Nanostructured Membranes Based on Cellulose Acetate Obtained by Electrospinning, Part 1: Study of the Best Solvents and Conditions by Design of Experiments

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ABSTRACT: The electrospinning of cellulose acetate (CA) was investigated to develop biodegradable nanostructured membranes for the controlled release of drugs used to treat skin wounds. CA nanofibers were successfully prepared via the electrospinning in the four mixed solvents acetic acid : water; acetone : water; DMAc : acetone; DMAc : acetone : water. Design of experiments (DOE) was applied to see what combinations of parameters could affect the production of electrospun microfibers and nanofibers to optimize the process. The results of this work indicated that both the processing parameters and the solvent mixtures were responsible for the fiber diameter and nanostructure membrane appearance. The optimized condition for each solvent mixture was obtained and compared with each one of the others. The best conditions achieved were dimethylacetamida (DMAc) : acetone with 17% of CA, which provided homogeneous and free bead fibers with an average diameter of 295 nm. © 2012 Wiley Periodicals, Inc. J Appl Polym Sci 000: 000–000, 2012

Key words: cellulose acetate; electrospinning; biofibers; membranes; nanotechnology

INTRODUCTION

Electrospinning is becoming an attractive process due to its simple and inexpensive method of producing nanofibers, from a wide variety of polymer solutions. The development of nanofibers made from natural polymers[1] or polymer blends,[2,3] impregnated with nanoparticles or drugs,[4] as well as ceramic precursors,[5] has been successfully demonstrated.

The process is based on one electrode connected to a high voltage source, which is fixed in the capillary tube containing the polymer solution, while the other electrode is fixed to a metal collector, usually a copper or aluminum plate.[6]

The capillary and the collector are usually kept at short distance from each other, and during the tests, the polymer solution is pressed by the syringe plunger, until it reaches the tip of the needle. The drop formed at the needle tip is initially pendant due to the surface tension, with a nonzero net charge due to the action of the electric field. Electrical charges on the surface of the counter electrode cause a force directly opposite to the surface tension. Increasing the electric field to a critical value, electrostatic forces overcome the surface tension, resulting in a hollow cone of fluid, which is ejected, known as the Taylor cone.[6]

From the time when the solution is transferred from the syringe until the time it is collected, the solvent evaporates and the dry fibers are deposited,[1] usually in the form of a nonwoven blanket. Alternatively, one could obtain these electrospun fibers aligned, with various degrees of order and direction, by using a dynamic collector.[7,8]

Although the fundamentals of electrospinning are simple, the process is complex due to the large number of parameters that influence the shape, diameter, and the dimensions of the resulting fiber. Among these parameters, we can mention the solution viscosity, electrical conductivity, surface tension, the polymer molecular weight and its distribution, the electric field strength, the nature of the counter electrode, and atmosphere of the process.[9] Due to these great numbers of parameters, we use statistical

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analysis as a tool in the evaluation of multiple factors acting simultaneously in the electrospinning process.

Thus, the effect of spinning parameters such as solution concentration, voltage, distance, and speed on the fiber diameter can be determined by using a design of experiments (DOE), which is still rarely used for this type of experiment. Cellulose acetate (CA) is an interesting choice among the various possibilities available as polymer, because it is one of the most common commercial cellulose esters.[10]

Due to the ease of obtaining films with a porous structure, CA is one commonly used ester for applications such as semipermeable membranes in dialysis, ultrafiltration, and reverse osmosis.[1] However, the success of obtaining nanofibers from CA is dependent on the selection of an appropriate solvent for the electrospinning of a particular polymer.

Liu and Hsieh[11] investigated the use of acetone, acetic acid, and dimethylacetamide (DMAc) as solvents, following the Hildebrand solubility parameters. The most consistent fiber diameters were obtained in the range of 100 nm to 1 μm, with a mixture of acetone : DMAc as the solvent.

Another study made by Son et al.[12] tested acetone : water as a solvent and had good results in electrospinning by controlling the pH. Similarly, Ma et al.[13] also electrospun CA in acetone : dimethylformamide : trifluoroethanol, which resulted in fibers with a diameter of 200 nm to 1 μm.

