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A simple green route to obtain poly(vinyl alcohol) electrospun mats with improved water stability for use as potential carriers of drugs

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ABSTRACT

Poly(vinyl alcohol) (PVA) is a hydrophilic, biocompatible and nontoxic polymer. However, because of its low water-resistance, some applications for PVA-based materials are limited (e.g., drug delivery systems and wound dressings). In the current work, PVA mats containing tetracycline hydrochloride (TC) were successfully developed by electrospinning. In order to improve the water stability of the systems, the cross-linking of the PVA matrix was induced by citric acid (CA) addition together with heating treatments (150 °C or 190 °C for 3 min). TC presence led to a strong increase in the electrical conductivity of the blends and as a result, fibers with about 44% lower diameter (270 nm) than that of the corresponding unloaded mats (485 nm) were obtained. Laser scanning confocal microscopy images indicated that TC was well distributed along the PVA nanofibers. The mats were evaluated by FTIR, which revealed chemical interactions between PVA hydroxyl groups and CA carboxylic ones. The treatment at 150 °C for 3 min proved to be the more suitable for the preparation of TC-containing mats with improved water resistance, maintaining the TC antimicrobial activity against both *Escherichia coli* and *Staphylococcus aureus* almost unaltered. These mats showed a burst release of TC, giving around 95% of the drug within the first hour of immersion in water.

1. Introduction

Over the past decades, the growing interest in sustainability and Green Chemistry has led to increase the use of ecofriendly materials and processes. Poly(vinyl alcohol) (PVA) is a hydrophilic semicrystalline polymer produced by polymerization of vinyl acetate to poly(vinyl acetate) (PVAc), and the subsequent hydrolysis of PVAc to PVA. This polymer is widely used industrially and also has the advantages of being biocompatible, biodegradable and nontoxic [1].

Electrospinning is an emerging technology for the production of mats of continuous micro- or nanofibers by an electrostatically driven jet of polymer solution (or polymer melt) [2]. This electrohydrodynamic technology has gained high impact for polymer processing, mainly because it allows the control of fiber morphology, diameter and even porosity. Moreover, the production of fibers for biomedical applications by electrospinning is an attractive alternative for the entrapment or encapsulation of bioactive molecules [1,3–6]. A wide variety of micro- and nanofibers have been fabricated by electrospinning using polymers from natural sources (e.g., collagen, elastin, fibrinogen and silk fibroin) and synthetic polymers (e.g., poly(vinyl alcohol), poly(ε-caprolactone) and poly(lactic acid)) [7–10]. Among them, PVA produces a stable jet during electrospinning and allows obtaining bead-free nanofibers [1, 11–13].

Recently, PVA-based materials have been gaining attention globally because of the advantage of being used as environmentally friendly water-soluble packaging (e.g., detergent and agrochemical packaging, and laundry bags for hospitals). However, the use of PVA in other applications (e.g., semipermeable membranes, wound dressing and tissue substitute) is limited due to its low water stability [12]. Therefore, PVA-based materials are often treated to ensure prolonged structural integrity and to enhance their performance. For this purpose, several strategies have been developed, including freeze–thaw inducement of crystallization, heat treatment, acid-catalyzed dehydration, irradiation and radical production [14]. Bifunctional aldehydes have also been used in the cross-linking of PVA (e.g., glutaraldehyde) [14]. However, some of them are toxic and expensive [15,16]. Citric acid (CA) constitutes a green route for PVA cross-linking. This natural compound has the advantages of being abundant and of low cost. Moreover, CA is currently used as preservative, food additive and cleaning agent [17]. Other important advantages of the use of CA as cross-linker are its low toxicity and high biocompatibility, extending the applications of cross-linked materials to the biomedical field. Being a polycarboxylic acid, CA may react with the hydroxyl groups of PVA chains and lead to

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intermolecular-type and intramolecular-type ester linkages among them [17–19]. Commonly, the cross-linking reaction between PVA and CA is induced by heating at temperatures ranging between 130 and 220 °C for long periods of time (*c.a.* 2 h) [17]. This approach can lead from the partial to the total degradation of heat-sensitive bioactive compounds present in the polymer.

Tetracycline hydrochloride (TC) is a broad-spectrum and inexpensive antibiotic, highly effective in the inhibition of the synthesis of bacterial proteins, which has been used extensively in the treatment of human and animal infections [20].

The aim of the current work was to fabricate PVA electrospun mats to carry TC, using a green route. Citric acid (CA) (a natural cross-linker) was added to the mats, which were then heat-treated (150 °C or 190 °C for 3 min) in order to improve their water stability. The morphology, the size, the chemical conformation, the thermal behavior, the water solubility and the antimicrobial activity of the TC-PVA/CA electrospun mats were evaluated before and after the heat treatments. To the best of our knowledge, this is the first time that TC-containing PVA electrospun mats with improved water stability have been produced using this approach and preserving their antimicrobial activity against typical Gram-positive and Gram-negative microorganisms, *Escherichia coli* and *Staphylococcus aureus*, respectively.

