Research Article

Fabrication of antibacterial and hemostatic electrospun PVA nanofibers for wound healing

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Abstract
Health care professionals have always had problems treating and healing wounds. Today, many of these problems have been resolved with the use of advanced wound dressings. The main aim of this work was to fabricate the wound dressings using the electrospinning method blending Tranexamic acid (TXA) with Polyvinyl alcohol (PVA) to investigate the blood coagulation properties. Also, the blending of Ceftriaxone (CTX) with Polyvinyl alcohol (PVA) was done to consider antibacterial properties. The effects of drug concentration changes on these properties were also considered. Morphological results demonstrated that nanofiber was produced uniformly and without beads. SEM image indicated that the average diameter of the nanofiber of PVA with 10 and 20 mg/ml of TXA was 110, 124 nm, respectively and the average diameter of PVA nanofibers was with 0.1, 1, 8 µg/ml of CTX was 258, 273 and 379 nm, respectively. The antibacterial properties of Gram-negative (*Escherichia coli*) and Gram-positive bacteria (*Staphylococcus aureus*) were studied and the results demonstrated that the antibacterial properties increased with increasing MIC. In PVA/CTX dressing with MIC: 8 µg/ml reached 100%. Both PVA-TXA (10 mg/ml) and PVA-TXA (20 mg/ml) dressings demonstrated the acceptable ability of blood coagulation. PVA-TXA (20 mg/ml) with an average absorption of 0.031 had higher blood coagulation ability.

Keywords Nanofiber · Electrospinning · Polyvinyl alcohol · Tranexamic acid · Wound dressings

1 Introduction

Wound healing is a complex tissue regeneration process that promotes the growth of new tissue for providing the body with the necessary barrier from the outside environment. In the class of non-healing wounds, diabetic wounds, and ulcers, dressing materials showed only a slow improvement with currently available technology [1–4]. The process of wound healing follows a complex process consisting of different biological, physical, and chemical factors. Wound healing, though being a continuous overlapping process can be differentiated into various stages as follows: (1) Haemostasis, (2) Inflammation, (3) Proliferation, (4) Re-modeling and formation of scar tissue. Bleeding occurs immediately following damage to the tissue [2, 5–7]. Several methods have been presented to fabricate wound dressing material. Muzzarelli et al. [8] formed a reinforced wound dressing material through a freeze-drying method. They concluded that Dibutyryl chitin (DBC) is adequate for contacting intact and wounded human tissues. Mi et al. [9] fabricated a sponge-like chitosan membrane as a wound dressing using casting processes. Their results demonstrated that the asymmetric chitosan membrane could be properly used as a wound dressing. De Cicco et al. [10] investigated nano-particulate powder using nanospray drying technologies for wound dressing. In their study, all nano spray-dried formulations gave a burst effect, adequate for preventing infection

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spreading at the beginning of therapy. Moreover, Kobsa et al. [11] produced an electrospun nanofiber scaffold to treat the cutaneous wounds. They found that nanofiber PLA/PCL scaffolds can effectively control DNA delivery.

Electrospinning is a proper and easy method consisting of four main parameters: 1. High voltage–power supply, 2. Spinneret, 3. collector, and 4. Micro-pomp (feeding system) [12, 13]. Electrospun nanofiber has been widely employed in biomedical applications such as tissue engineering [14–17] and wound dressing [18–20]. Kyziol et al. [21] used the electrospinning method to produce sodium alginate nanofiber loaded with ciprofloxacin hydrochloride. In their study, using the biopolymer, and cross-linker, makes the scaffolds promising for different biomedical applications such as wound healing, and drug delivery system. Mohseni et al. [22], presented a porous wound dressing from polycaprolactone (PCL) and PVA nanofibers with flexibility, and hydrophilicity that obtain requisite physical properties for wound dressing. They indicated that coating fibronectin was stated as a proper method to enhance the biocompatibility of scaffold incorporated with silver sulfadiazine (SSD). Furthermore, Mohseni et al. [23] considered the antimicrobial wound dressing loaded with silver sulfadiazine (SSD) or AgNPs and evaluate their efficiency in the process of wound healing. Based on their results, PCL/PVA nanofibers conjugated with AgNPs are promising wound dressing for the full-thickness wound. Jatoi et al. [24] developed a novel antibacterial wound dressing using PVA nanofiber. Their experimental results confirmed good bactericidal and suggest a sustained antibacterial wound dressing biomaterial. Also, several researches have been done to investigate the blood clotting ability of dressings. Wiegand et al. [25] carried out different examinations for evaluating the efficacy of cotton gauze (Gazin ^{R}, Lohmann & Rauscher, Germany), collagen SC (Suprasorb ^{R} C, Lohmann & Rauscher, Germany) and collagen PC (PuracolTM, Medline Industries Inc., USA), and oxidized regenerated cellulose (Tabotamp ^{R}, Johnson & Johnson, USA) to improve blood clotting, coagulation, and platelet activation. Gu et al. [26] produced pure chitosan nanofiber utilizing the electrospinning technique. Their results showed that the sonicated chitosan nanofiber mat can act as a hemostatic wound dressing.

