



Mini Review

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Use of Silk Fibroin as Wound Dressings - An Innovative Concept



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Abstract

New applications for medical biotextiles have been identified with the development of nanotechnological manufacturing technologies. Combination of nanotechnology and biotextile technology has resulted into a new field called bionanotextiles. Bionanotextiles are used in many areas which include wound dressings, bandages and tissue scaffolds. Silk fibroin (SF) from the cocoon of *Bombyx mori*, is one of the most favourable wound dressing materials due to its unique properties including biocompatibility, permeability, biodegradability, morphologic flexibility, and proper mechanical properties. The modification of antimicrobial properties of SFs can provide a barrier for bacterial penetration as wound dressing materials. In the present study, antibacterial polyethylenimine (PEI) (10, 20 and 30% (w/w)) was blended with SF and bionanotextiles were successfully fabricated by electrospinning. In addition, silk fibroin nanofibers were also functionalized with sulphate group in order to test whether they exhibit an antibacterial activity or not. Fibroin based bionanotextiles were characterized by scanning electron microscope (SEM), Fourier transform infrared spectroscopy (ATR-FTIR), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). The cytotoxicity evaluations were carried out by L929 fibroblasts with MTT assay. The indirect cytotoxicity results demonstrate that all fibroin and PEI/fibroin extracts have no cytotoxicity on L929 cancer cell line. PEI/fibroin bionanotextiles showed strong antibacterial activities against gram positive *Staphylococcus aureus* and gram negative *Pseudomonas aeruginosa*.

Keywords: Silk Fibroin; Polyethylenimine; Antibacterial Polymeric Blends; Bionanotextile Wound Dressing; Electrospinning

Introduction

Medical textiles are used in many areas which also include bandages, wound dressings, surgery sutures, cartilage regeneration, artificial skin, heart valves, cardiac patches and preventive clothing [1-3]. The 1990s term of the "biotextiles" was defined as "structure composed of textile fibers and designed for use in a specific biological environment (e.g. surgical implant) where its performance depends on its interaction with cells and biological fluids as measured in terms of its biocompatibility and biostability" [4]. With the development of nanotechnology, the use of fibers and textiles in medicine has dramatically increased. Recent technologies have allowed traditional functionality of textiles to be extended. Nanotechnology and material science have added smart properties (e.g. high surface area, high productivity at low cost) to new generation textiles [5]. The "bionanotextile" term is defined as biopolymeric based textile produced by nano technological manufacturing method.

Silk has been used in textile industries for centuries. The silk protein from silkworm *Bombyx mori* contains two fibroin

proteins held together by a glue-like protein called sericin. When sericin is presented to a body, it is detected as an antigenic factor by T-cells and causes immunologic reactions. Therefore sericin is needed to be removed from the cocoon fibers by a process called degumming. These degummed *B. mori* silk fibers exhibit unique properties as biomaterials [6-11]. Silk fibroin (SF) is one of the most favourable wound dressing materials due to their unique properties including good biocompatibility, permeability, biodegradability, morphologic flexibility and proper mechanical properties [12].

Wound healing process is complex and involves the interactions between cells, extracellular matrix components and growth factors. Different natural polymer-based engineered wound dressings which substitute in the form of film, gel, sponges, and electrospun mats of chitosan, fibrin, elastin, gelatin, and hyaluronic acid are known to be used for wound healing stimulation [13]. The ideal wound dressing should perform following functions: Absorb excess exudates of wound, provide

thermal insulation and mechanical protections, prevent bacterial contaminations, allow gaseous and fluid exchanges, be non adherent to the wound and easily removable without irritation, provide some debridement action and be nontoxic, nonallergic, nonsensitizing, sterile and nonscarring. Open wounds are generally infected by micro-organisms such as bacteria, fungi, and viruses. The first step in infection is adherence of bacteria to wound interface [14,15]. In order to overcome this problem antibiotics, antimicrobial agents such as metallic nanoparticles have been utilized in wound healing applications.

