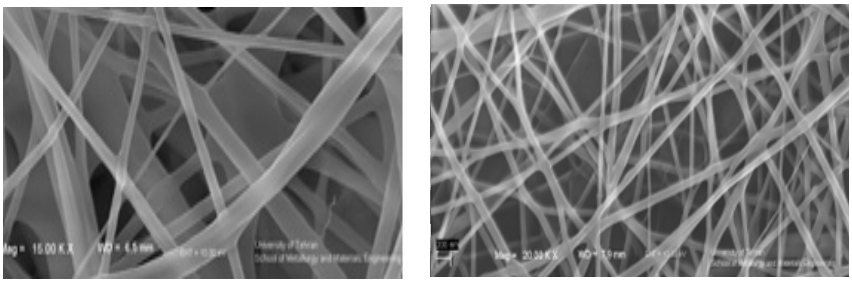


Fig. 3. Distribution curves of the diameters of electrospun CS/PEO nanofibers (samples containing tetracycline (0.4%wt))

the wound dressing because it keeps an acceptable level of moisture which can prevent the surface of the wound to be dried across all stages of wound healing. This culminates in the fact that the nanofibrous scaffold does not attach to the wound and when removing it from the wound surface, the patient does not face discomfort, and also passage of oxygen on it takes place easily. Therefore, it can maintain its mechanical properties during the usage and enhance the speed of improvement and wound healing.

Evaluation of swelling of nanofiber scaffolds

In order to determine the water absorption, the CS/PEO nanofiber scaffolds containing different percentages of tetracycline were built. The samples



a b

Fig. 4. SEM images of primary nanofibers containing 0.4%wt tetracycline (a) and nanofibers after immersion in acetate buffer for 24 hours at 37°C (b)

were weighed separately and immersed in acetate buffer solution with pH 5.5 at 37 °C. After 24 hours, the samples were weighed followed by measurement of the inflation rate. As the Fig. 5 shows, CS/PEO nanofibers had the lowest water absorption and the addition of tetracycline to nanofiber scaffolds increased water content. So that, the greatest water absorption level has been reached for the CS/PEO/ tetracycline (0.8%wt) nanofibrous scaffold where the tetracycline plays the role of plasticizers. It was commonly thought that plasticizers work by embedding themselves between the chains of polymers and spacing them apart (increasing the free volume).

FTIR analysis

Fig. 6 demonstrates the infrared spectroscopy of the PEO/CS polymer mixture nanofiber. All of the characteristic bands of the CS and two absorption bands related to the stretching vibrations of C-H group were emerged at 1242 and 1281 cm^{-1} regions by adding PEO. Furthermore, due to presence of PEO in the nanofiber, the intensity of absorption peak increased at 2930 cm^{-1} because of C-H group. The FTIR spectra also showed the absorption peaks for O-H and N-H stretching at 3480 cm^{-1}. The shift in ether, amine, and hydroxyl bands in CS/PEO nanofiber might be attributed to formation of a hydrogen bond between the poly ether oxygen and amino hydrogen in PEO and CS. Therefore, the strong interaction between CS and PEO has decreased viscosity and facilitated electrospinning due to the formation of hydrogen bond. Fig. 7 illustrates FTIR spectrum of CS/PEO/tetracycline. The bands located between 1594-1630 cm^{-1} are ascribed to the stretching mode of the C=O bonds of amide group and carbonyl groups attached to the tetracycline ring. Two absorption bands related to the stretching vibrations of O-H and N-H groups in the CS and tetracycline were appeared at 3420 and 3100 cm^{-1},respectively.

Drug release rate and kinetic investigation

The cumulative release rate profiles of tetracycline from the optimized electrospun samples to the buffer solution are plotted in Fig. 8. The release rate for these samples containing 0.4 %wt tetracycline after 48 h was 59.08%.