By investigating the promotion of community standards, there is a need for products that can simultaneously act in several operations together. Also, this is evident in wound dressing. In this regard, few researches have been carried out on wound dressing that can perform both as a wound dressing and as a blood coagulant. In this study, an attempt was made to fabricate the wound dressings using the electrospinning method blending TXA with PVA for considering blood coagulation properties. Furthermore, the blending of CTX with PVA was done to investigate antibacterial properties. The effects of drug concentration changes on these properties were also studied in detail.

2 Experimental section

2.1 Loaded PVA nanofibers with drug

Poly (vinyl alcohol) (PVA, Mw = 89,000, Sigma–Aldrich, USA) solution was produced by dissolving 5% wt/wt PVA in distilled water for 4 h at 85 °C. Ceftriaxone (Sigma–Aldrich, USA) (MIC: 0.1, 1, 8 µg/ml) and Tranexamic acid (Caspian tamin, Iran) (10, 20 mg/ml) added to the polymer matrix directly and stirred for 2 h for loading drugs in PVA. Electrospinning was done in a voltage of 20 kv, 12 cm from tip to collector, and feed rate of 1.2 ml/h and fabricated of nanofiber was collected on an aluminum foil.

2.2 Characterization

Morphology of electrospun nanofiber was investigated with scanning electron microscopy (FE-SEM, Sigma, Zeiss German (. The fiber diameter was captured using Image J (NIH, USA) software. The viscosity of polymer solutions was evaluated with Brookfield's viscometer DV-II + PRO at a temperature of 24 °C at 100 rpm.

2.3 Coagulation of blood

The blood clotting test was implemented based on previous studies [27]. Hence, the dressings PVA, PVA/TXA 10 mg/ml, PVA/TXA 20 mg/ml were cut to 1×1 cm^2 dimensions and placed in glass bottles. 0.1 ml of human blood was mixed with anticoagulant agent acid-citrate-dextrose at a ratio of 9:1 added to each composite nanofiber mats and placed in a 25 ml plastic Petri dish, followed by addition of 10 µL of 0.2 M $CaCl_2$ solutions for initiation of blood clotting and PVA mat was employed as a negative control. Then, they were incubated at 37 °C for 10 min. Also, 15 ml of distilled water was added dropwise without disturbing the clot. Afterward, 10 ml of solution was taken from the dishes and centrifuged at 1000 rpm for 1 min. The supernatant was collected for each sample and kept at 37 °C for 1 h. 200 µl of this solution was transferred to a 96-well plate. The optical density was tested at 540 nm with a plate reader (Dynex Technologies USA).

2.4 Investigation of platelet activation

To evaluate platelet activation for 3 dressings including PVA, PVA/TXA 10 mg/ml, and PVA/TXA 20 mg/ml were cut to 1×1 cm^2 dimensions. Platelet Rich Plasma (PRP) was isolated from the blood by centrifugation of blood

at 2500 rpm for 5 min. 100 µl of PRP was poured onto the composite nanofiber mat and incubated at 37 °C for 20 min. Then, composite nanofiber mat was washed three times with PBS solution and fixed with 0.1% glutaraldehyde solution. The mat was dried and the SEM image was taken [27].

