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Development of Antibiotic Releasing Electrospun Nanofibrous Mats Based on Gelatin

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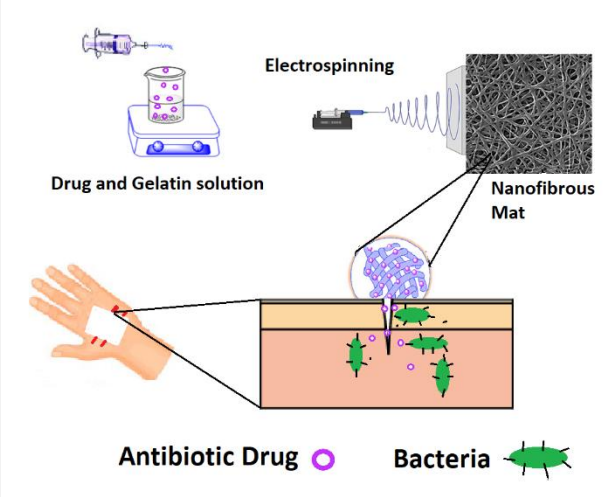
ABSTRACT

This work aimed to prepare pH-sensitive nanofibrous mats as a drug-releasing system using a green method. Gelatin nanofibers were first prepared by electrospinning and then cross-linked with glutaraldehyde. To evaluate the capability of this product as a drug delivery system, vancomycin was loaded into the nanofibrous mats in different doses as a model antibiotic drug. The chemical structure of the prepared material was investigated by (Fourier transform-infrared) FT-IR. Field emission scanning electron microscopy (FE-SEM) observations showed that uniform bead-free nanofibers with an average diameter of 157 nm were successfully fabricated. The drug release studies revealed that the relative rate of drug release in buffer media with pH =2.0 was higher than that in a buffer solution with pH =7.4. The drug release mechanism of samples was determined by the Korsmir-Pepas model. Moreover, the incorporation of vancomycin into the nanofibers provided an effective antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* microorganisms. The developed antibiotic-loaded nanofibrous mats can be considered a promising novel antimicrobial wound dressing material.



Keywords: Antibacterial property, drug delivery, electrospinning, gelatin, nanofibers

1. Introduction

The development of nanofibers with different material compositions, structures, and functionalities has been extensively pursued due to their unique properties such as high surface-to-volume ratio, the presence of very small pores, and excellent mechanical properties. Among the different methods that have been used so far to produce ultra-fine fibers, electrospinning is the most common technique because of the ease of the process and its wide applicability to many different polymeric materials [1, 2]. The fibers produced using this technique have unique properties such as

a substantial high surface area with a large number of small pores. Consequently, this technique is recognized as a straightforward tool in various fields such as optical sensors, filtration devices, facemasks, wound dressings, tissue engineering, antibacterial bandages, medical prostheses, and drug delivery systems [3-10].

However, different complex synthetic pathways and modifications have been usually done to produce polymeric electrospun nanofibers with desirable features for drug delivery and biomedical applications [5]. Recently, natural polymers such as gelatin, chitosan, alginate, etc. have attracted much attention in the field of drug delivery due to their biodegradability, biocompatibility, similarity to body tissues, and low-cost [11-13]. Among them, gelatin is a

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polyampholyte biomacromolecule obtained by hydrolyzing collagen continuing both anionic and cationic functional groups, which makes it an ideal candidate for targeted-drug delivery application [14, 15].

However, neat gelatin, especially in the form of electrospun nanofibrous mat has low stability in aqueous solutions and easily dissolves, which results in abrupt cargo release in biological media [16]. Different chemicals such as genipin [17], oxidized sucrose [17], oxidized phenolic compounds [18], citric acid [19], and glutaraldehyde [20-22] have been utilized to crosslink gelatin nanofibers. Among them, glutaraldehyde has been proposed as an efficient crosslinking agent for gelatin nanofibers. As it was shown that glutaraldehyde-crosslinked gelatin mats preserve their fibrous morphology in warm water and have significantly improved tensile strength and modulus [20-22]. Besides, the glutaraldehyde-crosslinked gelatin mats acted as a desired delivery system for the hydrophobic drug piperine [23, 24], and vitamins A and E [25].

