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Production and characterization of caffeic acid-loaded microfibrous polycaprolactone mats obtained by electrospinning technology

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***Abstract*—** *Microfibrous polycaprolactone (PCL) mats containing caffeic acid were manufactured by electrospinning technology. Electrospun PCL fibers were processed with different concentration of caffeic acid, such as 0.10, 0.25, 0.50, and 1.00% in mass (m/m). The morphologies were observed by scanning electron microscopy (SEM). All produced fibers exhibited random direction and different values of diameters. The caffeic acid did not significantly affect the diameters of the PCL fibers in terms of mean±SD, but some compound concentrations caused the anomaly formation in the electrospun fibers' structure, with the exception of 0.10% CA. Wettability tests in the microfibrous PCL mat with or without caffeic acid showed hydrophobic behavior due to air effect, same with the caffeic acid amount increase. On the other hand, contact angle measurements decrease with the caffeic acid amount increase. The same occurred with the caffeic acid-loaded PCL films. The chemical characterization by FTIR showed the influence of the concentrations of CA in the PCL microfibers, indicating the presence of hydrogen bonds, with the exception of 1.00% CA. We suggest that the 0.10% caffeic acid concentration is the most suitable, mainly due to the absence of anomalies on the surface of the PCL microfibers for future investigations, such as antimicrobial and cytotoxicity tests, drug release, etc.*

I. INTRODUCTION

Electrospinning is widely used to produce fibers, generally of a polymeric nature [1]. These electrospun fibers are obtained from a polymer solution or polymer melt [2]. The technique is low cost and easy to implement when compared to other fiber manufacture methods [3]. Moreover, other techniques, i.e., dual syringe [4], coaxial [5], melt [6], and multiple needle electrospinning [7], are derivations of traditional electrospinning. For this reason, electrospinning technology has been used extensively in manufacturing fibers that can acquire nanometric dimensions [1-3].

The electrospun fibers during their processing are deposited on a grounded metallic collector [8]. After this continuous deposition, a fibrous mat is formed with typically porous, light weight, and flexible characteristics [8,9]. Other denominations for the fibrous mats obtained via electrospinning are found in the literature, i.e., nanofibrous membrane [10], membrane [11,12], nonwoven mat [13], -nano and -microfibrous mats [14,15].

The applications of electrospun fibers are diverse and include the sensors [16], biosensors [17], filtration [18], purification [19], biomedical [20], and pharmaceutical fields [21].

Concerning the biomedical field, electrospun fibers have achieved prominence in the controlled release of drugs, which are delivery devices that generally combine biodegradable and biocompatible polymers with drugs [19-22]. And in the production of scaffolds for cell proliferation aiming application in tissue engineering [22].

The most widely used biodegradable and biocompatible polymers in the biomedical field are poly (glycolic acid) (PGA), poly (L-lactic acid) (PLLA), poly (lactic-co-glycolic acid) (PLGA), poly (L-lactide) (PLA), poly (D-lactic acid) (PDLA), and poly (ε-caprolactone) (PCL) [22,23].

PCL is a biodegradable polymer of synthetic source, aliphatic polyester and semicrystalline, has interesting properties, such as good mechanical properties, is biocompatible, and non-toxic [23,24]. PCL is soluble in organic solvents and is considered a polymer excellent to produce PCL fibers by electrospinning [24,25].

Electrospun PCL fibers with diameters of 1.660 ± 1.120 μm were prepared using chloroform and acetone as solvents. The PCL fibers of micrometric scale exhibited a smooth surface in their morphology shown by SEM image [25]. Nevertheless, Li et al. [26] produced PCL fibers of nanometric diameters around 200±78 nm with a diameter maximum of 613 nm and diameter minimum of 97 nm. The authors reported that this optimization to reduce the fiber PCL diameters was due to the use of H_2O as an additive in the PCL solution in glacial acetic acid that increased the electrical conductivity due to the acetic acid ionization.