Electrospun nanofibers with incorporated antibacterial agents such as chitosan [16,17], silver nanoparticles [18,19], zinc oxide [20,21], and chlorhexidine [22,23] have demonstrated potential use in bio-medical applications. Antibiotic-resistant bacterial infections have increased considerably in recent years. Traditional antibiotics are generally ineffective on bacterial infections. Therefore recent studies have focused on the new antimicrobial agents such as polymers, lipids and peptides. Host defense peptides have shown potential as alternatives to the currently available antibiotics. However these peptides have challenges, such as bioavailability and high product cost [24]. Wide range of metallic nanoparticles have been developed and used to modify textile fibers for their antimicrobial activity [25-27]. Recently silver nanoparticles have gained much interest because of their broad spectrum of antimicrobial activity. Incorporated silver wound textiles and catheters are used in biomedical applications [28]. Even with the wide usage of Ag nanoparticles in wound dressings, there are few reports about their cytotoxicity and genotoxicity and these reports show that Ag based cytotoxicity varies depending on the particle size [29,30]. The disadvantages of silver ion eluting systems are temporary antimicrobial activity and silver ions based cytotoxicity. To solve this problem scientists are working on nonleaching and permanent antimicrobial surfaces.

Antimicrobial synthetic polymers have gained much popularity owing to the permanent antimicrobial activity, especially the cationic compounds which are promising candidate materials for biomedical applications. PEI (polyethylenimine) is a polycationic and antimicrobial polymer [31-35]. PEI has been utilized as drug carrier in biomedical applications because of their ability to enter cells or permeabilize cell membranes [24]. On the other hand, it has been used in gene therapy applications [36,37], filtration technologies [38] and tissue engineering [39]. Electrospinning is an effective technique which can be utilized to produce useful ultrafine bio nano textiles. Due to their large surface area, bionanotextiles have received much interest in various applications such as medical textiles, filtration and drug delivery systems [40]. In comparison to conventional wound dressing materials bionanotextiles produced by electrospinning technology have advanced properties. These properties are controlled liquid evaporation, excellent oxygen permeability and prevention of bacterial infections with ultrafine pores. Porous structure of bionanotextiles absorb wound exudates efficiently

and prevent wound drying up [3].

In the literature there are many studies about electrospinning of silk fibroin, but reports on electrospinning of PEI are relatively scarce. In this study, for the first time in literature, it was aimed to fabricate PEI/fibroin antibacterial bionanotextiles serving as wound dressings with stable, non-leaching antibacterial activity. For this purpose polyethylenimine (PEI) was added to silk fibroin and hydrophilic polycationic, and antibacterial composite bionanotextiles were fabricated by electrospinning technique. On the other hand, previous studies have demonstrated that the sulfated silk fibroin has anticoagulant activity [41,42]. Highly sulfated biomolecules such as heparin are widely used as an antimicrobial agent [43]. Also in the light of this information silk fibroin nanofibers were functionalized with sulphate group in order to test their antibacterial activity.

The morphological, chemical, thermal characterizations of bionanotextiles were done by scanning electron microscopy (SEM), Fourier transform infrared (ATR-FTIR) spectroscopy, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), respectively. Moreover, cytotoxicity studies of the bionanotextiles were performed and their antibacterial activities against *Pseudomonas aeruginosa* and *Staphylococcus aureus* were evaluated.

Technical Details

The materials used include cocoons belonging to *Bombyx mori* species, polyethylenimine, formic acid, dialysis membrane, NaHCO₃, CaCl₂, glutaraldehyde, methanol, Pyridine, Dulbecco's modified Eagle's medium, fetal bovine Serum, L-glutamine, trypsin-EDTA, penicillin-streptomycin solution, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), *S. aureus* and *P. aeruginosa* bacterium, tryptic soy agar. Regenerated silk fibroin solution has been prepared. The nano fibre has been electrospun. In order to increase the stability of the fibres, the electrospun mats have been treated by methanol and also exposed to glutaraldehyde vapour. Methanol was used as a solvent to induce the structural change from amorphous to β sheet conformation and crystallization. Methanol was used as a solvent to induce the structural change from amorphous to β sheet conformation and crystallization. The electrospun silk based bionanotextiles have been further cross linked by glutaraldehyde. Then the bionanotextiles were rinsed with MQ water [38]. Surface morphologies of bio nano textiles were observed on scanning electron microscope. ATR-FTIR analysis was performed. Thermal analysis was done with Differential scanning calorimetry (DSC), Thermogravimetric analysis. Static contact angle measurements of bio nano textiles treated with 90% (v/v) methanol and glutaraldehyde vapor cross-linked have been determined. The cytotoxicity of the bio nano textiles was evaluated. Antibacterial activity of the bio nano textiles was tested against gram-positive *S. aureus* and gram negative *P. aeruginosa*.