The main goal of our present work is to explore the potential of glutaraldehyde-crosslinked gelatin mats as a carrier for controlled delivery of vancomycin as a model antibiotic in wound dressing applications. Vancomycin is a hydrophilic antibiotic used to treat infections caused by gram-positive bacteria that do not respond to other antibiotics [12]. For instance, it has been reported as a treatment for complex skin infections, bloodstream infections, endocarditis, and bone infections. Based on our knowledge, this is the first report assessing the potential of the glutaraldehyde-crosslinked electrospun gelatin nanofibrous mats for vancomycin delivery application.

Herein, a series of nanofibrous mats based on gelatin were prepared using an electrospinning technique and then stabilized with glutaraldehyde vapor. In addition, various contents of antibiotic drugs were loaded into the mats. The samples were characterized using FTIR and FE-SEM. Effects of the vancomycin content in samples and pH of buffer solution on the drug release behavior of nanofibers were comprehensively investigated. At last, the antibacterial activity of the developed mats against the E. coli and S. aureus bacteria was studied.

2. Materials and methods

2.1. Materials

Gelatin from porcine skin (G2500, type A, gel strength ~ 300) was obtained from Sigma-Aldrich Co. Germany. Acetic acid, hydrochloric acid solution (37 wt.%), monosodium phosphate, disodium phosphate, sodium hydroxide, hydrogen potassium phthalate, potassium chloride, and glutaraldehyde were prepared from Loba Chemie Pvt. Ltd of Mumbai, India. Vancomycin powder was prepared by Dana Pharmaceutical Company, Iran. *Escherichia coli* and *Staphylococcus aureus* bacteria were generously provided by the Central Laboratory of the University of Maragheh. Other chemicals were prepared from local suppliers.

2.2. Fabrication of electrospun nanofibers

To prepare a 20% w/v gelatin solution, a required amount of gelatin powder was added to a beaker containing deionized (DI) water and acetic acid with a volume ratio of 2:8. The solution was mixed with a magnetic stirrer (100 rpm) at room temperature for 3 h to completely dissolve the gelatin. Pre-determined amounts of vancomycin were then added and stirred at room temperature for another 3 h at 100 rpm.

An electrospinning device (Fanavaran Nano-Meghyas Co. Ltd., Iran) was used to prepare nanofibers. Optimal conditions for the preparation of gelatin nanofibers were set to be a solution flow rate of 0.32 mL/h, needle tip to collector distance of 20 cm, applied voltage of 22 kV, and collector rotation speed of 100 rpm. After completing the electrospinning process, nanofibers were allowed to dry at room temperature for 12 h. The nanofibers were then placed in a desiccator containing glutaraldehyde solution (25 wt%) for 12 h to crosslink and stabilize the gelatin nanofibers. Gelatin nanofibers containing 0.1, 0.25, and 0.5 wt% vancomycin (based on gelatin content) were prepared and abbreviated as Gel/vcm (0.1%), Gel/vcm (0.25%), and Gel/vcm (0.5%), respectively

2.3. Evaluation of vancomycin release from nanofibers

In the first step, various vancomycin solutions in phosphate buffer with pH values of 7.4 and 2.0 were prepared, followed by measuring their absorption intensity at 201 nm using the UV spectrophotometer (Shimadzu 1800, Japan). Finally, calibration curves were plotted. In drug release experiments, 0.1 mg of nanofibers containing vancomycin

were poured into a 25 mL buffer solution in a baker and placed at room temperature on a shaker (Parzan Pajooh Co., Iran) of 10 rpm. In specific time intervals, 0.2 mL of the solution was transferred to a vial and then 0.2 mL of fresh buffer was added to the drug-releasing solution. The sample was diluted 5 times with buffer and its absorbance at 201 nm was measured using the UV spectrophotometer. Based on calibration graphs, the amount of the released drug time was calculated.