The versatility of the electrospinning technology allows the production of electrospun fibers containing others material types [1], i.e., polymer nanoparticles [25], metallic or ceramic nanoparticles [1], drugs [1,3], oils [2], and bioactive compounds [27].

Caffeic acid is a phenolic compound from vegetables widely used in pharmacological and cosmetic areas. It is an excellent antioxidant used to prevent premature aging; it has antimicrobial activity and is even capable of acting as a cancer inhibitor [28].

Electrospinning has been used to manufacture caffeic acid-based biodegradable polymer fibers [29-31]. These electrospun fibrous mats presented potential biomedical and packaging applications.

This work aims to show the production and characterization of PCL fibers containing caffeic acid to define the suitable concentration of phenolic compound in electrospun fibers.

II. EXPERIMENTAL

1.1 Materials

Were used poly(caprolactone) (PCL, MM=80,000 g/mol) and caffeic acid (CA, MW=180.16 g/mol) purchased from Sigma-Aldrich. The solvents chloroform and acetone were purchased from Labsynth. Potassium bromide (KBr, MW=119.00 g/mol) purchased from Merck. Deionized water with electrical conductivity of 0.5 $\mu S/cm^2$ was used.

1.2 Prepare of the solutions

The PCL solution was prepared by mixing chloroform (3.16 g) and acetone (3.16 g) into a glass flask under mechanical stirring for 15 minutes. Posteriorly, 1g of PCL was added to the solvent mixture for dissolution, which lasted 24 hours.

Caffeic acid was only used after preparing the PCL solution, and different amounts of the compounds given percent by mass, such as 0.10, 0.25, and 0.50% CA, were added to the solution under mechanical stirring for 4 hours until its complete dispersion.

1.3 Prepare of the PCL fibers loaded with caffeic acid

In order to prepare the caffeic acid-loaded PCL fibers, the PCL solution containing the caffeic acid was placed into the syringe with a metallic needle of diameter $Ø_{needle}$ = 0.8mm. After that, conducted to the electrospinning, which

was parameterized with flow rate of Q=8mL/h, applied tension of V=14 kV, and work distance of d_w=180 mm. The electrospun fibers were manufactured on the grounded metal rectangular collector at temperature of T = 22.0±0.5 °C and relative humidity of RH = 57.0±1.0 %. Fig. 1 shows a schematic illustration of the experimental setup this work.

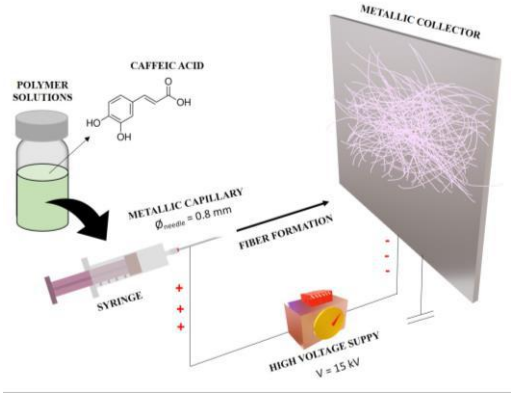

Fig. 1: Schematic illustration showing basic electrospinning items and the PCL solution with CA.

1.4 Morphological characterization

The morphology of the electrospun PCL fibers and caffeic acid-loaded PCL fibers was observed by Scanning electron microscopy – SEM (ZEISS, Evo MA-15 model). Before analyzing the samples in SEM, they were coated with gold sputtering (BAL-TEC, SCD 050 model).

1.5 Measurements and Statistical analysis of fiber diameters

ImageJ software (free version) was used to measure the fiber diameters from SEM images of 1,000X magnitude. The average values and standard deviations (average ± S.D.), minimum diameter (D_{min}), and maximum diameter (D_{max}) were represented based on methods described in the literature [25].

1.6 Chemical Characterization

Chemical characterization was performed by infrared spectroscopy – IR. Samples were mixed with potassium bromide (KBr) in 1:100 and pressed to 2.5kN for 5 minutes to produce tablets with 15 mm diameter containing the samples. After that, they were analyzed in the spectrometer (Thermo Scientific – NICOLET iS5, model) in the 400 – 4000 cm^{-1} range, 16 scans with a spectral resolution of $4cm^{-1}$.