2.5 Antibacterial activity

First, the agar culture medium for the growth of bacteria was produced for examination. *Escherichia coli* (AATCC 11303) and *Staphylococcus aureus* (AATCC 25938) were employed for determining anti-bactericidal property. Microbial culture was prepared in growth enrichment broth for 24 h of incubation for obtaining a high concentration of test organisms. Therefore, bacterial suspensions with a concentration of 1.5×10^8 CFU ml^{-1} were produced and added 10 µl suspensions dilute of *S. aureus* and *E. coli* to dressing with 1×1 cm^2 dimension. Then, organism inoculated dressing is incubated for 24 h under the favorable condition of nutrient and temperature. Finally, the number of bacterial colonies culture media was counted, and by Eq. (1) the percentage of bacteria was decreased [28].

$$R = 100\,(B-A)/B \quad (1)$$

where R is % reduction, A denotes the number of bacteria recovered from the inoculated treated test specimen swatches in the jar incubated over desired contact period, B represents the number of bacteria recovered from the inoculated treated test specimen swatches in the jar immediately after inoculation (at 0 contact time) [29].

3 Results and discussion

3.1 Viscosity and morphology of electrospun mats

SEM images were examined to investigate surface morphology of PVA, PVA/TXA, and PVA/CTX (Fig. 1). It was concluded that PVA nanofiber and PVA nanofiber loaded with TXA and CTX were fabricated uniformly and without the bead. Also, the addition of TXA and CTX to PVA did not change the morphology of nanofibers, but the diameter of nanofibers varied with changes in viscosity of the polymer solution [30]. Solution viscosity plays a major role in determining the size of fiber and morphology during polymer fiber spinning [31]. It was found that by adding CTX to the PVA polymer solution, the viscosity of polymer solution enhanced due to the size and structure of the CTX molecules, which lead to have more interaction with surrounding molecules. The other reason for increasing the viscosity was using CTX in powder form. It can be seen in Table 1, with the increase of CTX concentration, the viscosity raised, thereby increasing the diameter of nanofiber. The diameter of nanofiber loaded with CTX was higher than PVA nanofibers, this could be due to the drug entrapped within the polymeric chain of nanofibers resulting in the increment of fiber diameter [32]. Also, with the increase of TXA drug, the viscosity of PVA polymer solution had decreased because of the disruption in chain involvement of polymer chains. This reduction in the viscosity of polymer solution actually reduces the viscoelastic force in the electrospinning process. Another reason for the reduction of viscosity is using TXA in the form of a solution. The average diameter of the fabricated nanofiber reduced with decreasing viscosity [33].

3.2 The ability of blood coagulation

The hemostatic property of TXA mainly relates to its ability for inhibiting conversion of plasminogen to plasmin. Thus, it prevents excessive blood loss in hyperfibrinolytic conditions. Plasmin breaks down fibrinogen and a series of proteins which are involved in coagulation [34]. A general review of blood coagulation was carried out to analyze the potential of scaffold nanofibrous coagulation. After adding the blood, the nanofibrous coating was completely covered with blood. After 10 min of incubation, the dressings indicated complete blood coagulation. The red blood cells trapped in the clot were hemolyzed with water. The absorbance of the hemoglobin solution was obtained 540 nm. The amount of absorption above the hemoglobin solution shows a slower rate of blood coagulation [35]. From the measurements of hemoglobin absorption in 540 nm, as shown in Fig. 2, it was found that the PVA/TXA (20 mg/ml) sample had lower absorption values than the PVA/TXA (10 mg/ml). Also, PVA/TXA (20 mg/ml) and PVA/TXA (10 mg/ml) had higher blood coagulation ability than PVA (negative control). As illustrated in Fig. 3, the clots formed on PVA/TXA (20 mg/ml) were larger than the clots formed on PVA/TXA (10 mg/ml), and no clots were formed on pure PVA [36].