2.4. Antibacterial behavior assessment

In order to evaluate the antibacterial properties of the prepared nanofibers, the antibacterial activity of the Gel/vcm samples against gram-negative (e.g. *Escherichia coli*) and gram-positive (e.g. *Staphylococcus aureus*) was investigated at pH =7.4. For this end, the disk diffusion method (DDM) was conducted by culturing bacteria on the surface of the agar. The surface of LB nutrient agar plates was incubated with the bacteria strains at 37 °C for 24 h. The antibacterial activity of disc-shaped samples was determined by measuring zones of inhibition around each sample in an agar plate.

2.5. Characterization

Fourier transform-infrared (FT-IR) spectroscopy was performed by the Spectrum Tow Spectrometer (Perkin Elmer, USA) at room temperature. Microscopic images of gold-coated mats were taken by a field emission-scanning electron microscope (FE-SEM), MIRA3 TESCAN-XMU model.

3. Results and discussion

3.1. FT-IR

FT-IR spectrum of neat gelatin nanofibers, glutaraldehyde-crosslinked gelatin nanofibers, glutaraldehyde-crosslinked gelatin nanofibers containing 0.1% vancomycin, and pure vancomycin are presented in **Figure 1**. In the spectrum of gelatin, the peak appeared at 3298.6 cm^{-1} corresponding to the stretching vibration of N-H [26]. The peak at 1640 cm^{-1} is related to the stretching vibration of carbonyl (C = O) of amide [26]. The peaks at 1530 and 1236 cm^{-1} originated from N-H bending vibration of the amide II group and the stretching vibration of C-N of type III amide, respectively [27, 28]. In the crosslinked nanofibers, the characteristic peak of the aldimine group appeared in the wavenumber of 1450 cm^{-1} [15].

In the spectrum of pure vancomycin, the peak located at 3277.6 cm^{-1} corresponds to the –COOH group [29]. The absorption peaks at 1650 and 1585 cm^{-1} are related to the stretching vibrations of C=O and C=C, respectively. In addition, the peak observed at 1226 cm^{-1} corresponds to the stretching vibration of C-O of the phenol groups [27]. The crosslinked Gel/vcm (0.1%) sample shows a combination of the peaks related to the drug and the crosslinked gelatin samples. Meanwhile, the peak intensity of the gelatin carbonyl group at 1640 cm-1 was decreased and it became wider in the presence of the drug, which could be due to the formation of hydrogen bonds with the drug functional groups.