2. Materials and methods

2.1. Materials

Fully hydrolyzed polyvinyl alcohol (PVA, ELVANOL® T25) was supplied by Diatex (Buenos Aires, Argentina). The PVA molecular weight (M_w) is in the range of 50 to 55 kDa (E. I. DuPont Co., USA).

Tetracycline hydrochloride (TC) (Parafarm) was purchased from Droguería Saporiti (Argentina). Citric acid (CA) was supplied by Sigma-Aldrich (USA).

2.2. Preparation of the electrospun mats with and without drug

The stock solutions to prepare tetracycline hydrochloride-loaded electrospun mats (TC-PVA/CA) were prepared by dissolving 12.0 g of PVA in 100 mL of distilled water, under heating at 75 °C until complete dissolution. CA was added to the PVA solution at 5.0% (wt./PVA weight) under constant stirring for 30 min. After total dissolution, the blends were cooled down to room temperature and then TC was added at 5.0% (wt./PVA weight) under constant stirring for 30 min. Finally, the solutions were sonicated for 5 min to remove bubbles. PVA/CA blends without TC were also prepared under identical conditions.

The viscosity and the electrical conductivity of the electrospinning solutions were measured in a rheometer (RS 600, Haake, Germany) and a conductivity meter (Mettler Toledo, USA), respectively.

The electrospinning process was carried out using a horizontal setup as shown in Fig. 1. The solutions contained in 10-mL syringes were pushed employing a syringe pump (Apema PC11U, Argentina) with controlled feed rate (0.5 mL h^{-1}) through a 21G needle (0.8 mm).

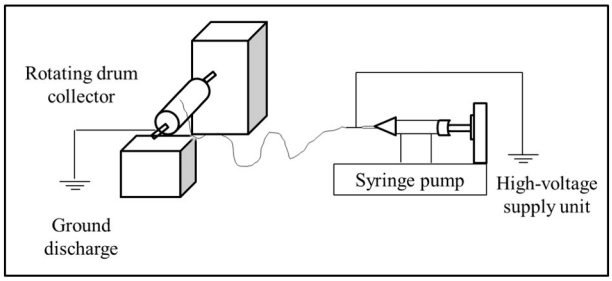

Fig. 1. Schematic representation of the electrospinning process.

Electrical voltages in the range of 20 to 35 kV were applied to the needle using a high-voltage supply unit (50 kV, 20 mA).

The polymer ejected from the needle tip was collected on a rotating drum of 6-cm diameter covered by aluminum foil, located at 20 cm from the tip. The collector was connected to the negative electrode of the power supply (ground), while the spinneret filled with the polymer solution was connected to the positive terminal (Fig. 1). For the morphological study, the collection time was about 5 min; while for the rest of the experiments the collection time was about 5 h. The thickness of the resulting electrospun mats collected during 5 h was between 20 and 30 μm. The electrospun mats were treated at 150 °C or 190 °C for 3 min, in order to improve their water stability. These conditions were chosen based on both literature reports [14,17] and the results of preliminary experiments on the water stability of the mats and the thermal degradation of the drug.

2.3. Scanning electron microscopy and confocal laser microscopy

The morphology of the resulting fibers was examined by scanning electron microscopy using a field emission gun (FE-SEM) (SUPRA 40, Carl Zeiss NTS, Germany). The electrospun mats were sputtered with a thin layer of gold prior to SEM observation. The fiber sizes were determined from the micrographs using the ImageJ free software [21]. The results were reported as average values from at least 100 measurements. In order to evaluate the distribution of TC in the electrospun nanofibers, a confocal laser scanning microscope (CLSM, FV 300, Olympus, Japan) equipped with an Argon ion laser (488 nm) was used. The recording was done focusing with a 20× objective (NA = 1.40). The emission of TC was detected in the range of 500–560 nm [22].

2.4. Water solubility of the electrospun mats

Samples cut into 5 × 5 cm were weighed and submerged in 20 mL of distilled water (pH = 6.0) at room temperature (22–25 °C) for 24 h. Later, the water was removed and the samples were dried at 50 °C until constant weight (around 2 h). The mass loss during dissolution in water was calculated with the following equation:

$$S(\%) = \left(\frac{W_0 - W_1}{W_0}\right) \times 100$$

where W_0 is the initial dry weight of the sample and W_1 is the dry weight after dissolution in water.

2.5. Determination of the drug content of electrospun mats

Samples of untreated and heat-treated TC-PVA/CA mats were weighed and immersed in an exact amount of distilled water at room temperature. After 24 h, aliquots of the solutions were removed and their UV–vis spectra were spectrophotometrically measured in a range from 200 to 500 nm (SHIMADZU UV-1800, Japan). A TC standard solution was prepared and its UV-VIS spectrum was also recorded for comparison. The concentrations of drug released from the untreated and heat-treated TC-PVA/CA mats were determined at 357 nm with an appropriate calibration curve. The results were expressed as mg of TC per gram of electrospun mat.