Bionanotextile Morphology

Several parameters affect the fiber morphology, polymer concentration in solution, flow rate, applied voltage, tip to collector distance, diameter of the needle, polymer/solvent dielectric constant, etc. When fibroin and sulfated fibroin polymer solutions were prepared by low concentrations (8% (w/w)) bead formation was observed (Figure 1a). In our study we found that polymer concentration is the most important parameter for forming smooth and uniform fibers. To overcome this problem fibroin concentrations were increased and optimized to 13% (w/v). Fibroin bionanotextiles had an average diameter of

$246 \pm 6\text{nm}$ (Figure 1b). All other electrospinning parameters, including the distance between the tip and collector, solution flowrate, and syringe and needle diameters were held constant (voltage: 20kV, distance: 20cm, flow rate: 0.1mL/min). Fibroin is a candidate material which offer unique properties including good biocompatibility, biodegradability, morphologic flexibility to be used as biomaterial. However, its only deficiency is the lack of antimicrobial activity. It is well known that silk fibroin has good viscosity and the addition of silk fibroin into other polymer solutions can significantly improve the spinnability of the polymers [44].

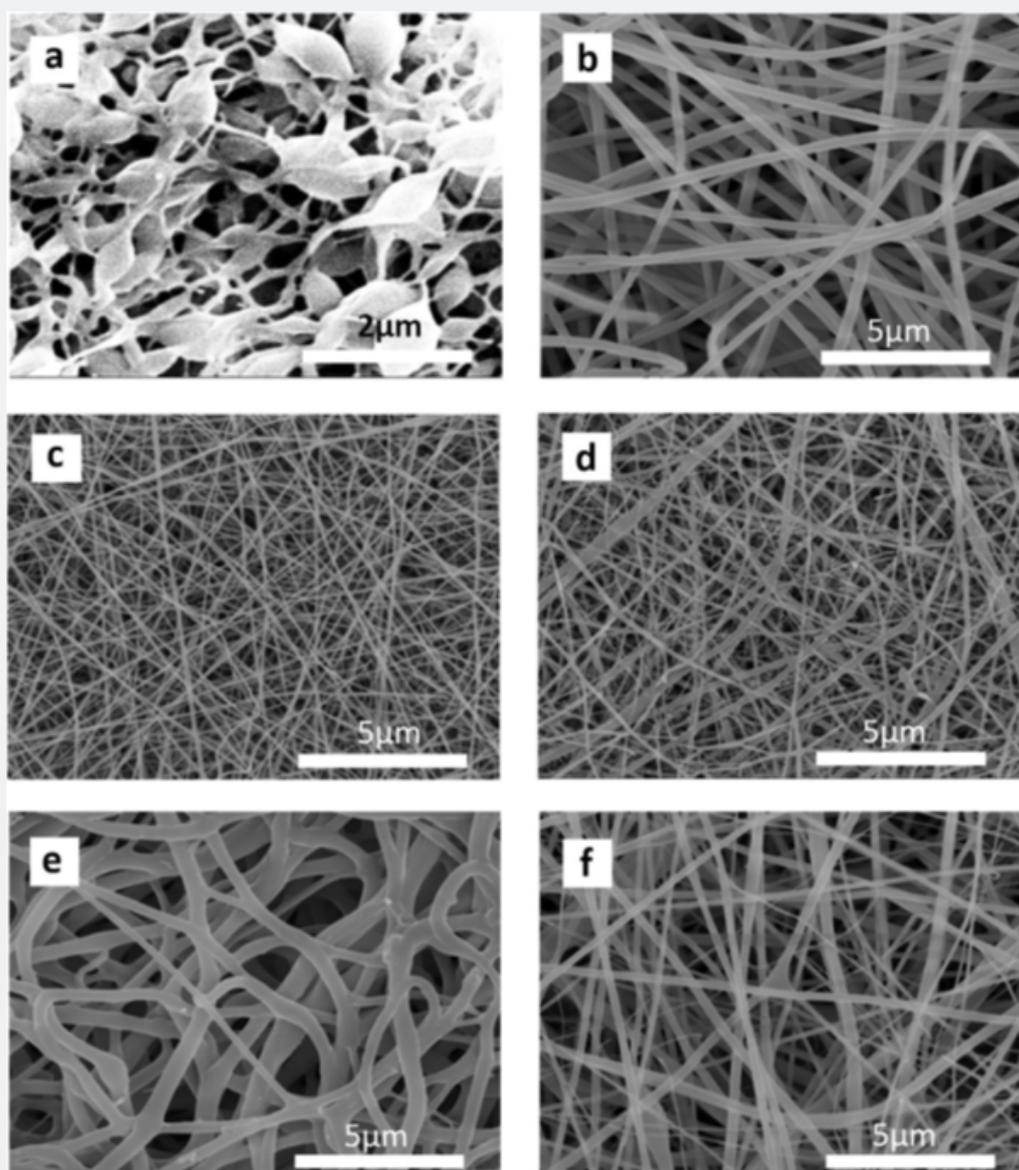


Figure 1: SEM images of the bionanotextiles. (a) 8% (w/v) fibroin bionanotextiles with bead formation, (b) smooth and homogeneous 13% (w/v) Fib, (c) PEI10/Fib, (d) PEI20/Fib, (e) PEI30/Fib and (f) 13% (w/v) S/Fib bionanotextiles (voltage: 20 kV, distance: 20 cm, flow rate: 0.1 mL/min, magnification: 20,000 \times).

There is only one report about electrospinning of PEI in the literature [39]. In this study we mixed PEI and fibroin to improve spinnability of PEI. When we mixed PEI and fibroin at 13% (w/v) concentration beads were observed among the nanofibers. The polymer concentration is directly related to the viscosity, surface tension, and conductivity of the polymer solution. As mentioned above the polymer concentration is a critical parameter to control morphology of nanofibers [38]. To improve spinnability of polymer solution we increased concentration of polymer to 15% (w/v) and by this optimization we managed to overcome bead formation. All other parameters were held constant (voltage: 20 kV, distance: 20 cm, flow rate: 0.1 mL/min). Different concentrations of PEI (10, 20, 30% (w/w)) were added to fibroin solution and made into fibers by electrospinning