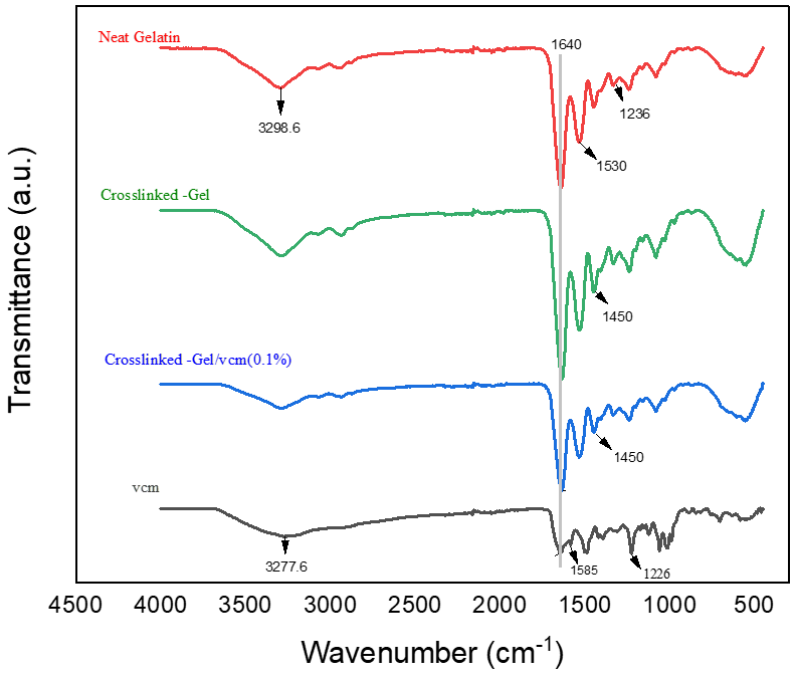

Figure 1. FTIR Spectra of neat gelatin, glutaraldehyde-crosslinked gelatin, glutaraldehyde-crosslinked Gel/vcm (0.1%), and neat vancomycin (vcm).

3.2. FEESM analysis

FE-SEM images of drug-free gelatin nanofibers and the gelatin nanofibers containing 0.1% drug are shown in **Figure 2**. It can be seen from FE-SEM analysis that bead-free and uniform electrospun nanofibers are fabricated in both samples. Moreover, FE-SEM images were used to determine the average diameter of electrospun nanofibers through ImageJ and Origin software, and the resultant graphs are shown next to the corresponding FE-SEM images. The average diameter of drug-free and drug-loaded gelatin nanofibers was determined to be 157 and 168 nm, respectively, indicating that the diameter of gelatin nanofibers slightly increased in the presence of a drug.

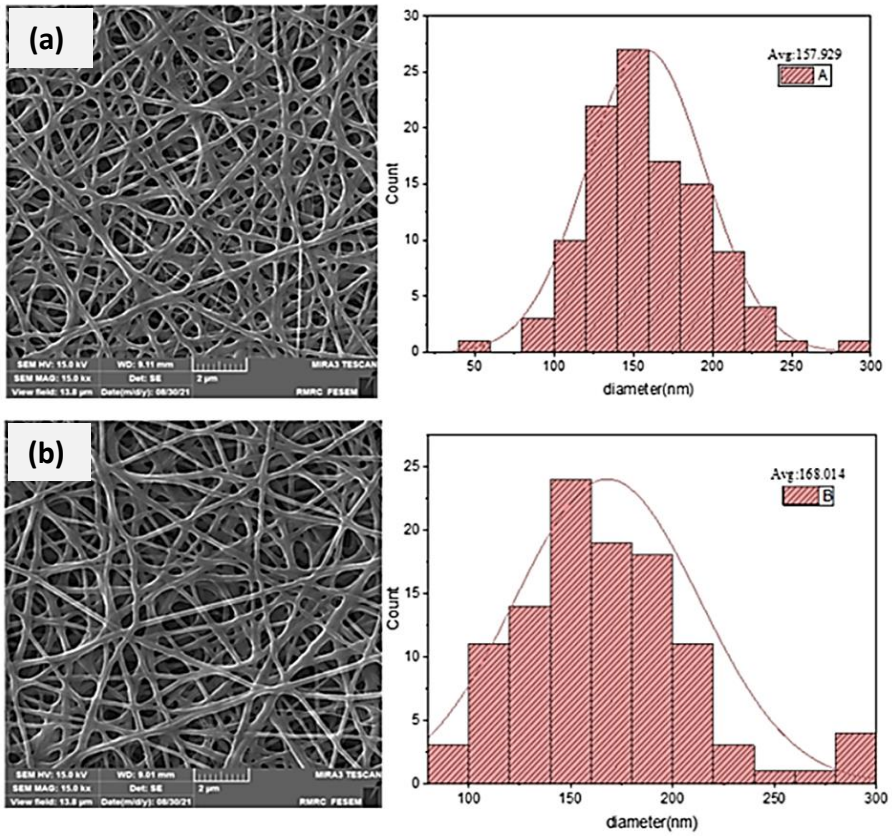

Figure 2. FESEM micrographs and fiber size distribution of the crosslinked electrospun nanofibrous mats of (**a**) gelatin and (**b**) gelatin with 0.1 wt% drugs (Gel/vcm (0.1%).