The major potential application of these electrospun nanofibers are in healthcare, pharmaceutical and cosmetic industries, for repairing and regenerating the skin and organs,[14,15] drug delivery vectors and therapies,[16,17] biocompatible biodegradable[18] implants, medical diagnosis and instrumentation,[19,20] tissue protective agents against infections,[21] cosmetics,[22] molecular medicine, supplements, and body care applications in the field of dentistry.

The aim of this study was the evaluation of the influence of spinning parameters and solvent in both diameter and morphology of CA nanofibers, obtained by electrospinning. The DOE was used as an auxiliary tool to investigate the best parameters to obtain nanostructured membranes, with well-controlled fiber diameter, to be used as devices for the controlled release of drugs.

EXPERIMENTAL

Materials

CA (white powder; M_r = 29,000; degree of substitution = 40%) supplied by Sigma-Aldrich; DMAc and glacial acetic acid from Merck; Acetone supplied by Synth; deionized water.

Preparation and characterization of CA polymer solutions

Polymer solutions of CA, with different concentrations, were prepared by dissolving the appropriate polymer mass in four different solvent systems at room temperature, that is, 13 and 17% (w/w) of CA in acetic acid : water (3 : 1 w/w); 17 and 19% (w/w) of CA in acetone : water (85 : 15 w/w); 17 and 19% (w/w) of CA in DMAc : acetone (1 : 2 w/w), and 14 and 17% (w/w) of CA in DMAc : acetone : water (32 : 63 : 5 w/w).

All polymer solutions were characterized by viscosity analysis using a Brookfield Programmable Rheometer Model DVII (Germany), coupled with a thermostatic bath from Marconi, model MA184 (Piracicaba, Brazil); surface tension, using a Krüss Tensiometer, model K6 (GmbH), and analysis of the conductivity, using a conductivity meter Analion, model C708 Plus (Ribeirão Preto, Brazil). All measurements were performed in triplicate at 25°C.

Electrospinning

The CA solutions were electrospun at room temperature (25°C) and humidity (50%), using a 20 mL glass syringe with a metallic needle 4 cm long and 0.8 mm in diameter.

The positive pole of a high voltage from Hewlett-Packard, Model 3406A, was connected to the metallic needle of the syringe, while the ground electrode was used to ground the copper plate collector, with dimensions of 30 × 40 cm.

The feed stream was controlled by a KdScientific, Model 100 pump, connected to a syringe. The distance from the needle to the collector varied between 7 and 10 cm; the applied voltage was 15 and 25 kV; and the flow rate between 1 and 4 mL/h, depending on the DOE.

Samples of the nanostructured membranes were collected in aluminum foil used to coat the copper plate during the experiments. In each test, about 3 mL of polymer solution was electrospun.

Characterization of the electrospun membranes

The morphology and distribution of the fibers in nanostructured membranes, the value of their diameter range and the presence of beads, among other things, were analyzed by scanning electron microscopy (SEM). For this purpose, two devices were used: an Electron Probe Microanalyzer, JEOL JXA-840A (Tokyo, Japan), and a Scanning Electron Microscope Leica LEO 440i.

Five to seven images were obtained for each sample, with a different magnitude, which were analyzed using the software Image Tool to measure the average diameter of the 50 measurements registered by each sample.

TABLE I
Experimental Parameters Used During the Electrospun of CA Nanofibers in Solvent Mixtures, the Average Diameter of the Fiber and the Membrane Aspect