1.7 Wettability and Contact angle measurements by ImageJ software

The wettability test was performed using water, where on the surface of the sample was placed a 10 µL drop using a pipette. The water drop was observed with a digital microscope (TQC – Lite plus model, with 1.000X resolution) at room temperature. ImageJ software (version free) obtained the contact angle measurements (in triplicate) using the Low Shape Axisymmetric Drop Shape Analysis tool. Casting films with and without CA were prepared for comparative study.

III. RESULTS AND DISCUSS

Fig. 2 shows the SEM images of the PCL fibers with 500X magnitude and 20 µm scale (a), 1,000X magnitude and 10 µm scale (b), 5,000X magnitude and 2 µm scale (c). They reveal the morphological characteristic of the electrospun fibers that exhibited random direction. This effect is typical in electrospun fibers produced with a static rectangular metallic collector [32]. Fibers with different diameters were observed. About this, the main disadvantage of electrospinning technology is no guarantee of equal diameters for all electrospun fibers [33], which was expected.

In Fig. 2c is presented the surface morphology of the PCL fibers, showing the rough surface of the fibers. This surface morphological characteristic for electrospun PCL fibers occurs due to the solvent nature used [34] or the effect of the humidity [35]. On the other hand, it is more common to observe smooth surface morphology in electrospun PCL fibers, as reported Moraes Segundo *et al.* [25] that obtained PCL fibers of smooth surface.

The Fig. 2d – 2p are shown the morphology of the caffeic acid-loaded PCL fibers with different amounts of the compound. All the SEM images showed that the electrospun fibers remained in random direction.

In particular, the PCL fibers with 0.10% CA did not present anomaly in their structure (see Fig. 2d and 2e), whereas the Fig. 2f shows the caffeic acid existence in the fibers.

PCL fibers produced with 0.25% CA showed that the amount of caffeic acid used to bring on an excess of the compound out of electrospun fibers can be seen by SEM images in Fig. 2g and 2h. Moreover, the presence of precipitated caffeic acid was observed and is showed in Fig. 2i. However, this concentration did not cause the formation of anomalies in the fiber structure. Differently for the concentrations of 0.50 and 1.00% CA, the anomaly formation and CA precipitation were observed, as shown in SEM images of Fig. 2j – 2m and Fig. 2n – 2p, respectively.

Electrospun PCL fibers presented diameters of 2.50 ± 1.12 µm, D_{min} = 0.48 µm, and D_{max} = 4.60 µm. These values on the structural dimensions of the micrometric-sized fibers explain the name given to the nonwoven mat, like a microfibrous PCL mat.