2.6. Release studies

Samples of TC-PVA/CA mats were carefully removed from the aluminum foil, weighed and immersed in an exact amount of distilled water at room temperature. Aliquots of supernatant were removed at different times for 24 h, and the amount of the drug dissolved in the withdrawn solution was quantified as described above (Section 2.5). Finally, the cumulative amount of drug released from the specimens for each specified immersion period was calculated.

2.7. Antibacterial activity of the electrospun mats

The antimicrobial activity of the electrospun mats against the Gram(+) bacterium *S. aureus* (ATCC 25922) and Gram(−) bacterium *E. coli* (ATCC 25922) was tested. The assays were carried out according to the disc diffusion method of the U.S. Clinical and Laboratory Standards Institute [23]. Discs (3 mm) were placed on Mueller Hinton agar (Merck, Darmstadt, Germany) plates previously seeded with 0.2 mL of microbial inoculums containing 10^5 to 10^6 CFU mL^{-1} of *E. coli* or *S. aureus*, and then incubated at 37 °C for 48 h. The antimicrobial activity was displayed by clear zones around the disc specimens.

2.8. Fourier transform infrared spectroscopy (FTIR)

FTIR was performed in a Nicolet 380 (Thermo Scientific, USA) equipped with an attenuated total reflectance (ATR) module. The samples were placed on the ATR accessory and were then analyzed under transmission mode, taking 64 scans per experiment with a resolution of 4 cm^{-1}. The FTIR data were normalized with respect to the CH_2 bending signal located at around 1426 cm^{-1}, which was not expected to change after the cross-linking reaction [24].

2.9. Thermogravimetric analysis (TGA)

The thermogravimetric analysis (TGA) was performed in a SHIMADZU DTG-60 (Japan). Samples (3.0–5.0 mg) were placed in aluminum pans inside the thermogravimetric balance and then heated under dry nitrogen atmosphere (20 mL/min) in the range of 30 to 500 °C at a heating rate of 10 °C min^{-1}.

2.10. Statistical analysis

The statistical analysis was performed using the Systat Inc. software (Evanston, USA). The experiments were performed in triplicate, and the data were reported as mean ± standard deviation. Assumptions of normality and variance-homogeneity were tested with the Shapiro-Wilk and Levene tests, respectively. When these assumptions were not satisfied, the nonparametric test of Kruskal-Wallis was performed. Analysis of variance (ANOVA) and Tukey pairwise comparisons were carried out using a 95% confidence level ($\alpha = 0.05$).

3. Results and discussion

3.1. Physical properties of the electrospinning solution and morphology of the electrospun mats

The electrospinning solutions with and without TC showed similar viscosities ($p > 0.05$), obtaining values of 3.19 ± 0.08 Pa s and 3.96 ± 0.06 Pa s, respectively. With respect to the electrical conductivity, higher values were obtained for the TC-PVA/CA solutions (1405.0 ± 5.1 μS cm^{-1}) than for the PVA/CA ones (821.0 ± 2.6 μS cm^{-1}) ($p < 0.05$). This behavior could be attributed to the ionization of some TC groups upon the dissolution of the drug in water [25]. Similar observations were reported by Haroosh, Dong and Lau [3] working on the fabrication of electrospun mats based on TC-containing poly(lactic acid)/poly(ε-caprolactone) blends. These authors found that when the TC concentration increases from 1 to 5 wt%, a remarkable enhancement of electrical conductivity from 31 to 90 μs cm^{-1} occurs.

The electrospinning solutions led to randomly oriented nanofibers, regardless of the TC presence (Fig. 2). However, TC-PVA/CA electrospun nanofibers showed lower diameters than the PVA/CA ones ($p < 0.05$), under all applied electrical voltages (20–35 kV) (Fig. 2). This behavior could be attributed to the higher electrical conductivity of the TC-PVA/CA blend compared to the PVA/CA one. The increase in the electrical conductivity of the solutions generally led to fibers with smaller diameter due to both: (i) the high content of electric charges carried by the electrospinning jet. Thus, higher elongation forces are imposed on the jet under the electrical field; and (ii) the increase in bending instability during the electrospinning [13,26]. Therefore, the jet path becomes longer and thin nanofibers are obtained.