Solvent mixture	Run	% CA	Potential (kV)	Needle-collector distance (cm)	Average fiber diameter (μm)	Membrane aspect (arbitrary scale)
Acetic Acid : water (3 : 1 w/w)	1	13	15	7	0.06 ± 0.01	1.7 ± 0.6
	2	13	25	10	0.06 ± 0.02	1.7 ± 0.6
	3	13	15	10	0.09 ± 0.03	1.7 ± 0.6
	4	13	25	7	0.08 ± 0.02	1.7 ± 0.6
	5	17	15	10	0.18 ± 0.06	2.7 ± 1.2
	6	17	15	7	0.17 ± 0.05	3.0 ± 1.0
	7	17	25	10	0.19 ± 0.06	2.7 ± 1.2
	8	17	25	7	0.19 ± 0.08	3.3 ± 1.5
	BC[a]	18	25	7	0.17 ± 0.05	4.5 ± 1.2
Acetone : water (85 : 15 w/w)	1	17	25	10	2.3 ± 0.3[b]	7.0 ± 1.0
	2	17	15	10	2.3 ± 0.4[b]	8.3 ± 2.1
	3	17	15	7	2.4 ± 0.4[b]	7.7 ± 1.2
	4	19	15	7	3.6 ± 0.6[b]	8.0 ± 1.7
	5	19	25	10	3.2 ± 0.4[b]	8.0 ± 1.7
	6	17	25	7	1.7 ± 0.3[b]	8.7 ± 1.5
	7	19	15	10	3.4 ± 0.5[b]	8.0 ± 2.0
	8	19	25	7	3.2 ± 0.5[b]	7.3 ± 1.5
	BC[a]	17	25	7	1.7 ± 0.3[b]	8.7 ± 1.5
DMAc : acetone (1 : 2 w/w)	1	17	15	7	0.415 ± 0.2	9.0 ± 1.0
	2	19	15	10	0.595 ± 0.2	8.0 ± 1.7
	3	17	25	10	0.295 ± 0.4	9.0 ± 1.4
	4	19	25	10	0.480 ± 0.2	8.3 ± 1.2
	5	19	25	7	1.010 ± 0.5	3.3 ± 1.5
	6	17	25	7	0.435 ± 0.2	4.0 ± 1.0
	7	17	15	10	0.405 ± 0.2	8.3 ± 1.2
	8	19	15	7	0.535 ± 0.2	9.0 ± 0.0
	BC[a]	17	25	10	0.295 ± 0.4	9.0 ± 1.4
DMAc : acetone : water (32 : 63 : 5 w/w)	1	14	15	10	0.310 ± 0.1	5.6 ± 0.6
	2	17	15	10	0.575 ± 0.1	9.0 ± 0.0
	3	17	25	7	0.325 ± 0.2	5.3 ± 0.6
	4	14	25	7	0.420 ± 0.1	3.0 ± 0.0
	5	17	25	10	0.595 ± 0.2	7.3 ± 0.5
	6	17	15	7	0.605 ± 0.2	8.7 ± 0.6
	7	14	15	7	0.340 ± 0.1	4.7 ± 0.5
	8	14	25	10	0.400 ± 0.1	3.7 ± 0.5
	BC[a]	15	15	10	0.360 ± 0.1	8.5 ± 0.6

[a] Best condition.
[b] Average fiber width.

An arbitrary scale was created for assessing the aspect of the membranes with values in the range of 1–10, where 1 corresponded to the absence of fibers, 5 signified the formation of fibers with many defects and, finally, 10 corresponded to the fibers with a good size and uniformity. Two images per sample were evaluated by three independent people, who did not know the evaluation given by the others. The mean value was obtained in this assessment for each membrane and used in membrane analysis.

RESULTS AND DISCUSSION

As mentioned earlier, a useful tool in the evaluation of multiple factors of a system is the DOE. To optimize the conditions for obtaining CA membranes, a 2^3 factorial design with 3 factors (distance between needle-collector, voltage and CA concentration) in two levels (high and low) was done for each solvent system. As a response the diameter and the aspect of each nanostructured membrane was chosen, considering factors such as the concentration of CA, the applied voltage and the distance between the needle tip and the collector. Such factors, which were varied at two levels as shown in Table I, were chosen, as they were easy to control. Minitab software was used for statistical analysis. The results obtained for each solvent system studied are shown below, in Table I and the results obtained for viscosity, conductivity, and surface tension for the same system in Table II.