3.3. Drug release studies

The effect of the drug loading content on the drug release profile was first evaluated in a buffer solution with pH 7.4, and the obtained results are presented in **Figure 3**. The drug release profile of gelatin nanofibers containing 0.1%, 0.25%, and 0.5% vancomycin are compared in Figure 3. In the initial stage, due to the rapid swelling of nanofibers, the drug release rate from nanofibers is relatively high. Another reason for this phenomenon can be due to the presence of some free moieties of the drug on the surface of nanofibers. For better clarification of the effect of drug loading on the initial drug release amount, vancomycin release graphs of samples in the first 180 min are compared in Figure 3 (b). It can be seen that with decreasing drug loading in the nanofibers, the drug release rate decreased, and the release occurred in a sustained manner. As the nanofibers containing 0.1% drug exhibited relatively controlled release behavior in the first 180 min. Nearly 64% of the drug was released during 180 min (**Figure 3b**) and then the release gradually continued until 1500 min (**Figure 3a**).

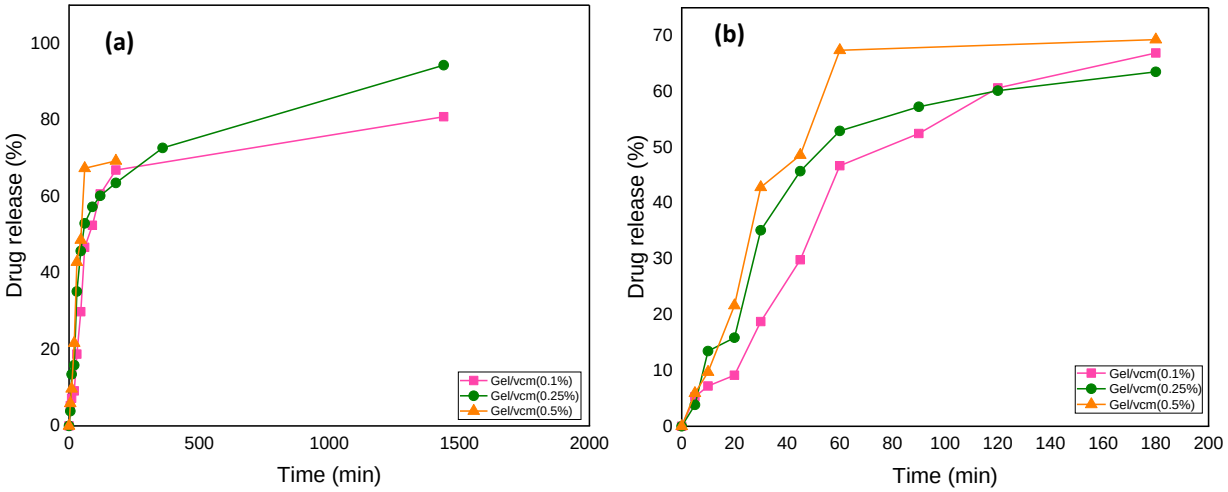

Figure 3. Investigating the effect of drug loading content on the drug release profile of gelatin-based nanofibrous mats at pH 7.4 after (**a**) 1480 min and (**b**) 180 min.