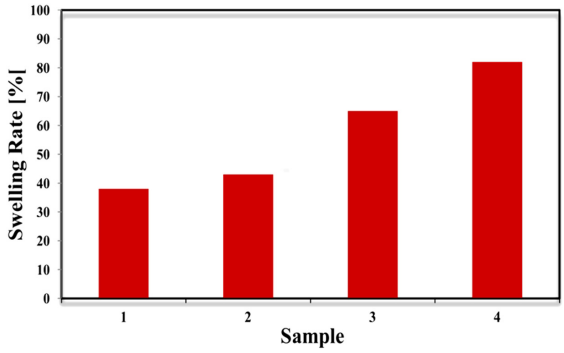


Fig. 5. Scaffold water absorption of nanofibers:(1) CS/PEO,(2) nanofibers containing 0.4%wt tetracycline, (3)nanofibers containing 0.6%wt tetracycline,(4) nanofibers containing 0.8%wt tetracycline

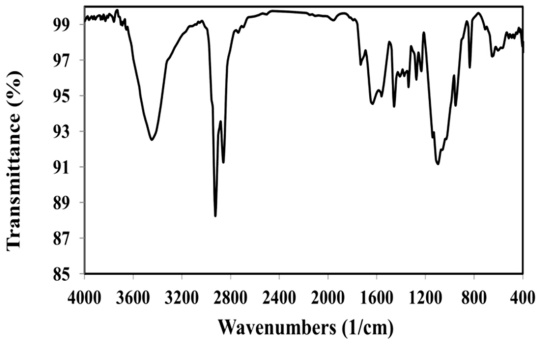


Fig. 6. FTIR spectrum of PEO/CS

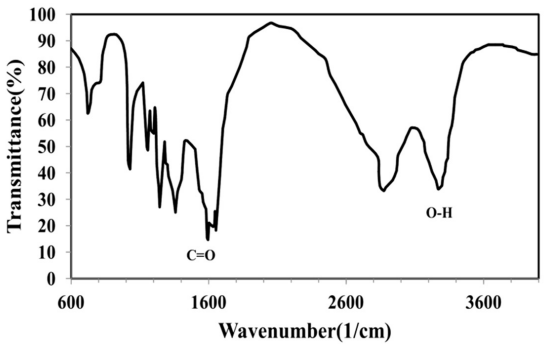


Fig. 7. FTIR spectrum of PEO/CS/tetracycline

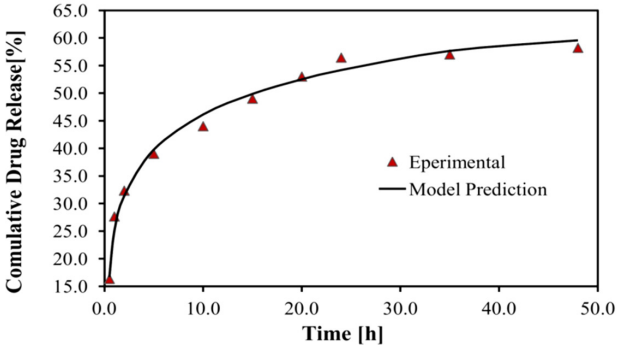


Fig. 8. The release percentage of tetracycline from electrospun mats containing 0.4% wt tetracycline vs. time

Overall, the trend of the release of the active ingredient from the gridded nanofibrous scaffold consists of four stages. The sudden release of the active ingredient occurs at the first stage. At this stage, a significant amount of the active ingredient is released at a high rate. However, as can be observed in Fig. 8, since the release degree of the active ingredient is low within the early hours, thus we do not face burst effect, which is one of the important advantages of the synthesized nanofibrous scaffold. Indeed, the amount of the drug on the surface of the nanofibrous scaffold (with a high area to volume ratio) is washed using the acetate buffer solution and diffused into the surrounding aqueous environment through the pores presented in the nanofiber polymer background. Although the release of the active ingredient during the early hours plays an important role in phagocytosis, the release of small amounts of it during later hours may not be desirable. The second stage in the release of the active ingredient from the nanofibrous scaffold, is where the burst release stops and instead, the slow trend of release starts. The release takes place according to diffusion at this stage. As part of the active ingredient has been already released in the first stage of the release, at this stage the active ingredient passes through pores of the nanofibrous scaffold and enters the buffer environment. Following the second stage comes the stage of release of drugs that have been trapped in the scaffold. At this stage, the drugs deeply trapped inside the scaffold are released due to polymer destruction and breakdown of bonds and production of oligomers and monomers, which then enter the buffer environment [33]. It is not possible to determine a certain boundary between the mentioned stages. This means that after the onset of the release experiment, the polymer gradually starts to degrade and reaches its maximum following the second stage. The diffusion continues at this stage and eventually in the final stage of release, the concentration of the active ingredient in the nanofibrous scaffold declines. Even with the destruction of polymer, the release rate is very low and the diagram's slope is very small, though the drug is still remained in the nanofiber. As can be observed in the Fig. 8, the greatest degree of active ingredient liberation