CA electrospinning with acetic acid : water (3 : 1 w/w) solvent mixture

Table I presents the parameters measured for each experiment developed to obtain nanofibers of CA in

TABLE II
Variation of the Viscosity, Conductivity, and Surface Tension for CA in Solvent Mixtures

Solvent mixture	% CA	Viscosity (mPas)	Conductivity (μS)	Surface tension (mN/m)
Acetic Acid : water (3 : 1 w/w)	13	1650	116.7	35.8
	17	5400	81.6	36.5
	18	6575	79.4	38.6
	19	8800	74.8	39.0
Acetone : water (85 : 15 w/w)	16	400	13.1	31.1
	17	450	13.8	31.7
	19	875	12.6	32.3
DMAc : acetone (1 : 2 w/w)	17	550	7.6	28.9
	19	925	7.4	30.3
DMAc : acetone : water (32 : 63 : 5 w/w)	14	275	7.9	29.6
	15	375	8.7	30.0
	17	625	8.0	31.1

acetic acid : water, and Table II shows the results obtained for viscosity, conductivity, and surface tension for this system. As seen in Table II, by increasing the concentration of CA, in the system acetic acid : water, the viscosity increases sharply and the conductivity decreases, while the change in surface tension does not vary much. Furthermore, the other systems did not vary in the same proportion, although the results are meaningful to the viscosity. Regarding to the conductivity and surface tension of the other systems, the values remained in the same order of value.

It can be observed, in Table I, that the average diameter of the fiber obtained in the experiments was less than 200 nm; but the scores were very low, indicating the presence of many defects. A large number of beads and low fiber formation was also observed. Therefore, none of the experiments showed a satisfactory minimum value 7 for the desired membrane aspect.

The Pareto chart for effects is shown in Figure 1, which shows the significance of each factor (distance, voltage, and concentration) in the response obtained. It was found that the factor of greatest importance, and the only significant one, was the CA concentration of the solution.

Figure 2 represents the plot for main effects on the membrane aspect obtained in the acetic acid : water (3 : 1 w/w). The chart shows how the effects can influence individually the output parameters, which are indicated by the slope of the lines in each quadrant. It can be observed that the curve with the higher slope is the one corresponding to the concentration, which was elected the most influential factor in relation to the others, as seen in the Pareto's chart in Figure 1.

Based on these data, we carried out an experiment to optimize the results obtained from the CA solutions at 18 and 19% (w/w), proceeding similarly with the other variables, that is, distance and voltage, using the best conditions for the first round of experiments (distance from the collector was 7 cm, applied voltage 25 kV and solution flow rate of 1 mL/h).

Figure 3(a) shows the SEM image obtained for the best condition of the first round of experiments, whose electrode distance from the collector was 7 cm and the applied voltage 25 kV. The solvent mixture for this case was acetic acid : water (3 : 1), using a solution flow rate of 1 mL/h. Figure 3(b,c) are images obtained with solutions of higher concentrations.

A significant improvement in the appearance of the membrane with reduction in the number and size of the beads, could be noted when the concentration of CA increased, after comparing Figure 3(a–c). The best result in the appearance of the membrane was that corresponding to CA solution 19% (w/w), but the high viscosity of it caused constant troubles for the solution flow through the needle. Consequently, the optimal concentration for this solvent system was

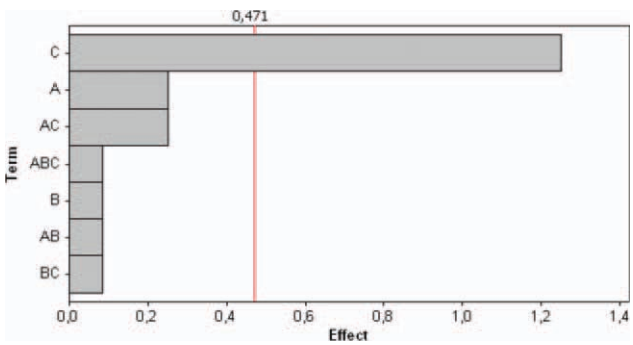

Figure 1 Pareto chart of each effect A, B, or C and their interaction for the membrane aspect using acetic acid : water (3 : 1 w/w) as solvent system: (A) needle/collector distance, (B) potential, and (C) concentration. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