without any bead formation. PEI is a cationic active polymer and it is expected that the addition of cationic charges would increase the charge density in polymer solution and result in thinner fibers compared to fibroin bionanotextiles [44]. PEI10/Fib bionanotextiles had an average fiber diameter of 144 ± 5 nm and membranes showed a porous structure with smooth fiber orientation (Figure 1c). At a PEI/fibroin weight ratio of 20:80 (Figure 1d), the average fiber diameter increased to 210 ± 4 nm. Following the increase in concentration of PEI to 30:70, average fiber diameter increased to 236 ± 9 nm (Figure 1e). It is due to the fact that, charged polymers possess a significantly larger atomic radius than other polymers, and consequently, higher positive charges in electrospinning solution may result in instabilities in the electrospinning jet [44]. High concentration of PEI in water (more than 50% w/v) might decrease the surface tension of polymer solution and significantly affect the solution viscosity. Regarding this, when the concentration of PEI was higher than 30%, bead formation was observed and average fiber diameter was increased accordingly (Figure 1).

PEI is soluble in several solvents such as ethanol, methanol, chloroform, or hot water [45]. For this reason, in this study PEI containing bionanotextiles were crosslinked with GA instead of methanol treatment. Conventional crosslinking approach of immersing polymers into aqueous GA solution is not feasible for crosslinking the present nanoscale thin bionanotextiles. At first stage PEI/fibroin bionanotextiles were exposed to glutaraldehyde vapor for 24h but results of SEM analysis show that the fiber structure has been corrupted during the vapor treatment. To determine optimum crosslinking condition, bionanotextiles were exposed to GA vapor for a timescale of 0.5, 1, 3, 6, 12 and 24h. It was found that the bionanotextiles treated in the GA vapor up to 0.5 and 1h could be totally dissolved in the 37 °C water thus, crosslinking in GA vapor for 3 h was selected to crosslink bionanotextiles. Vapor of aqueous GA (25%) solution contains water vapor. Higher GA concentration and increased cross-linking time can change morphology of bionanotextiles. After long exposure time to GA vapor, the nanofibers were swollen and flattened because of the vapor phase [38,46]. Results show that with PEI concentrations of 10, 20, 30% (w/w), nanofiber diameter was increased to 175 ± 12 , 350 ± 8 and 392 ± 14 respectively after 3 h of crosslinking.