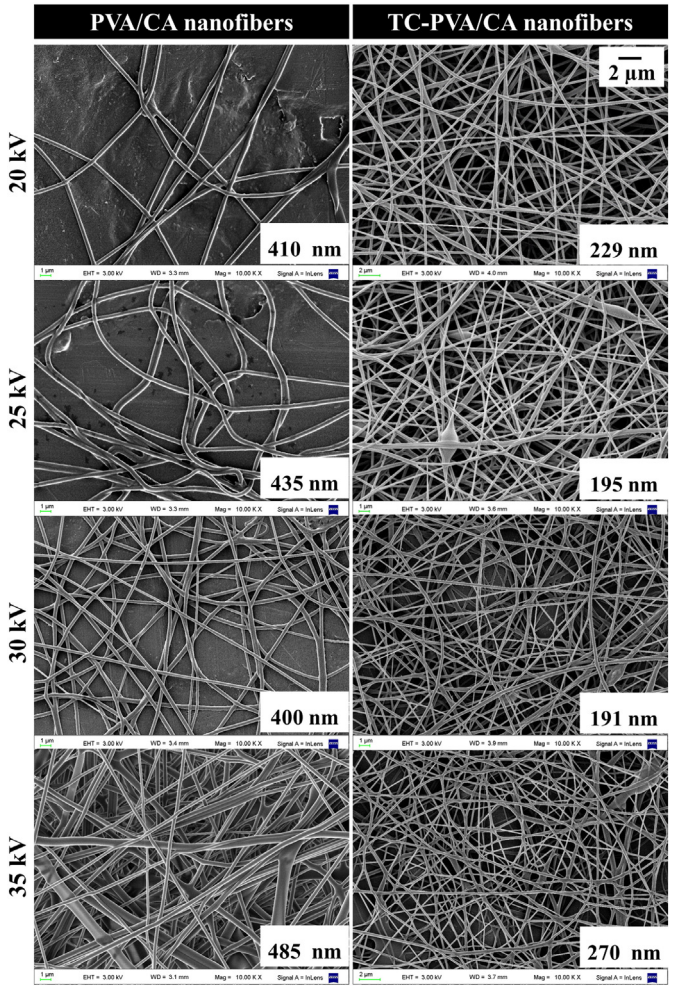

Fig. 2. SEM micrographs of PVA/CA mats (left column) and TC-PVA/CA mats (right column) obtained at different electrical voltages.

When the applied voltages were between 20 and 30 kV, few PVA/CA fibers were accumulated in the collector and nonhomogeneous fibers were formed (Fig. 2). Therefore for characterization studies, the PVA/CA and TC- PVA/CA mats were fabricated by fixing the electrical voltage at 35 kV, the needle-collector distance at 20 cm and the injection rate at 0.5 mL/h.

Fig. 3 shows images obtained by confocal scanning laser microscopy of the TC-PVA/CA nanofibers. The fluorescent drug appears in green on a dark polymer background.

The TC autofluorescence observed in the matrix is indicative of a good distribution of the antibiotic along the nanofibers [22].

3.2. Water solubility of the untreated and heat-treated mats

The untreated mats were almost completely disintegrated in water due to their high porous surface area. This behavior of the nanofibers is very advantageous when it is compared with that of the PVA powder, which is not water-soluble at room temperature. Water solubility values of 39% and 72% were obtained for heat-treated PVA/CA and TC-PVA/CA mats at 150 °C for 3 min, respectively. The higher water solubility of the TC-PVA/CA mats could be attributed to the good solubility of the antibiotic in water (*c.a.* 18 mg/mL) [27] and also to their higher surface area in comparison with the PVA/CA ones (Fig. 2). The heat-treated

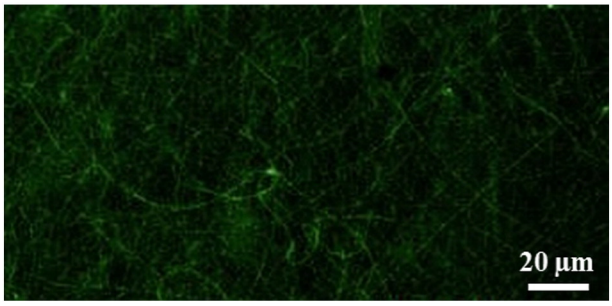

Fig. 3. Confocal laser microscopy image of the TC-PVA/CA mats. The fluorescent drug appears in green on a dark polymer background. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mats at 190 °C for 3 min showed good integrity after soaking and very low values of water solubility (*c.a.* 2%), regardless of the presence of TC. These results suggest that the decrease in water solubility of PVA/CA electrospun mats is strongly dependent on the temperature and the heat treatment time. Stone, Gosavi, Athauda and Ozer [17] reported the in situ citric acid cross-linking of alginate/PVA electrospun nanofibers activated by heat treatment at 140 °C for 2 h. The non-cross-linked electrospun nanofibers dissolved immediately, while cross-linked electrospun fibers remained intact after being immersed in deionized water or simulated body fluid for 2 days. In addition, these authors found that the cross-linked materials were thermally more stable. By using PVA-cross-linked electrospun mats with maleic anhydride, Peresin and coworkers found that the formation of ester groups increased when the reaction times increased from 15 to 120 min at a constant temperature of 140 °C [12]. This last time led to mats with higher integrity not only in water, but also in low polarity solvents such as DMF, acetonitrile, methanol and chloroform.

3.3. Release studies

Fig. 4 shows the UV–vis spectra of the drug released from the untreated and heat-treated TC-PVA/CA mats after 24 h of immersion in distilled water (Section 2.5). In addition, the spectrum of a TC standard solution is shown for comparison.