pH-dependent drug release assessment was also performed by immersing Gel/vcm (0.1%) nanofibers in buffer solutions with pHs of 7.4 (simulated intestinal fluid) and 2.0 (simulated gastric fluid) to investigate their potential for use as pH-responsive materials for oral drug delivery application [19, 30]. As can be seen in **Figure 4,** the release amount of the drug in a buffer with pH 7.4 is lower than that in a buffer with pH 2.0 at the same time. Furthermore, results presented in **Figure 4b** indicate that these nanofibers released the drug faster at pH 2.0 as compared with that at pH 7.4 in the initial step. 45% of the drug was released in the first 20 min at pH 2.0. While only 9% of the drug was released from the nanofibers at pH 7.4 at the same time. Gulsun et al. [30] recently prepared indomethacin-loaded gelatin electrospun nanofibers followed by glutaraldehyde vapor crosslinking. It was observed that release rates reach 75.6% and 85.9% within 1 and 3 h from nanofibers at pH 7.4, respectively. Another study showed that glutaraldehyde-crosslinked gelatin mats have a drug release of 87.7 ± 2.1, 85.6 ± 2.9, and 77.6 ± 5.8% after 24 h for a model hydrophobic drug, piperine at pH values of 8, 7.4, 6 and 1.2 respectively [23].

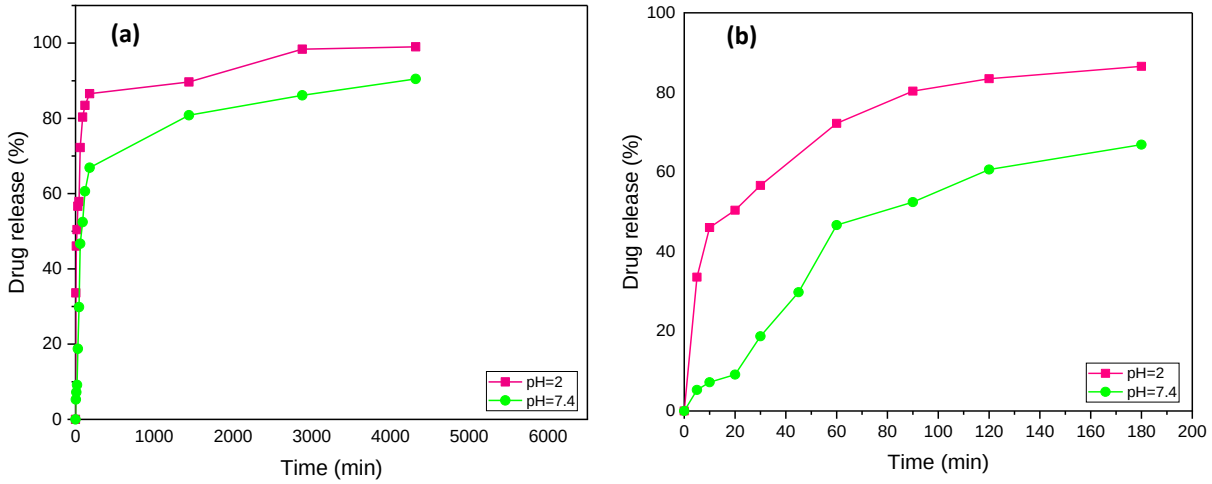

Figure 4. Comparing the drug release profile of Gel/vcm (0.1%) nanofibrous mats in buffer solutions with pH values of 2 and 7.4 after (**a**) 4200 min and (**b**) 180 min.

3.4. Drug release mechanism

Vancomycin release data were adapted to the Korsmir-Pepas model (Equation 1). This equation is used to describe the drug-release behavior of polymeric systems [31].

$$\log(\frac{M_t}{M_\infty}) = n\log(K) + n\log(t) \quad (1)$$

where, $\frac{M_t}{M_\infty}$ represents a fraction of the drug released at a time of t, K is a kinetic constant, and n is the diffusion coefficient for drug release. The value of n determines the mechanism of drug release. The $n \leq 0.45$ indicates the mechanism of Fickian diffusion, while $0.45<n<0.89$ illustrates non-Fickian transport, Case II transport if n = 0.89, and for n > 0.89 the mechanism is Super Case II transport. n = 1 demonstrates the fact that the drug release kinetics is not time-dependent and the mechanism is zero-order [32]. As mentioned before, the release of vancomycin was performed at two different pH levels of 7.4 and 2.0. The drug release data were examined by the Kursmir-Pepas model, and the results were listed in **Table 1**. Results indicate that more than one mechanism for drug release can be observed. For instance, the drug release mechanism from gelatin nanofibers changed from Fickian to non-Fickian by increasing pH from 2.0 to 7.4 [19].