Average diameters of bionanotextiles with changing exposure time to glutaraldehyde vapor time have been determined, which may be attributed to the swelling of PEI/fibroin bionanotextiles in GA vapor. SEM images of the crosslinked bionanotextiles with changing time scale are shown in Figs. 2 and 3. It is well known that methanol, is highly effective in the crystallization of SF from random coil to β -sheet transition. We investigated the influence of the methanol treatment on the secondary structure of bionanotextiles by means of ATR-IR, DSC and TGA [47] (Figure 2&3).

Structural Characteristics of Bionanotextiles

ATR-FTIR measurements were implicated in order to determine the conformational changes of bionanotextiles treated with methanol and glutaraldehyde vapor. The infrared spectral region between 1700 and 1500 cm^{-1} usually used for the analysis of different secondary structures of silk fibroin. The peaks at 1610-1630, 1695-1700 and 1510-1520 cm^{-1} are characteristic of silk II, secondary structure of silk fibroin, whereas the absorption at 1648-1654 and 1535-1542 cm^{-1} are characteristic for silk I conformation. It is found that for the Fib and Fib-G bionanotextiles, amide I band shows one strong peak at 1651 cm^{-1} and amide II band shows one peak at 1534 cm^{-1} that is corresponded to silk I structure. The β -sheet structure is observed for samples immersed in methanol (Fib-M) with peaks at 1626 and 1518 cm^{-1} . This result proves that bionanotextiles have silk I structure. Otherwise, cross-linked PEI/fibroin bionanotextiles (PEI10/Fib-G, PEI20/Fib-G, and PEI30/Fib-G) show silk I structure peaks at 1654 and 1535 cm^{-1} . FT-IR spectra of sulfated fibroin showed a strong absorption at around 1200 cm^{-1} that is attributed to stretching vibrations of the SO_2 group.

Thermal Analysis

TGA results on fibroin, PEI/fibroin and S/fibroin bionanotextiles have been determined. For all samples curves can be divided in two regions. Region I recorded to loss of water and occurs at 100 °C. The second weight loss occurs in 270-370 °C. In region II high mass loss was observed and it's related to fibroin degradation. This is associated with the breakdown of peptide bonds. It is found that the amorphous samples of silk fibroin (fibroin, PEI/fibroin-G and S/fibroin) showed faster degradation curve and lower thermal stability than other crystalline sample (fibroin-M).

The DSC thermograms of bionanotextiles have been determined. DSC thermograms of Fib and Fib-G silk fibers displayed two endothermic peaks, one at around 80 °C is due to loss of water, and another at 270 °C is attributed to the thermal degradation of amorphous bionanotextiles (Fib and Fib-G). On the other hand, Fib-M showed an endothermic peak at 280 °C without exothermic transition.

This behavior is related to β -sheet structure of sample Fib-M and consistent with IR results. DSC thermograms of cross-

linked PEI/fibroin bionanotextiles (PEI10/Fib-G, PEI20/Fib-G, and PEI30/Fib-G). They show similar peaks like amorphous samples (Fib and Fib-G), one of them at around 190 °C is due to glass transition (T_g) of amorphous samples and another at 272 °C is attributed to the thermal degradation of amorphous bionanotextiles. Sulfated bionanotextiles showed two endothermic

peaks, one at around 80 °C is due to loss of water, and another peak at 270 °C is related to degradation of silk I structure. At the end of the experiments PEI20/Fib bionanotextiles were selected for the next steps because of their smooth and homogeneous morphology. Macroscopic images of bionanotextiles.