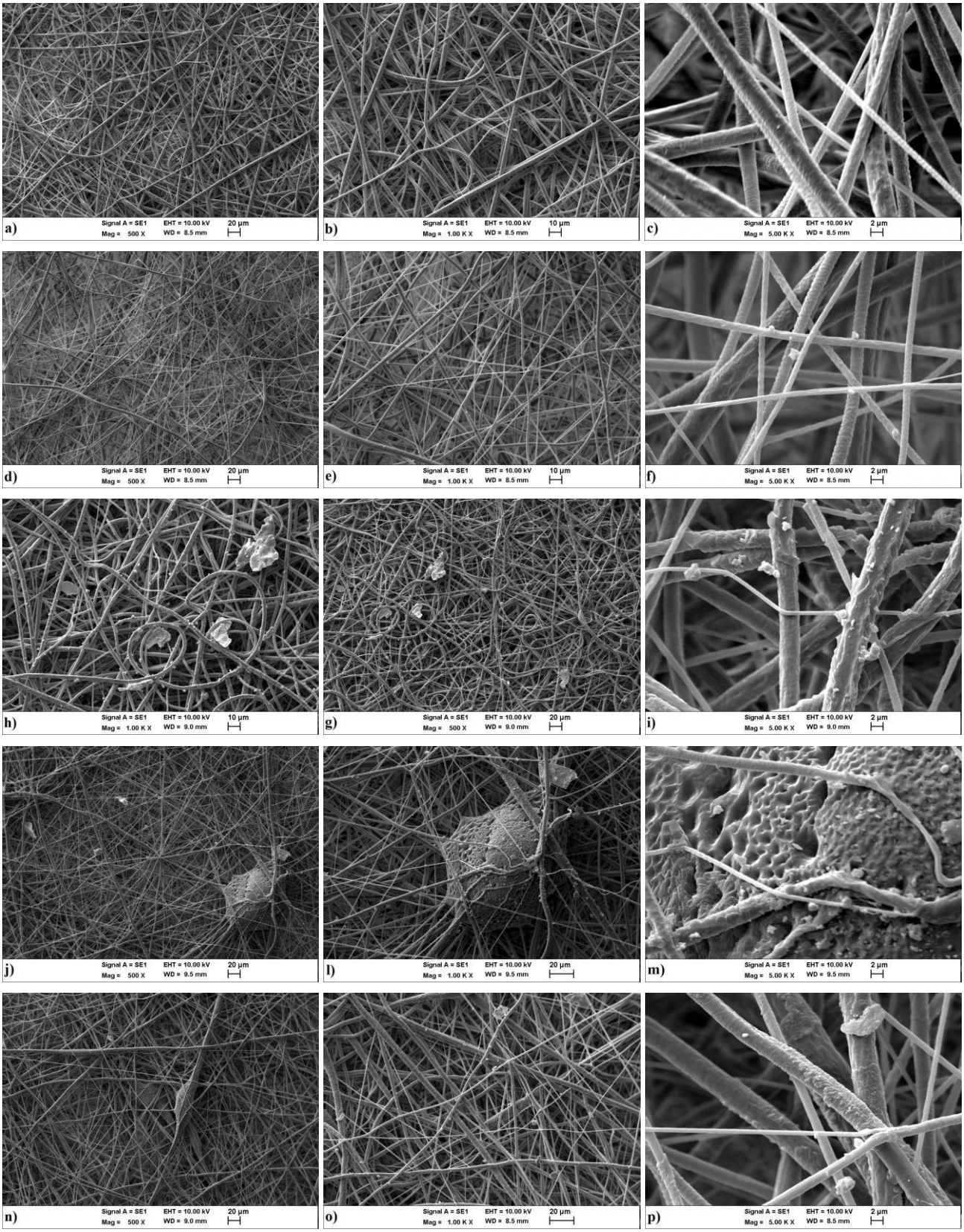

Fig. 2: SEM images of the PCL microfibrous mat (a – c), and with 0.10 % CA (d – f), 0.25% CA (g – i), 0.50% CA (j – m), and 1.00% CA (n – p), showing the morphologies of the fibers produced by electrospinning.