Table 1. Results of n, K, regression coefficients, and release mechanisms of vancomycin from Gel/vcm nanofibrous mats obtained from Kursmir-Pepas equation.

Sample	pH	n	K	R^2	Release Mechanism
Gel/vcm (0.5%)	7.4	0.801	0.303	0.802	Non-Fickian
Gel/vcm (0.25%)	7.4	0.738	0.253	0.965	Non-Fickian
Gel/vcm (0.1%)	7.4	0.610	0.267	0.983	Non-Fickian
Gel/vcm (0.1%)	2.0	0.286	0.205	0.931	Fickian

3.5. Antibacterial test

The antibacterial activity of nanofibers against Gram-negative (i.e. *Escherichia coli*) and Gram-positive (i.e. *Staphylococcus aureus*) was investigated and the obtained results were demonstrated in **Figure 5**. In this experiment, samples of nanofibers without the drug and nanofibers containing 0.1% of vancomycin were examined. In the images obtained from the antibacterial test after 24 h, the nanofibers containing the drug showed antibacterial activity. This property against *Escherichia coli* (inhibition zone around the sample with a diameter of 1.9 cm) was higher compared to *Staphylococcus aureus* (inhibition zone around the sample with a diameter of 1.2 cm). Drug-free nanofibers did not show detectable antibacterial properties against both types of bacteria.

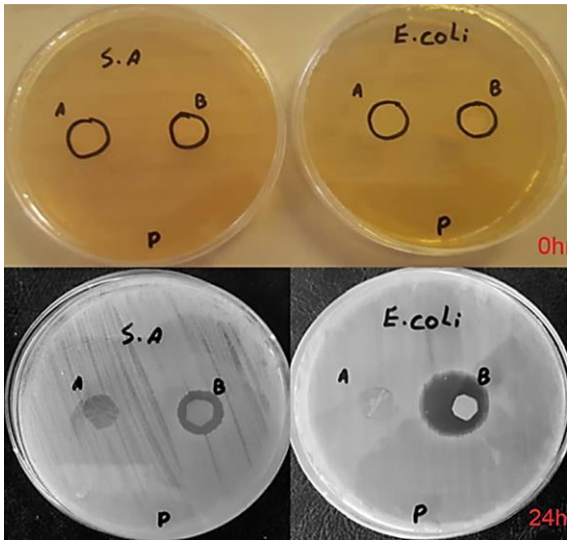

Figure 5. Photographs of antibacterial activity of nanofibrous mats of Gel/vcm(0.1%) against *S. aureus* (left image) and *E. coli* (right image) microorganisms after 24 h incubation.

4. Conclusion

In this study, a drug delivery system based on gelatin was successfully developed using a facile method. FE-SEM analysis showed that uniform bead-free nanofibers with an average diameter of 157 nm were fabricated. In-vitro drug release studies showed that the nanofibers have a pH-responsive drug release behavior. In addition, lowering the drug content from 0.5% to 0.1% in the nanofibers, resulted in a gradual and sustained drug release behavior. The Kursmir-Pepas model indicated that the drug release mechanism from gelatin nanofibers changed from Fickian to non-Fickian by increasing pH from 2.0 to 7.4. It was also found that the drug-loaded samples have good antibacterial properties against both Gram-negative (e.g. *Escherichia coli*) and Gram-positive (e.g. *Staphylococcus aureus*) bacteria. The developed antibiotic-loaded nanofibrous mats can be considered novel antimicrobial wound dressing mats.

Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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Declaration of competing interest

The authors declare no competing interest.

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Data availability

Data will be made available on request.

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