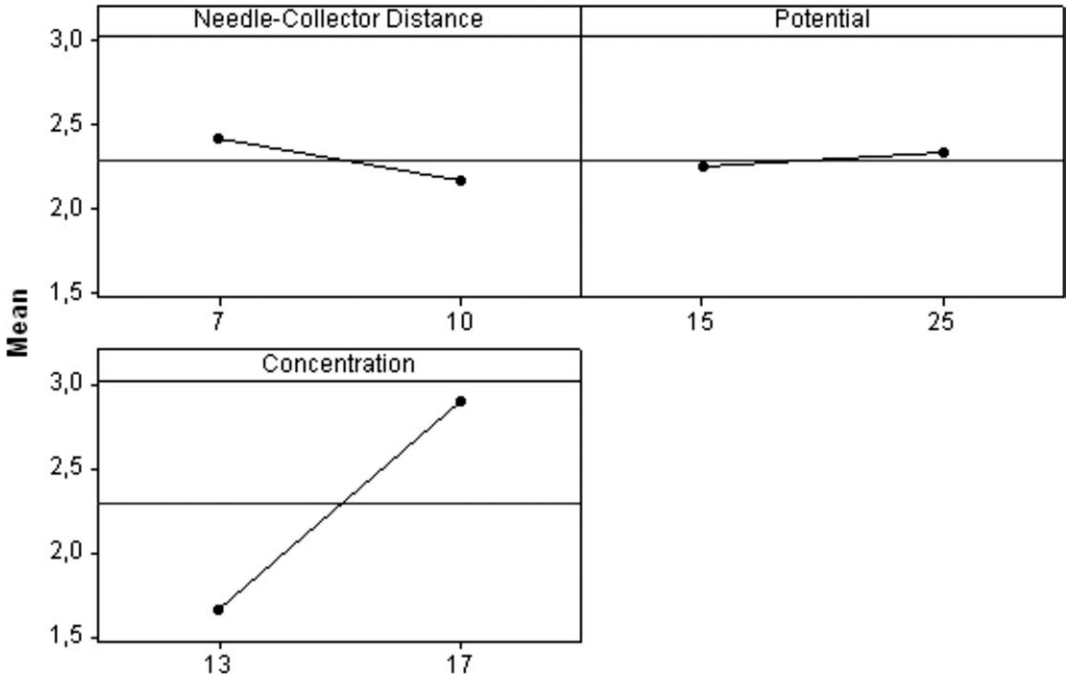

Figure 2 Main effect plot for membrane aspect for the electrospun membrane obtained in the Acetic acid : Water (3 : 1 w/w) system.

established at 18% (w/w) of CA, which allowed the work to be carried out.

CA electrospinning with acetone : water (85 : 15 w/w) solvent mixture

After replacing the pair of solvents, that is, acetic acid : water by acetone : water, the results shown in Table I, for membrane aspect and nanofiber diameter, and the results collected from analysis of the solution are shown in Table II.

In all tests, an abundant amount of electrospun fibers was preferably obtained in the form of ribbons. Because of this, the authors chose to show the values of width instead of the diameter in Table I. According to literature,[23] the geometry obtained for the fibers, in the form of ribbons, are attributed to the viscosity of certain solutions that prevent the evaporation of the solvent during the electrospinning process. Considering this solution of acetone : water, it was necessary to adopt a high feed rate (4 mL/h) in comparison with the other solvents used in this work, since for lower feed rates the solution evaporated dried on the tip of the needle, interrupting the electrospinning process.

It can be seen in Table I that the fiber width varied from 2 to 3 μm and the membrane aspect evaluation received a high value, meaning that they were apparently uniform and that this system is efficient to produce a large amount of fibers. In the experiments, the best result obtained was for run 6 (see Table I), although the diameter obtained was not below 500 nm, as desired.