3.3 Platelet activation

SEM images depict that pure PVA activated platelets. However, compared to active platelets across the surface of nanofibers, PVA 5%-XA (10 mg/ml) and PVA 5%-XA (20 mg/ml) have been less widely spread (Fig. 4). It was observed that TXA inhibited plasmin catalytic activity and not platelet aggregation because platelet aggregation increased with increasing TXA [37]. A remarkable number of adhered red blood cells, as well as thrombus formation, were observed [38]. SEM images also showed that more platelet activation was captured in PVA 5%-TXA (20 mg/

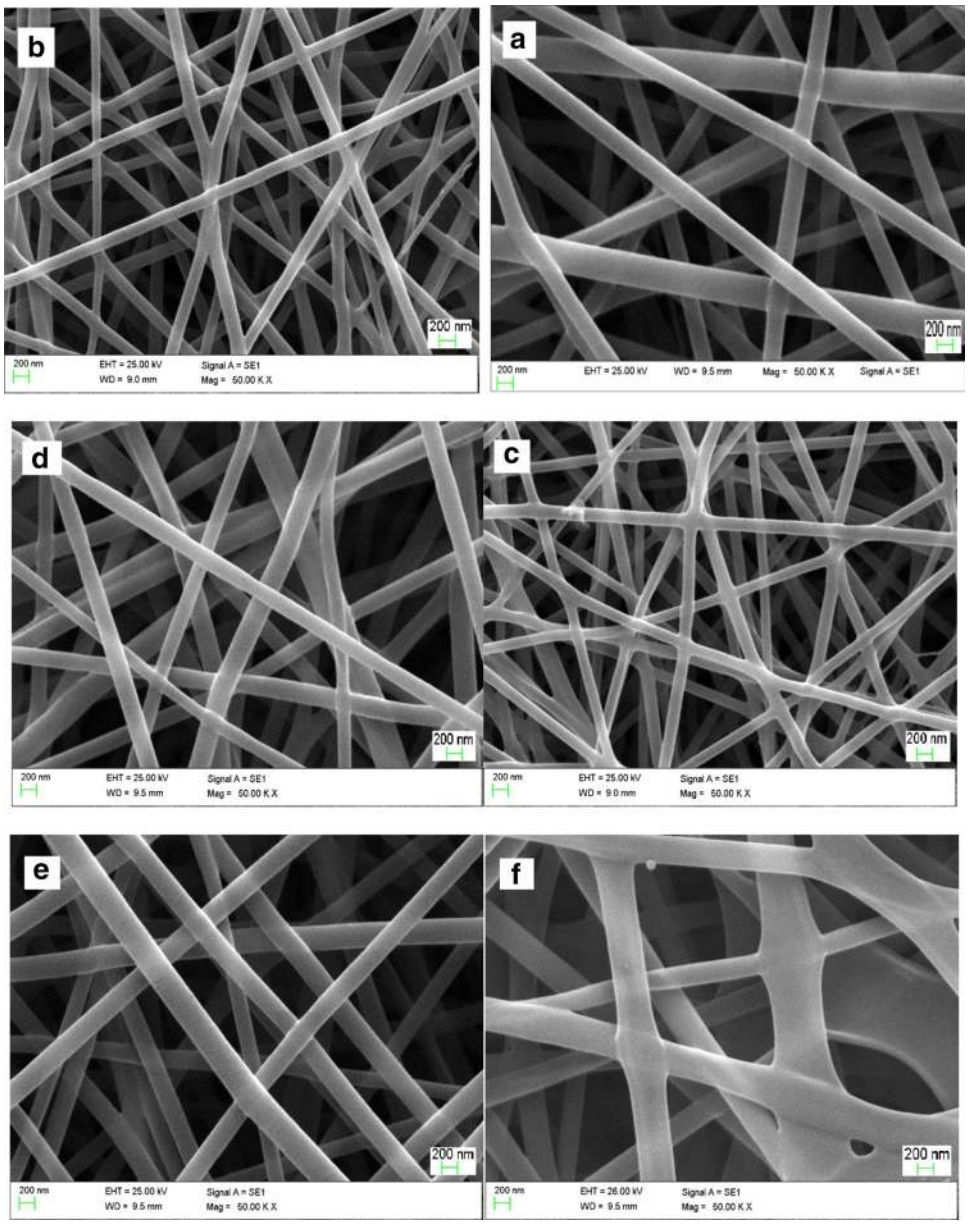

Fig. 1 Images of electron microscopy of nanofiber loaded with the drug **a** PVA 5%, **b** PVA 5%-TXA (10 mg/ml), **c** PVA 5%-TXA (20 mg/ml), **d** PVA 5%-CTX (0.1 µg/ml), **e** PVA 5%-CTX (1 µg/ml), **f** PVA5%-CTX (8 µg/ml)

Table 1 The effect of viscosity of polymer solution

Nanofiber diameter	Viscosity cp	Polymeric solution components
250 ± 84	384	PVA 5%
124 ± 55	234	PVA 5%-TXA (10 mg/ml)
110 ± 44	193	PVA 5%-TXA(20 mg/ml)
258 ± 93	396	PVA 5%-CTX(0.1 µ g/ml)
273 ± 99	416	PVA 5%-CTX(1 µ g/ml)
379 ± 225	476	PVA 5%-CTX(8 µ g/ml)

ml) nanofibers. Uniform distribution of platelets along the nanofibers indicated complete adhesion of the platelets and thus the ability to coagulate blood [39].

3.4 Antimicrobial test