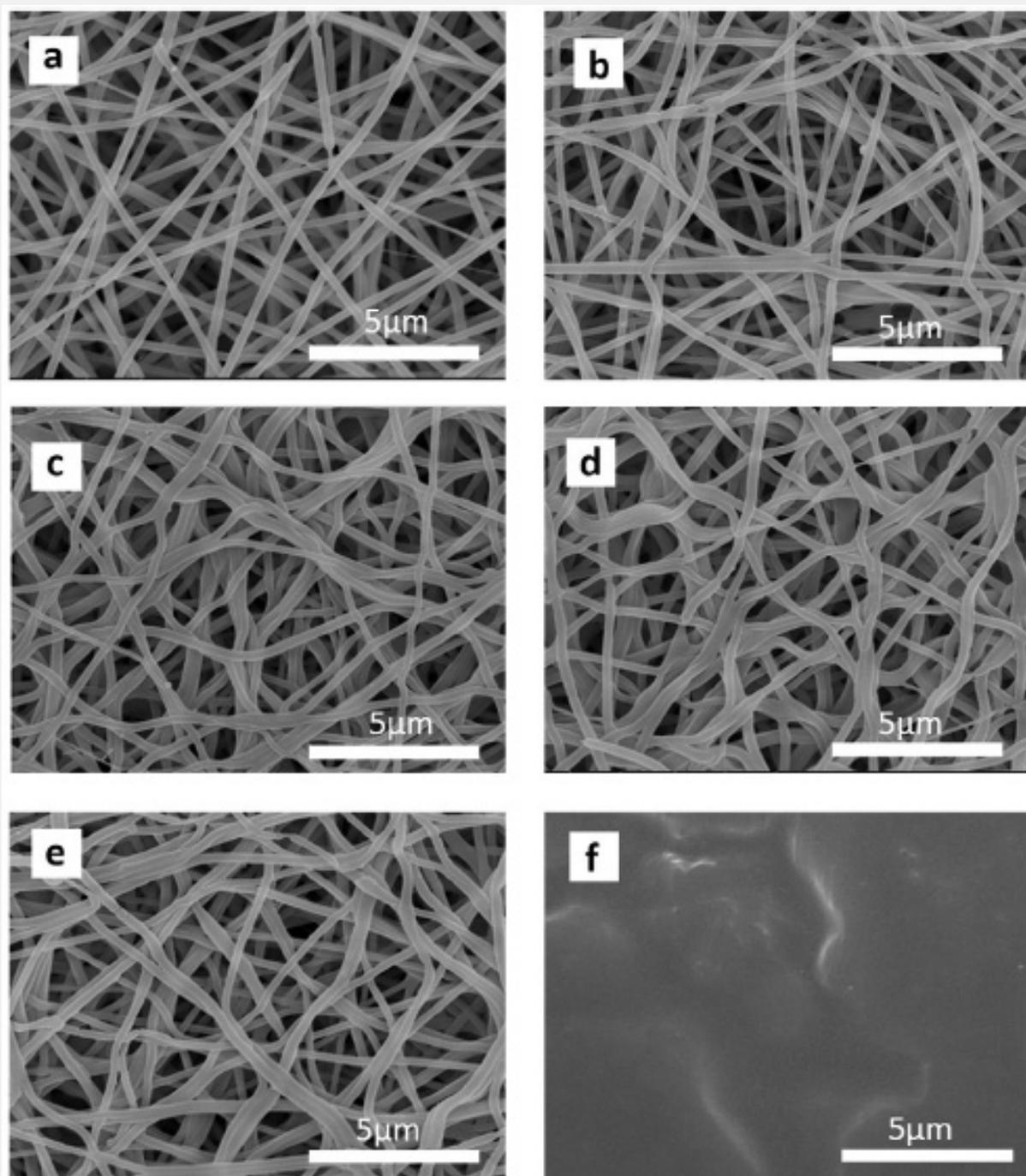


Figure 2: SEM images of 13% (w/v) Fib bionanotextiles were cross-linked in glutaraldehyde vapor for different time intervals. (a) 0.5 h, (b) 1 h, (c) 3 h, (d) 6 h, (e) 12 h and (f) 24 h (magnification: 20,000×).