from the gridded nanofibrous scaffold containing 0.4% wt has been 15.7% in the first 30 minutes. The level of liberation has reached to 28.6% after 1 h and increased to 34.5% within the second hour. Over time, the degree of release gradually declineds, and the liberation has continued up to 24 h. The maximum liberation level reached for the gridded nanofibrous scaffold containing 0.4 wt% of the active ingredient was calculated to be 59.08%. The liberation of active ingredient continued and remained constant up to 48 h which can be ideal for wound healing. In comparison with other works on the drug release from polymeric nanofibers, basic polyurethanes are considered non-degradable due to the need of long time for complete degradation and negligible degree of degradation. However, due to their biocompatibility, in vivo stability, and also favorable physical mechanical properties these polymers have been frequently used in biomedical devices such as drug delivery implants, tissue adhesives, skin wound dressings, etc [34–37]. As the non-degradability has limited the application of polyurethanes in controlled drug delivery, some second interventions are sometimes necessary to remove the device after the treatment.

Release kinetics from polymeric matrices

Studies on drug release kinetics provide important information about the function of material systems. To elucidate the detailed transport mechanism and the structure-function relationship of a material system, it is critical to bridge the gap between the macroscopic data and the transport behavior at the molecular level. Understanding the structure-function relationship of the material system is the key to successful design of a delivery system for a particular application. Moreover, developing complex polymeric matrices requires more robust mathematical models to elucidate the solute transport mechanisms.

Mathematical modeling of drug release kinetics provides a basis for the study of mass transport mechanisms that are involved in the control of drug release. There are several comprehensive reviews on mathematical modeling for bioerodible polymeric delivery systems, dissolution controlled drug delivery systems, microsphere delivery systems, and hydrogel networks. In general, diffusion, erosion, and degradation are the most important mechanisms for drug transport from polymeric matrices.

Further studies were done on tetracycline release rate mechanisms and the release data were analyzed by Korsmeyer–Peppas model. Based on this equation, the regression coefficients were calculated and the results showed that n=0.41. This result indicates that the levels of tetracycline release rate from CS/PEO nanofibers during the release time are probably related to the diffusion of the drugs located near the nanofiber surfaces. Also, this means that the release of drug from the polymer bed takes place through Fickian diffusion mechanism, which is associated with concentration gradient, diffusion distance, and the degree of swelling.

All of these results show that the tetracycline-contained CS/PEO polymer nanofibrous scaffold with a weight ratio of 90 to 10 can be an ideal choice for wound dressing that reasonably facilitates wound healing process.

CONCLUSION

The general objective of this research was producing a kind of suitable wound coverage out of biodegradable polymer nanofibers through electrospinning and investigating the operational conditions to optimize the mean diameter of the nanofiber containing the active ingredient. The results obtained from the stability test demonstrated that the samples containing the active ingredient, tetracycline, in the vicinity of acetate buffer solution, have maintained their structure for more than 24 h. The stability of the nanofibrous scaffolds is due to the presence of high percentage of CS (CS/PEO nanofibrous with a weight ratio of 90 to 10, respectively) and the joining of CS molecules, where water molecules can hardly enter into the scaffold grids. The study of drug release from this nanofiber showed that the liberation level is relatively high during the early hours and over time, high amounts of the drug diffuse from the inside of nanofiber into the aqueous environment. Kinetic studies of this drug release system also indicated that it has greater resemblance with the Korsmeyer-Peppas model, and according to this model, the kinetic degree of the drug release is estimated to be around 0.41.

ACKNOWLEDGEMENT

The authors are grateful to the University of Malek Ashtar for financial support.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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