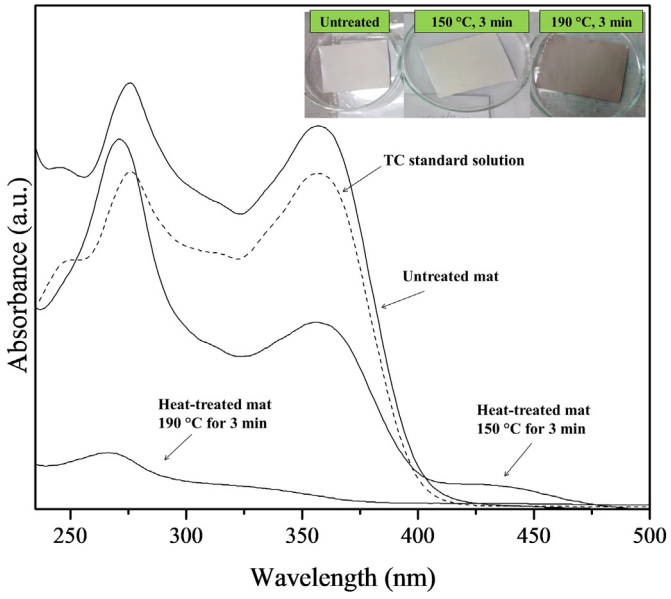

Fig. 4. UV–vis spectra of tetracycline standard solution (TC) and untreated and heat-treated mats. Inserts show digital images of the mats with and without heat treatment.

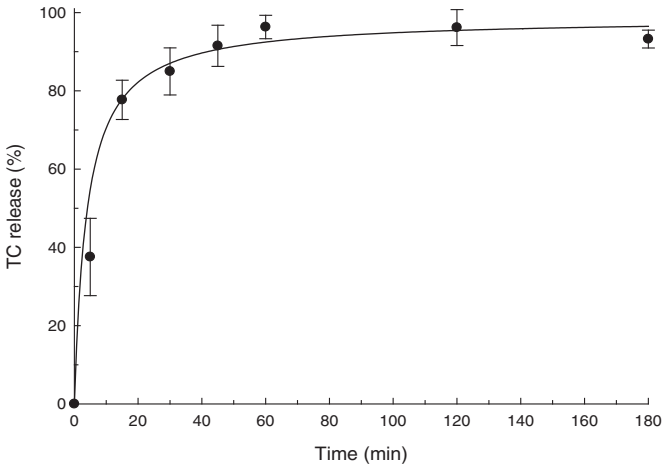

Fig. 5. Tetracycline hydrochloride release kinetics from heat-treated TC-PVA mats (150 °C for 3 min) to an aqueous medium.

TC standard solution showed the typical maximum absorption bands at 276 nm and 357 nm. A similar spectrum was found for drug released from the untreated TC-PVA/CA electrospun mats. In the case of the heat-treated TC-PVA/CA mats at 150 °C for 3 min, the band at

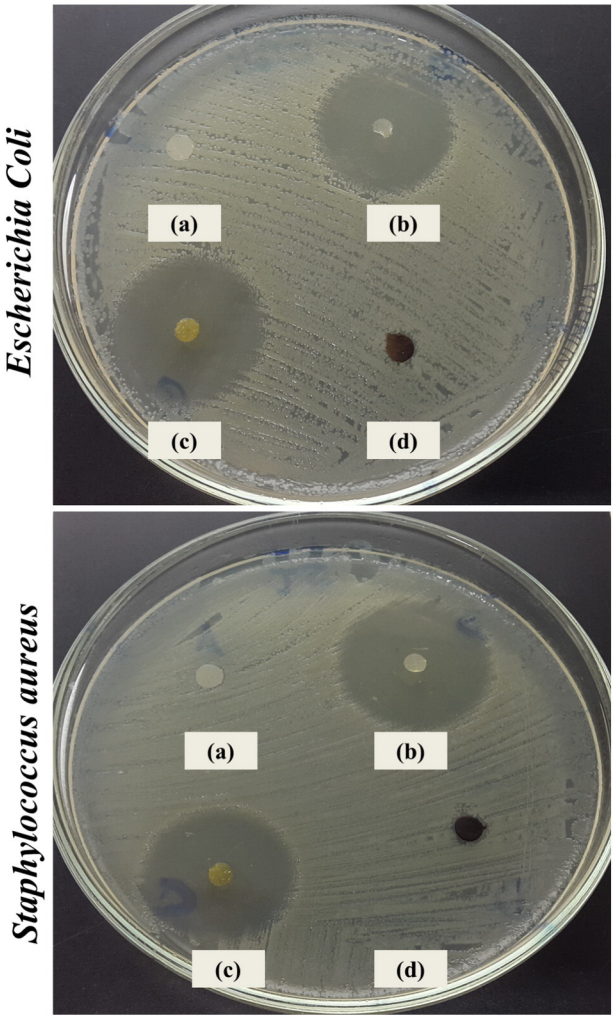

Fig. 6. Antimicrobial activities of the electrospun mats against *Staphylococcus aureus and Escherichia coli*. PVA/CA mat (a); untreated TC-PVA/CA mat (b) and heat-treated TC-PVA/CA mats at 150 °C for 3 min (c) and at 190 °C for 3 min (d).