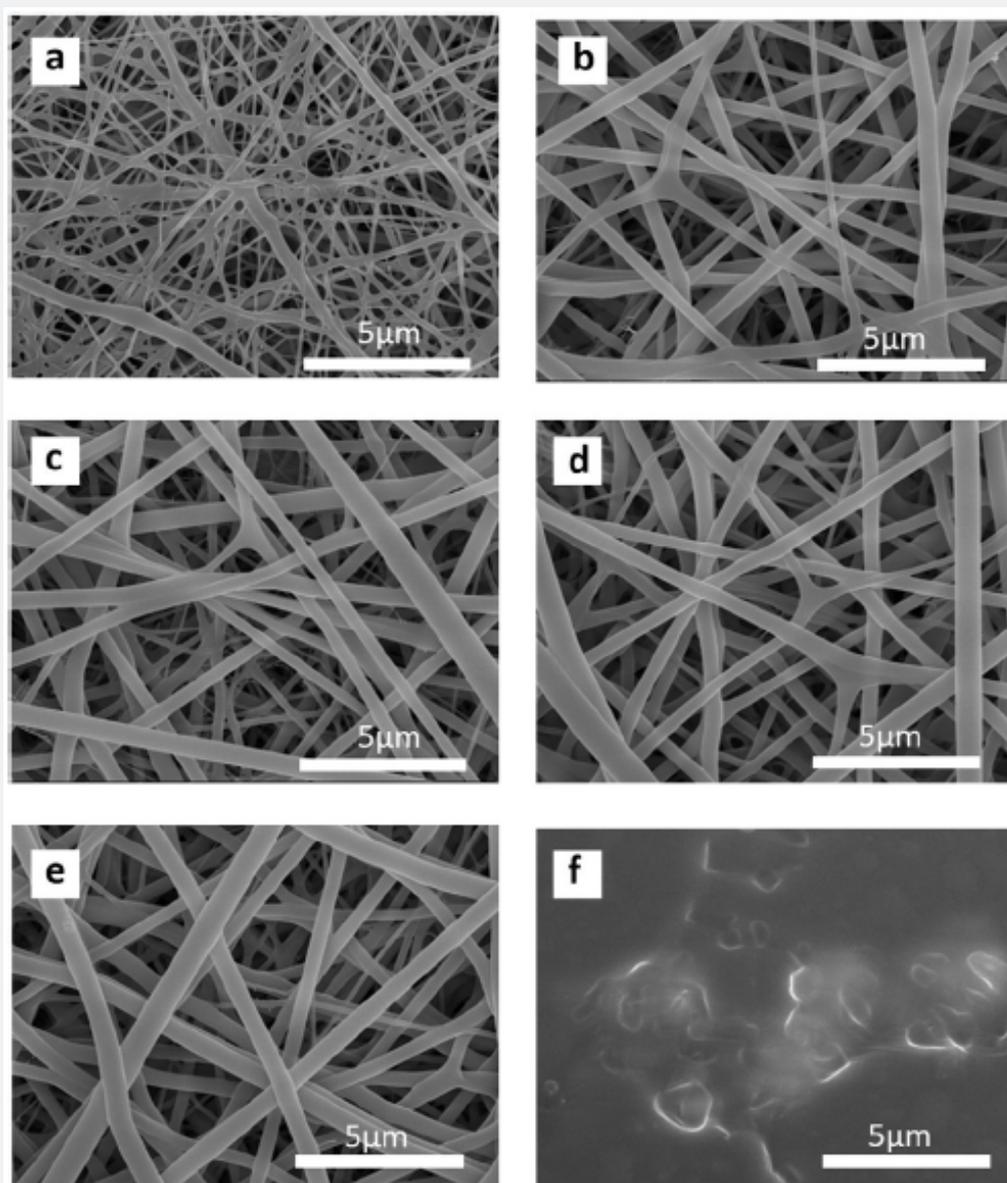


Figure 3: SEM images of PEI20/Fib bionanotextiles were cross-linked in glutaraldehyde vapor for different time intervals. (a) 0.5 h, (b) 1 h, (c) 3 h, (d) 6 h, (e) 12 h and (f) 24 h (magnification: 20,000 \times).

Surface Hydrophilicity

Wetting is an important property of a wound dressing surfaces. To investigate surface properties of bionanotextiles a water droplet was placed on the bionanotextile surface and contact angle measurement was read. Measurement of water contact angle on Fib-M surface was 100 °C indicating that silk fibroin is a hydrophobic material. S/Fib-M's contact angle was measured as 54°. These results show that S/Fib is more hydrophilic than fibroin-M because of its sulfate groups [48]. On the other hand, PEI10/Fib-G, PEI20/Fib-G and PEI30/Fib-G have contact angles of 109 °C, 142 °C and 155 °C, respectively. Compared to surfaces

of bionanotextiles, PEI/fibroin samples showed the highest contact angle measurement and hydrophobic property. A water droplet placed on this surface remains spherical and the reason is that glutaraldehyde reacted polyethylenimine (PEI-G) is more hydrophobic cationic polymer than polyethylenimine (PEI) [49]. Hydrophobicity of methanol treated silk fibroin materials (Silk II) showed a significantly higher contact angle than non-methanol treated materials (Silk I) [50].

A number of reports indicate that primary and secondary amine groups of PEI can be modified with stearic acid and glutaraldehyde. In this reactions carboxylic groups, of these

molecules react with amine groups in PEI and this modification can cause water contact angle larger than 150 °C [51]. In this study glutaraldehyde vapor was used in order to cross-link PEI and fibroin bionanotextiles. GA reacts with amine groups in PEI and fibroin and this reaction results in more hydrophobic bionanotextiles compared to other crystalline samples. Contact angle measurements have been determined.