The Pareto chart for effects, in Figure 4, shows the significance of each factor in the response. It was found that the factor of greatest importance, and the only significant one, was the concentration of CA in the solution.

Figure 5 represents the plot of the main effects for the average width of the fibers. It can be observed that the higher slope of the curve is in the line of concentration that is the determining factor in the width of the fibers and has a much greater influence than other factors in the Pareto chart (Fig. 4). It is important to note that the width of the fibers is reduced after decreasing the concentration.

A new experiment was carried out based on these results, using a 16% CA solution, but maintaining the same variables obtained in the best condition of the first round of experiments.

As shown in Figure 6, after decreasing the CA solution concentration from 17 to 16%, there is an increase in the width of the fiber from 1.7 to 3.1 μm, respectively. This result was very important because it gave us an idea of the minimum concentration of the CA solution necessary to keep the fiber formation instead of ribbons.

CA electrospinning with DMAc : acetone (1 : 2 w/w) solvent mixture

The results in Table I were obtained Using the organic solvent mixture DMAc : acetone. Each experiment

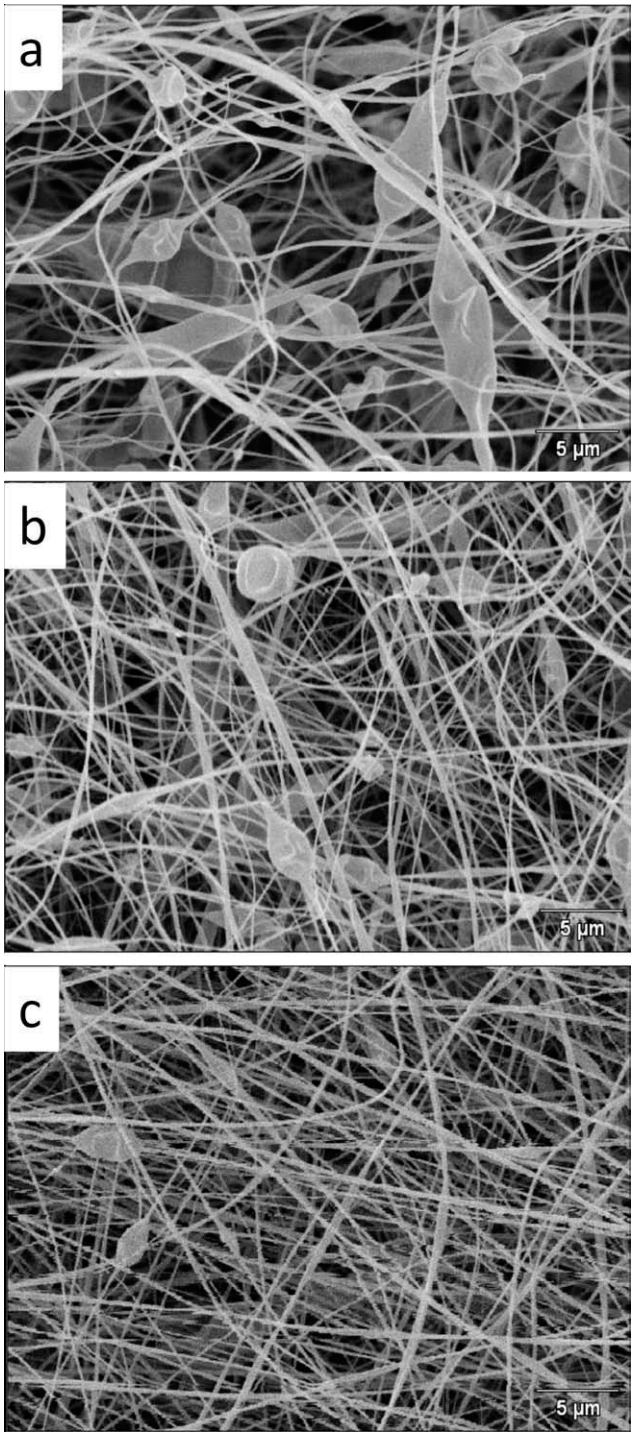

Figure 3 MEV images for electrospun membrane of CA solution, with magnitude 3000, obtained under the following conditions: acetic acid : water (75 : 25) as solvent; 7 cm distance between needle and collector; applied voltage of 25 kV and flow rate of 1 mL/h: (A) 17% (w/w) CA; (B) 18% (w/w) CA; (C) 19% (w/w) CA.

performed in the DOE and the results obtained in the analysis of the solution are shown in Table II.