Open wounds are very sensitive to infectious bacteria. Once the wound becomes infected, it needs additional treatments which are painful and caused to delay the healing. Using antimicrobial materials in wound dressings provides enhancement of protection [40]. Since ceftriaxone is used in the composition of nanofiber, ceftriaxone is a third-generation cephalosporin. Therefore, the nanofiber leads to inhibition of cell wall synthesis and inhibition of peptidoglycan cross-linking. They also play a role in activating bacterial cell autolysins that may be involved in bacterial cell lysis. The antibacterial property of nanofiber was evaluated by counting the

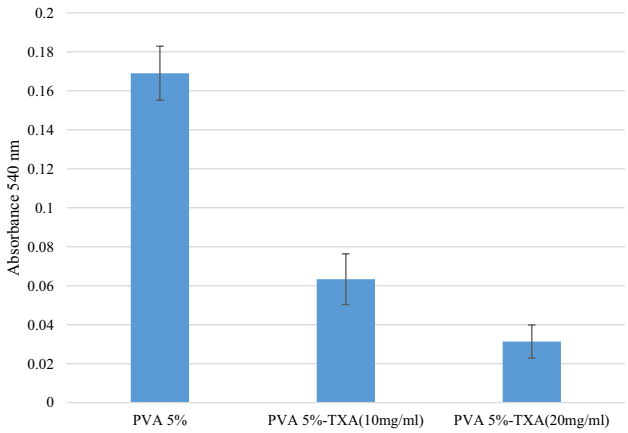

Fig. 2 Absorption value of hemoglobin solution

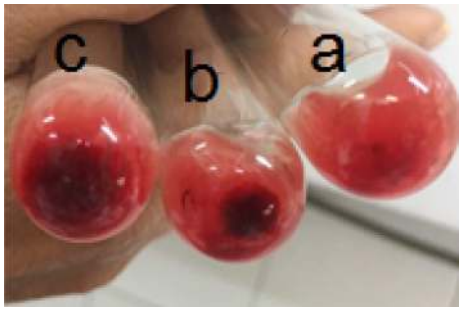

Fig. 3 Blood clotting coagulation **a** PVA 5%, **b** PVA 5%-TXA (10 mg/ml), **c** PVA 5%-TXA (20 mg/ml)

colony formation on the plates and calculating the percent inhibition using the formula R = 100 (B − A)/B. The results are presented in Fig. 5 to obtain the appropriate percentage of CTX antibiotics against Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria. As it can be seen, as the antibiotic concentration increased, the number of colonies decreased and the percentage of inhibition increased. As the antibiotic concentration reached 8 µg/ml, no colonies were observed on both Gram-negative and Gram-positive bacteria plates [41]. It was also observed in 0.1, 1 µ g/ml MIC: the rate of inhibition against *E. coli* gram-negative bacteria is higher than *S. aureus* gram-positive bacteria [42]. Therefore, it was concluded that the best value of using CTX for dressing was MIC: 8 µg/ml with more antimicrobial activity.