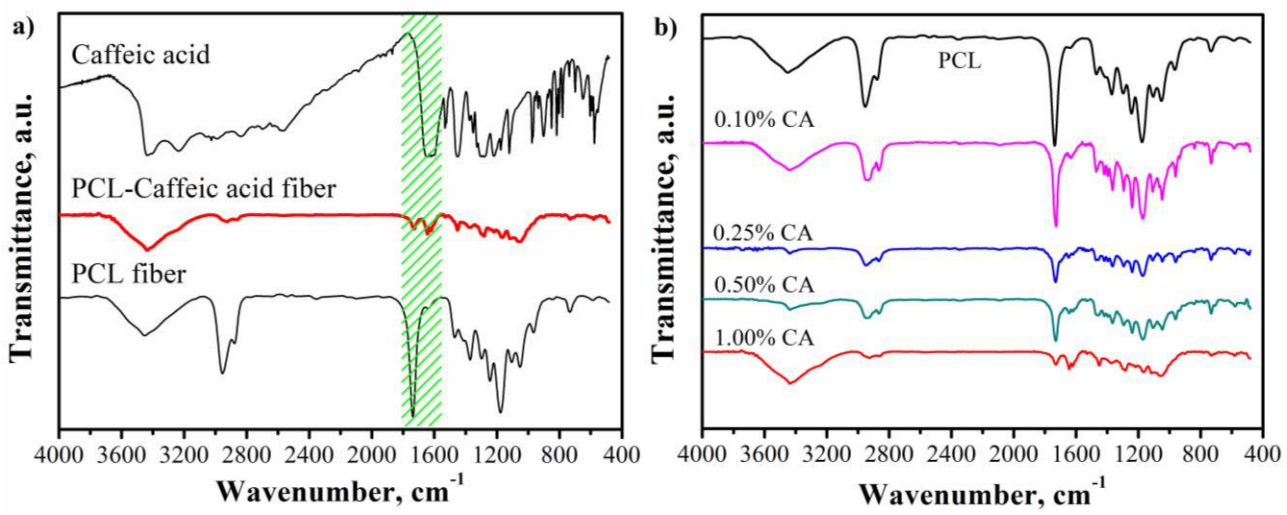

Fig. 6: Comparative FTIR spectra of caffeic acid, PCL fibers, and caffeic acid-loaded PCL fibers (a). FTIR spectra of PCL fibers without and with caffeic acid of 0.10%, 0.25%, 0.50%, 1.00% CA (b).

The diameter values of the PCL fibers with and without caffeic acid are listed in the Table 1. The results showed that we did not obtain nanometric size fibers to any concentration of caffeic acid used. Furthermore, the caffeic acid did not significantly change the fiber diameters that were expressed in mean ± S.D. In the graph presented in Fig. 3a show this effect.

Table.1: Structural measurements of the microfibers obtained from SEM images.

Microfibrous	***Diameters (mean±SD)***	***D_{min} (µm)***	***D_{max} (µm)***
PCL	*2.50±1.12*	*0.48*	*4.60*
PCL + 0.10% CA	*2.03±1.05*	*0.25*	*4.94*
PCL + 0.25% CA	*2.40±0.95*	*0.40*	*5.15*
PCL + 0.50% CA	*1.96±1.40*	*0.45*	*8.20*
PCL + 1.00% CA	*2.41±1.53*	*0.33*	*10.23*

CA = caffeic acid

Under other conditions, the Fig. 3b present the graph considering the mean and maximum (D_{max}) values of the fiber diameters containing caffeic acid. Then, we observed that the presence of fibers with larger diameters is related to the addition of caffeic acid.

Briefly on incorporating caffeic acid, small amounts of CA were incorporated successfully in PCL fibers by electrospinning technology. However, we suggest the concentration of 0.10% CA, which did not present anomalies in its structure and did not influence the diameter of the fibers, being the most suitable for future application studies, i.e., antimicrobial tests, cytotoxicity tests, drug release, etc.

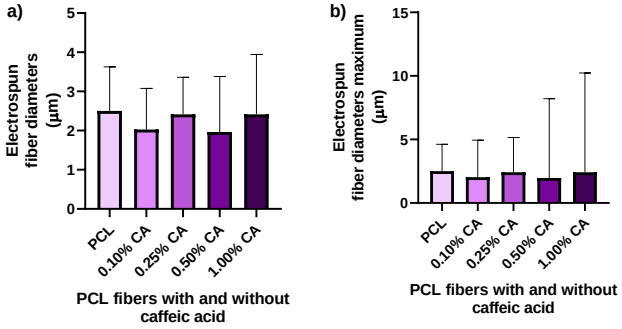

Fig. 3: Graphs of the fiber diameters expressed in mean ± S.D (a) and D_{max} (b) with and without CA.

Fig. 4 presents the graph of the contact angle measurements of the microfibrous mats and films with different CA concentrations. Contact angle when higher than 90° classifies a surface as hydrophobic and less than 90° as hydrophilic, using the water as solvent [36].

All microfibrous mats with or without CA showed contact angle greater than 90°, differently for the films with or without CA that exhibited contact angle less than 90°, as shown in Fig. 4, which shows the influence of the presence of air in the electrospun mats due to its porosity that forms air pockets [37].