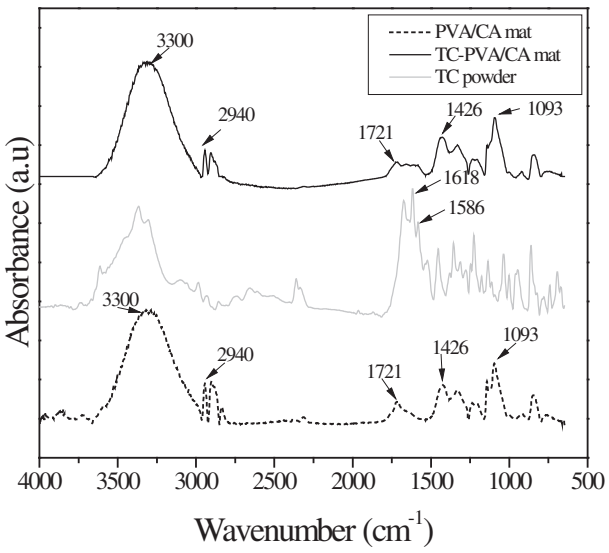

Fig. 7. FTIR spectra of tetracycline hydrochloride (TC) and PVA/CA and untreated TC-PVA/CA electrospun mats.

357 nm remained unaltered; however, a broad band between 400 and 500 nm was detected in the UV spectrum and a shift of the 250–300 nm band also (Fig. 4). Both facts could be attributed to TC dehydration by the heat treatment effect [28]. On the other hand, the TC typical signal at 357 nm was not detected in the UV–vis spectra of the drug released from the treated samples at 190 °C for 3 min, but another broad band between 250 and 300 nm was observed. Moreover, these samples showed a brown color on their surface (Fig. 4). Both facts were attributed to the partial to total TC degradation.

The heat-treated TC-PVA/CA mats at 150 °C for 3 min were selected to carry out the release studies taking into account both the TC content and the improved water stability compared with untreated TC-PVA/CA ones (Fig. 5). For these heat-treated samples, the maximum amount of released drug during the assay was similar to that of the untreated mats (*c.a.* 33 mg TC/g mat).

The heat-treated TC-PVA/CA mats showed a burst release of tetracycline hydrochloride, around 95% TC released within the first hour of assay (Fig. 5). This behavior could be attributed to both the dissolution of a fraction of the mats in the aqueous medium (*c.a.* 72% of water solubility) and to the high diffusion rate of TC molecules from the high porous surface area of the membranes to the aqueous medium. After this stage, the drug reached a steady release along 24 h of assay. A similar TC release pattern was observed by Haroosh, Dong and Lau [3] working with electrospun poly(lactic acid)/poly(ε- caprolactone) mats. It is well known that electrospun mats based on drug/polymer mixed solutions usually display burst drug release behavior via Fickian and/or non-Fickian diffusion [29,30]. This fact is helpful to fast suppress the microbial infections of wounds.