4 Conclusion

In this study, PVA nanofibers loaded with different drugs (TXA, CTX) were prepared using electrospinning process. SEM images revealed that PVA/TXA, PVA/CTX nanofibers were fabricated uniformly and without beads. In antibacterial analysis, PVA/CTX nanofibers were found to be good antibacterial properties against Gram-negative bacteria *E. coli* and the Gram-positive bacteria (*S. aureus*) because ceftriaxone is an antibiotic with a cell wall inhibition mechanism. PVA nanofibers loaded with TXA have good blood coagulation ability, and since TXA prevents the conversion of plasminogen to plasmin, it does not reduce platelet aggregation. Overall, PVA/CTX 8 µg/ml, PVA/TXA 20 mg/ml nanofibers can be employed as a distinguished product for wound dressing application because they have great potential than all other concentrations of CTX and TXA.

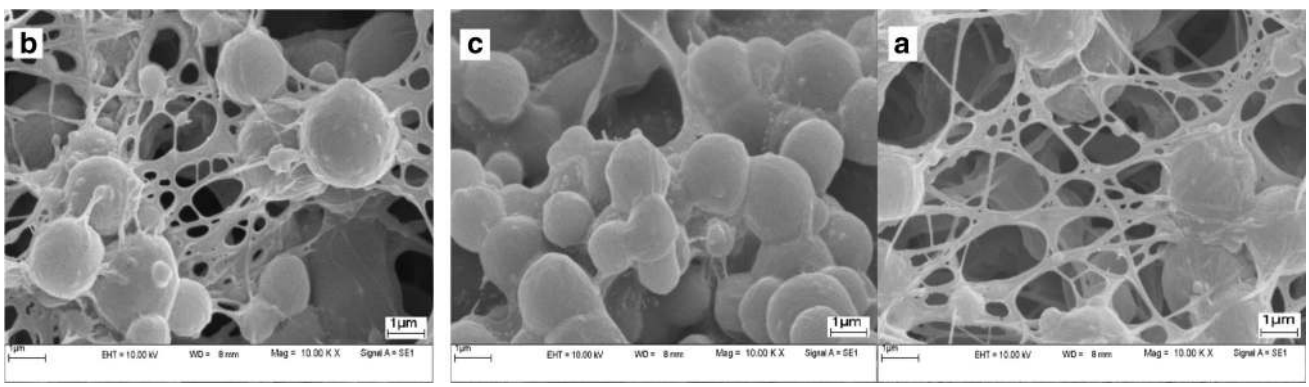

Fig. 4 SEM images of platelet activation **a** PVA 5%, **b** PVA 5%-TXA (10 mg/ml), **c** PVA 5%-TXA (20 mg/ml)

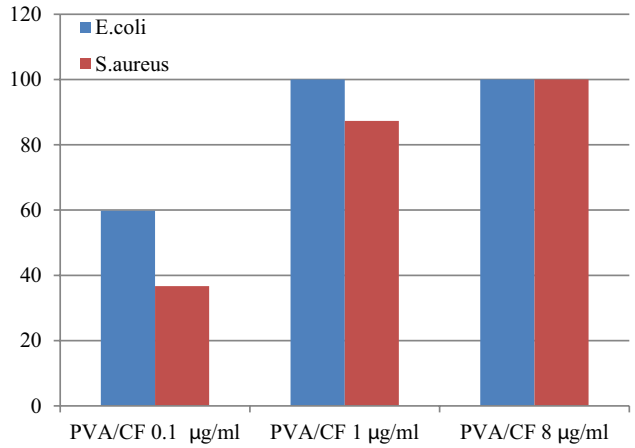

Fig. 5 Inhibitory percentage of PVA/CTX scaffold with MIC: 0.1, 1 and 8 µg/ml MIC: against Gram-negative *E. coli* and *S. aureus* Gram-positive

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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