Cell Viability

Cytotoxicity of the bionanotextiles was evaluated using MTT assay after 72h of extraction. The absorbance of the MTT crystals was read at wavelength of 570nm in a microplate reader. Cell viability was evaluated by counting percent viable cells after incubating them with bionanotextile extracts. Several researchers have reported PEI to be cytotoxic in many cells, but the molecular mechanism of its cytotoxicity hasn't been defined yet. PEI in its protonated form has been widely used as a gene delivery agent due to its high charge density from the protonated amines. Recent reports indicate that PEI based scaffolds with an excessive amount of positive charges are highly toxic in vivo while lower amounts of cationic charge are favorable [39,52]. Cell viability of PEI10/Fib and PEI20/Fib composite bionanotextiles, cross linked with GA vapor, was increased but in comparison to control group no significant difference was explicit. The reason was that PEI was positively charged and the cells were with the negative charge, and accordingly the electrostatic force between them would improve their adhesion.

At the same time, cells use amide groups as energy sources and they are also good for cell viability. On the contrary, cell growth and proliferation were decreased in the extract of PEI30/Fib membranes due to the fact that PEI30/Fib contains excessive amount of positive charges compared to others.

Antibacterial Activity

The antibacterial activity of bionanotextiles against gram-positive *S. aureus* and gram negative *P. aeruginosa* was tested by using AATCC Quantitative Test Method 100-1999 and viable cell-counting method. Antibacterial activity results have been determined. Polyethylenimine (PEI) containing materials have been widely used in biomedical applications due to their long-term antimicrobial activity with no developed resistance, minimal cytotoxicity to mammalian cells and biocidal ability for a broad spectrum of microorganisms [53]. PEI has an antimicrobial activity because of its polycationic structure and its interaction with microbial membranes would result in their disruption due to the polycationic structure [54,55]. The results demonstrate that Fib-M bionanotextiles don't show antibacterial activity against *P. aeruginosa* and *S. aureus*. However PEI containing bionanotextiles (PEI10/Fib-G, PEI20/Fib-G and PEI30/Fib-G) show high antibacterial activity against *P. aeruginosa* and *S. aureus*. In comparison to control group it was noticed that there was no growth on the electrospun PEI10/Fib-G, PEI20/Fib-G and PEI30/

Fib-G nanofibers. The antibacterial investigations demonstrated that PEI/Fib bionanotextiles could prevent adherence of the gram-positive or gram-negative bacteria. In contrast, about S/Fib-M bionanotextile bacterial colonies decreased from 3.94×10^3 CFU/mL to 1.1×10^2 CFU/mL against *P. aeruginosa* and for *S. aureus* no antibacterial activity was observed. Results showed that growth of bacterial colonies was too much (Too Numerous To Count) for *S. aureus*. Briefly, antimicrobial activity of bionanotextiles indicated that PEI is an effective and non-leaching antimicrobial agent to inhibit growth of gram-positive *S. aureus* and gram negative *P. aeruginosa*, when it is mixed with silk fibroin. Bionanotextiles which were designed in this study as wound dressing material, could be handled and produced easily.

Conclusion

New generation antibacterial bio nano textiles are the most advanced and efficient wound dressing materials in comparison to other conventional materials such as sponges, hydrocolloids and hydrogels. Bio nano textiles, due to their very high surface area to volume ratio, have excellent abilities such as controlled release of therapeutic drugs, a very high increase in adherence and proliferation of cells, etc. All these characteristics have highly extended bio nano textile applications on different wounds. In this study Fib, S/Fib and PEI/Fib composite bio nano textiles were successfully generated by electrospinning and all bio nano textiles were stabilized by methanol and GA vapor treatments. Optimum crosslinking time of 3 h was accepted for glutaraldehyde vapor treatment. Changes in the structure of the silk based bio nano textiles stabilized by different post-treatment methods were analyzed by ATR-FTIR, TGA and DSC. While Fib, Fib-G, PEI10/Fib-G, PEI20/Fib-G, PEI30/Fib-G and S/Fib bio nano textiles have silk I structure (random coil), Fib-M, S/Fib-M bio nano textiles have silk II structure (β -sheet). All of ATR-FTIR, TGA and DSC data are consistent with each other. Antibacterial activity and cytotoxicity results reveal that PEI containing bio nano textiles exhibit good antibacterial properties and ability to prevent bacterial adhesion over a long period of time.

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