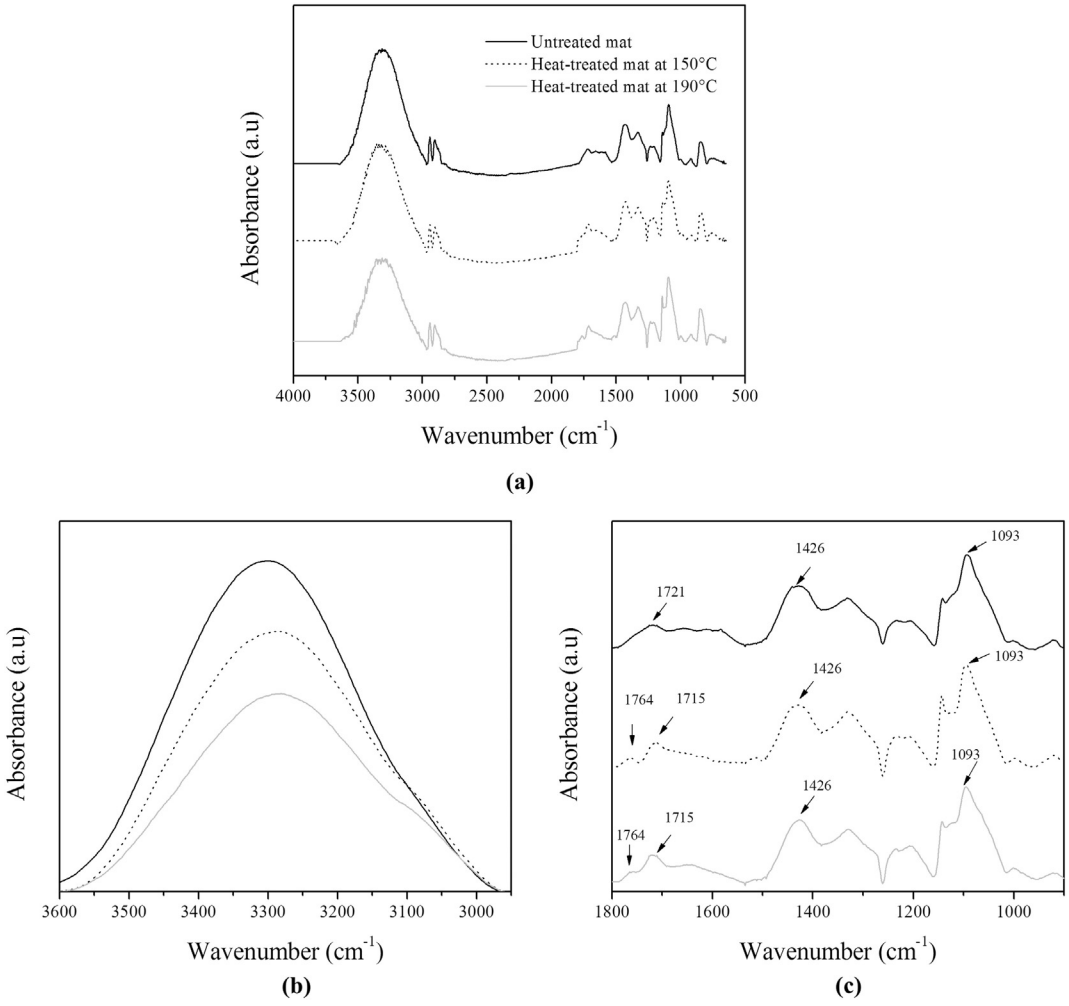

Fig. 8. (a) FTIR spectra of untreated and heat-treated TC-PVA/CA mats. In order to enable better visualization, panels b and c show the spectral region from 3600 to 3000 cm^{-1} and from 1800 to 1000 cm^{-1}, respectively.

3.4. Antibacterial activity of the electrospun mats

Fig. 6 shows the results of the antimicrobial activity evaluation of the electrospun mats against the Gram(+) bacterium *S. aureus* and the Gram(−) bacterium *E. coli*.

PVA/CA electrospun mats did not show an inhibition zone against *S. aureus* or *E. coli* bacteria (Fig. 6a). TC-PVA/CA electrospun mats, both untreated (Fig. 6b) and heat-treated samples at 150 °C for 3 min (Fig. 6c), showed similar effectiveness against *S. aureus* and *E. coli* bacteria (average diameter = 17 mm). These results suggested that the treatment at 150 °C for a short time showed no significant effect on the antimicrobial activity of TC. It has been reported that high temperature-short time treatment could leave TC almost unaltered [31]. As was expected, the TC-containing mats treated at 190 °C for 3 min did not show microbial inhibition against both microorganisms (Fig. 6d).

3.5. Chemical conformation of the electrospun mats before and after heat treatments

Vibrational spectra of TC powder, PVA/CA and TC-PVA/CA untreated mats are shown in Fig. 7. Both PVA/CA and TC-PVA/CA mats showed the bands of PVA assigned to the characteristic functional groups at 3300 cm^{-1} (O—H stretching), 2940 cm^{-1} (C—H from alkyl groups), 1721 cm^{-1} (C═O stretching), 1426 cm^{-1} (CH_2 bending) and 1093 cm^{-1} (C—O stretching) (Fig. 7) [32,33]. In addition, the TC-PVA/CA mats showed bands characteristic of TC at around 1618 cm^{-1} and 1586 cm^{-1} corresponding to the aromatic phenyl ring vibrations [34] (Fig.7).