PCL is considered relatively hydrophobic [38,39], which may be related to the hydrophilic carbonyl groups present in its structure. The PCL film had a contact angle of 79.88° ± 3.25° (less than 90°), corroborating with the literature [40].

Contact angle measurements also examined PCL films containing caffeic acid and cast films with concentrations of 0.10, 0.25, 0.50, and 1.00% CA that exhibited a contact angle of 78.11° ± 6.02°, 77.04° ± 11.83°, 72.04° ± 5.93°, and 72.41° ± 2.65°, respectively. High S.D. values may indicate a heterogeneous and aggregated distribution of CA on the surface of the PCL film.

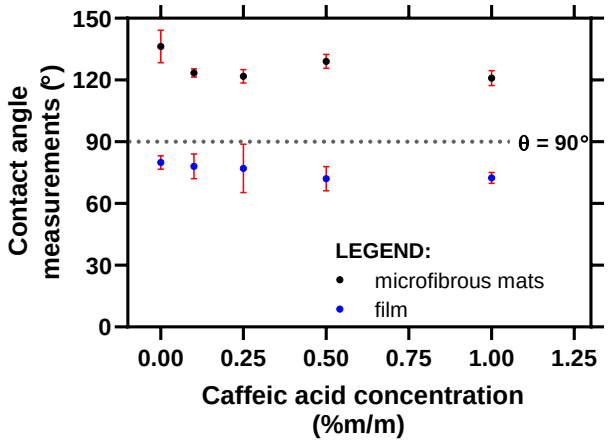

Fig. 4: Graph of the contact angle measurements versus different CA concentrations.

The contact angle for microfibrous PCL mats indicated a hydrophobicity because the contact angle was of 136.32° ± 7.84° (higher than 90°). In Fig. 5b is shown the graph of the contact angle for microfibrous PCL mats with CA concentrations (0.10, 0.25, 0.50, and 1.00%), where was decreased to 123.44° ± 1.06°, 121.81° ± 3.23°, 129.08° ± 0.43°, and 120.96° ± 3.65°, respectively (see the red dashed line in Fig 5b), indicating the influence of CA in reduce the hydrophobicity of microfibrous PCL. In Fig. 6b, a red dashed line shows the changes caused by the presence of CA, mainly for the concentration of 0.10% of CA that presented less variation in the contact angle, therefore, showing a better distribution of CA on the surface of the PCL fibers.

The chemical characterization was performed using infrared spectroscopy to determine the vibrational modes present in the polymeric matrices obtained before and after the addition of the antioxidant caffeic acid.

Fig. 6a shows three FTIR spectra corresponding to caffeic acid, caffeic acid-loaded PCL fibers and PCL fibers comparatively.

For caffeic acid, the main vibrational bands were identified, the –OH stretching from adsorbed water and hydroxyls present in the molecule at 3428 cm^{-1} and 3233 cm^{-1}, respectively; the –CH stretching at 2981 cm^{-1}; the carbonyl C=O stretching of the carboxylic acid at 1643 cm^{-1}; and the aromatic C=C stretching present in the aromatic ring at 1445 cm^{-1} [41-43].

For the PCL, the most relevant vibrational bands were determined, the asymmetric and symmetrical double of CH_2 at 2952 cm^{-1} and 2873 cm^{-1}, respectively; the carbonyl C=O stretching of the ketone group at 1735 cm^{-1}; and the –OH stretching of water adsorbed at 3449 cm^{-1}[44,45].