A great variation in the average diameter of the fibers obtained in the experiments was observed, ranging from 300 nm to 1 µm and a good value for the membrane aspect.

Table I shows the optimum point for the series of experiments, run 3, which correspond to an average fibers diameter of 0.295 µm, and score 9.0 for the membrane aspect. This indicated good fiber uniformity obtained in this solvent system. For the average diameter of the fibers, no effect or combination of effects was significant; however, for the aspect value of the membrane, the distance, the voltage, and their combination proved to be significant. Therefore, the greater the distance and the lower the voltage, the smaller the diameter of the fiber will be in this optimized system.

The SEM image of the electrospun membrane is illustrated in Figure 7 using the optimum condition obtained with the DMAc : Acetone (1 : 2 w/w) solvent mixture.

As the optimum point was registered within the round of experiments, it was possible to generate eq. (1) below that represents the behavior of this solution in the electrospinning process of CA in the DMAc : Acetone (1 : 2) solvent mixture:

$$\mathrm{DM} = 19.808 - 2.092d + 1.267v + 1.168c + 0.126\mathrm{dv} + 0.127\mathrm{dc} + 0.0764\mathrm{cv} - 0.008\mathrm{dvc} \quad (1)$$

where DM, average diameter (µm); d, distance between the needle tip and the metallic collector (cm); c, cellulose acetate concentration (% w/w); v, applied voltage (kV). This equation can be used to optimize the process and obtain smaller diameters in the DMAc : acetone (1 : 2) solvent mixture, if desired.

CA electrospinning with DMAc : acetone : water (32 : 63 : 5 w/w) solvent mixture

Table I illustrate the results obtained for each experiment done to obtain nanofibers of CA, using DMAc :

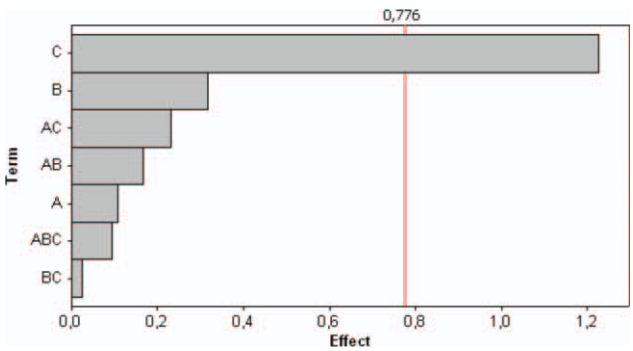

Figure 4 Pareto chart of each effect A, B, or C and their interaction for the membrane aspect using acetone : water (85 : 15) as solvent system: (A) needle/collector distance, (B) potential, and (C) concentration. [Color figure can be viewed in the online issue, which is available at wiley onlinelibrary.com.]