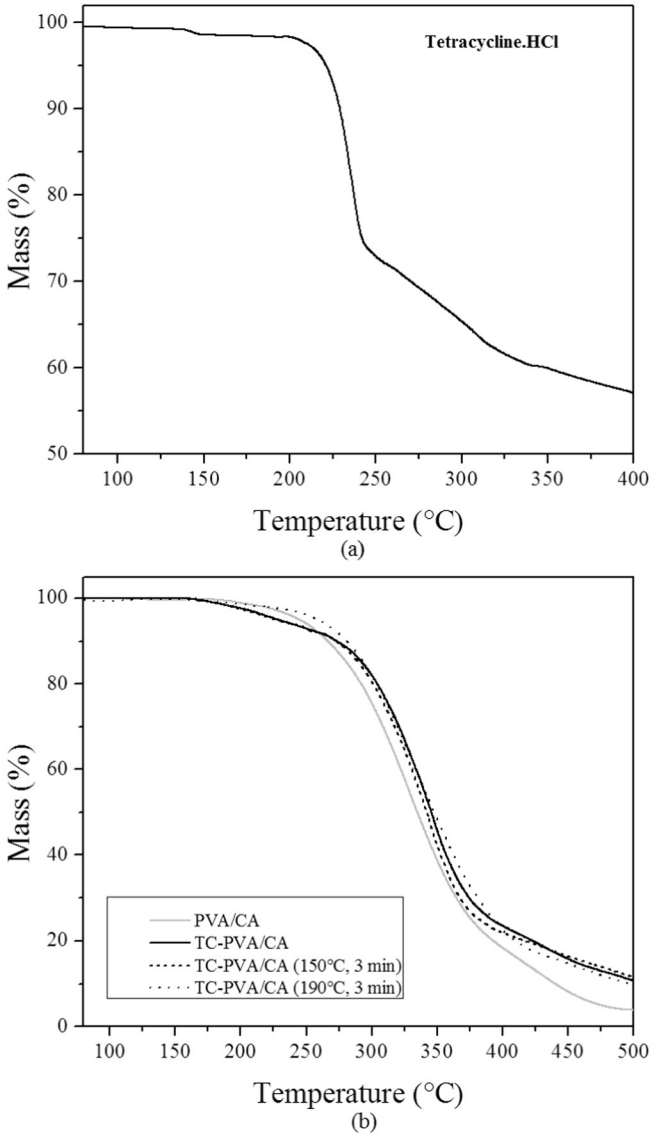

Fig. 9. TGA analysis curves: (a) tetracycline hydrochloride powder and (b) untreated and heat-treated electrospun mats.

The effect of the heat treatment on the chemical conformation of the TC-PVA/CA mats is shown in Fig. 8. The samples treated at 150 °C or 190 °C for 3 min exhibited a strong reduction of the bands located at around 3300 cm^{-1}, typically assigned to the hydroxyl groups, when compared to untreated mats (Fig. 8a). Such reduction of OH groups was greater when the samples were treated at 190 °C. Besides, FTIR spectra of both heat-treated samples showed new bands at around 1764 cm^{-1}, attributed to C═O stretching from aliphatic ester groups (Fig. 8b). This behavior suggests that the hydrogen bonding becomes weaker in the heat-treated electrospun mats due to the ester group formation by the chemical interactions between PVA hydroxyl groups and carboxylic ones of citric acid. The C═O band at 1715 cm^{-1} in the heat-treated samples could indicate that some carboxylic functions from citric acid did not completely react.

Shi and coworkers observed the appearance of a broad band at 1729 cm^{-1} in citric acid-cross-linked PVA films cured at 140 °C for 1 h [18]. This signal was attributed to a coalescence peak that was caused by the ester bond and carboxyl C═O bond in citric acid. Peresin et al. [12] reported the acid-catalyzed vapor phase esterification of PVA electrospun mats with maleic anhydride. These authors observed an increase in the intensity of the peaks between 1610 cm^{-1} and 1710 cm^{-1}, which was attributed to the changes in the characteristic bands of C═O, C═C, C–O–C and COOH by effect of ester formation.

3.6. Thermal stability of the electrospun mats

Fig. 9 shows the TGA analysis for TC powder and the electrospun mats (PVA/CA and TC-PVA/CA), with and without heat treatment.

The thermal degradation of TC followed the same pattern previously described in the literature (Fig. 9a) [35]. A small step of weight loss (c.a. 1.5%) between 100 and 150 °C was attributed to water loss. The mass loss events between 200 and 255 °C could be attributed to the elimination of HCl, isocyanic acid, water and carbon dioxide, as was confirmed using TGA-FTIR by Assumpção and coworkers [35]. Temperatures higher than 350 °C produced dimethylamine [35].

PVA/CA electrospun mats showed three well-defined thermal events (Fig. 9b). The first is associated with water evaporation (80–200 °C), the second with chain decomposition (200–400 °C) and the third with subproduct degradation (400–500 °C) due to cyclic conjugated compounds [36]. In the case of the heat-treated TC-PVA/CA mats, the presence of TC seemed to delay the thermal degradation of the PVA matrix (Fig. 9b). This behavior could be attributed to changes in the molecular packing of PVA molecules.

The heat-treated TC-PVA/CA mats at 150 °C for 3 min showed a thermal degradation pattern similar to that of the untreated mats. In the case of the heat-treated mats at 190 °C for 3 min, a delay in the thermal event associated with the loss of OH groups (80–200 °C) was observed (Fig. 9b). A decrease in the hydroxyl groups leads to a loss in the polar nature of the compound and as a result, the solubility of the polymer in water decreases [19].

FTIR and TGA analyses suggest that the heat treatment caused a strong reduction of OH groups due to both the temperature effect and the consumption of PVA hydroxyl groups in the esterification reaction with the carboxylic groups of citric acid.

4. Conclusions

Poly(vinyl alcohol) (PVA) electrospun mats with improved water stability were successfully prepared. According to FTIR analysis,

chemical interactions between the hydroxyl groups of PVA and the carboxylic groups of citric acid were produced by effect of the applied heat treatments. The treatment at 150 °C for 3 min allowed obtaining tetracycline hydrochloride-containing mats with lower water solubility than the untreated ones, but with similar effectiveness against both *Staphylococcus aureus and Escherichia coli*. The TC content in the mats remained almost unaltered after heat treatment and was almost fully released to the aqueous medium. On the other hand, the mats treated at 190 °C for 3 min were almost completely water-insoluble. This finding represents an important advantage for useful applications not only in the biomedical field but also for other purposes such as water filtration. Overall, the results suggest that the cross-linking of PVA/citric acid electrospun mats by treatment at high temperature and short time constitutes a suitable strategy to diversify the applications of these biodegradable materials, for instance, as antibiotic local delivery systems for wound healing.

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