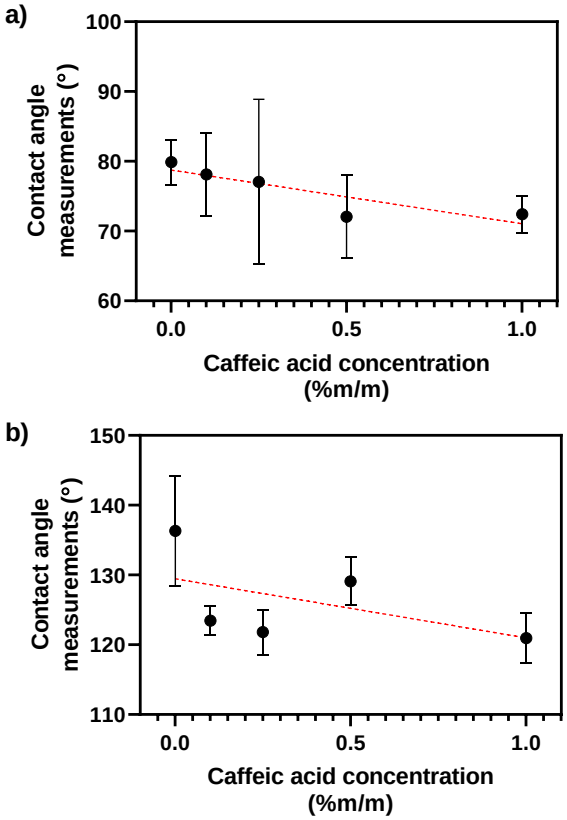

Fig. 5: Graph of the contact angle measurements versus different CA concentrations of the (a) films and (b) microfibrous mats.

Note that in the FTIR spectrum for the caffeic acid-loaded PCL fibers (red curve), there is a strong decrease in the intensity of the vibrational modes in the fingerprint region (1800 - 700 cm^{-1}) referring to the polymeric matrix of caprolactone indicating that the caffeic acid interacts strongly with the PCL polymer chains. In the vibrational region of the carbonyl (green region), the presence of two different types of carbonyl inherited from the ketone group of the PCL and the carboxylic acid of the caffeic acid is observed.

After the gradual addition of CA, we observed the chemical influence of CA in the PCL matrix. Fig. 6b shows the chemical influence of the progressive presence of the CA molecule in the polymeric matrix of the PCL. The increase in the concentration of CA reflects the

decrease in the transmittance of the vibrational bands of the PCL.

However, there is a limit. In concentrations below 1.00% CA, there is only interference in the transmittance of the vibrational modes, i.e., the intensity of the vibrational bands is reduced due to the action of the hydrogen bonding interactions between the CA and the PCL.

However, from 1.00%, there are significant changes in the shape of the vibrational bands in the fingerprint region of the PCL. In addition, the ratio between $C{=}O_{CA}/C{=}O_{PCL}$ has changed dramatically, indicating a strong internal interaction of the caffeic acid molecules with PCL, probably due to the chelating property of the phenolic antioxidants to which the molecule belongs. Caffeic acid has a considerable antioxidant action and also a metal ion chelating capacity [46,47].

These results showed that the incorporation of small amounts of CA in the PCL fibers form the hydrogen bonding interactions, fundamental in drug delivery systems and CA carriers, with the exception of 1.00%.

This reinforces the suggestion of the concentration of 0.10% of CA, since it did not present anomalies in its structure, being the most suitable for antimicrobial tests, cytotoxicity tests, drug release, etc.

IV. CONCLUSION

Caffeic acid-loaded microfibrous PCL mat was prepared by electrospinning, testing different caffeic acid concentrations. The CA concentration that best produced electrospun fibers without anomaly was 0.10%. The SEM morphologies showed that all processed fibers had random orientation, and the addition of 0.10% of CA did not significantly change the diameters of PCL fiber (2.50 ± 1.12 µm), whereas for fibers of PCL loaded with 0.10% CA was 2.03 ± 1.05 µm. In addition, the wettability changed, and the contact angle decreased from 136.32° ± 7.84° to 123.44° ± 1.06°, respectively. The chemical characterization by FTIR showed that the increasing presence of CA affected in the decrease of the transmittance of the vibrational bands due to the action of the hydrogen bonds between CA and PCL, an important attribute in the caffeic acid-loaded microfibrous PCL mat, with the exception of 1.00% CA.

Through these results, we suggest using a 0.10% concentration as a reference for future research, mainly in the pharmaceutical and cosmetic fields.

2. Acknowledgements

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