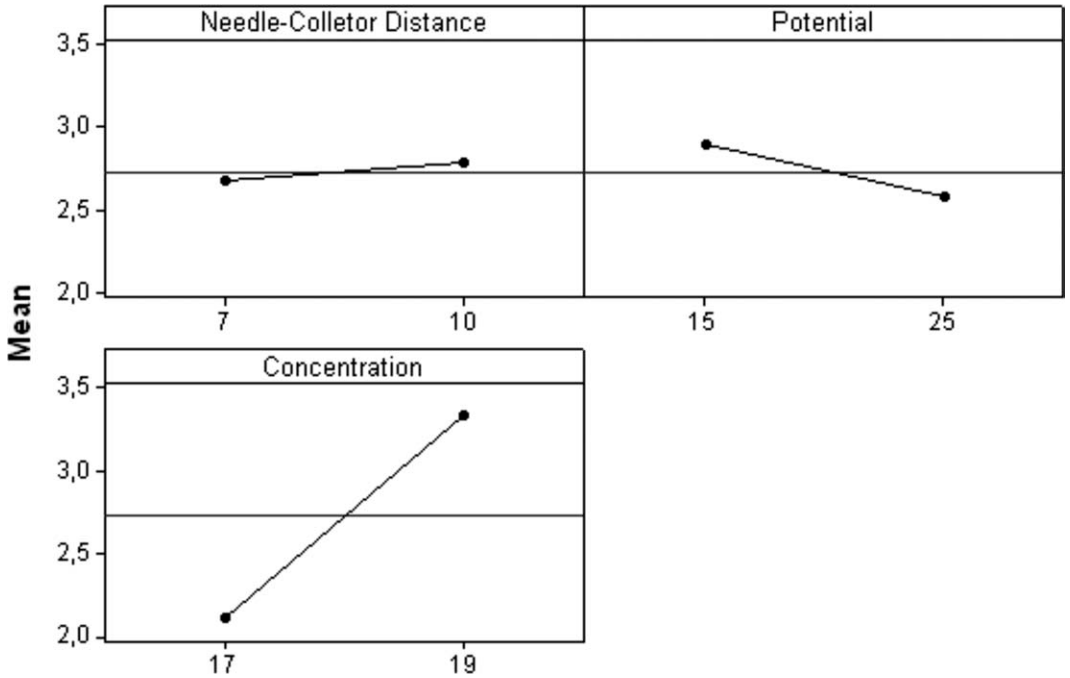

Figure 5 Main effect plot for the width of the electrospun fiber using the acetone : water (85 : 15 w/w) system.

acetone : water solvent system. The results collected in the solution analysis are shown in Table II.

As seen, the diameter of the fiber obtained in the experiments varied from 300 to 600 nm, with a great variation for the membrane aspect and the results are within the desired range.

Figure 8 shows the Pareto plot for effects and their interaction for membrane aspect, with the significance of each factor on the response obtained. It was found that the concentration of CA in the solution and the applied voltage were the most relevant and significant effects. The Pareto chart of the effects compare the relative magnitude and the statistical significance of both main and interaction effects. The effects are plotted in decreasing order of the absolute value. The reference line on the chart indicates which effects are significant, using a level of significance α of 0.05.

The interaction plot for the average diameter of the fiber is represented in Figure 9, which shows how the factors affect the output parameters and their combinations. Interactions plots are used to visualize the interaction effect of two factors on the response and to compare the relative significance of

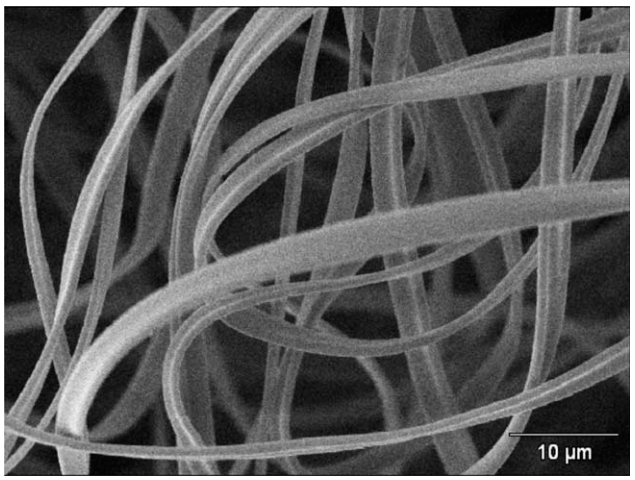

Figure 6 MEV images for the electrospun membrane of CA solution 16% (CA), with magnitude 2000, obtained under the following conditions: acetone : water (85 : 15) as solvent; 7 cm distance between needle and collector; applied voltage of 25 kV and flow rate of 4 mL/h.

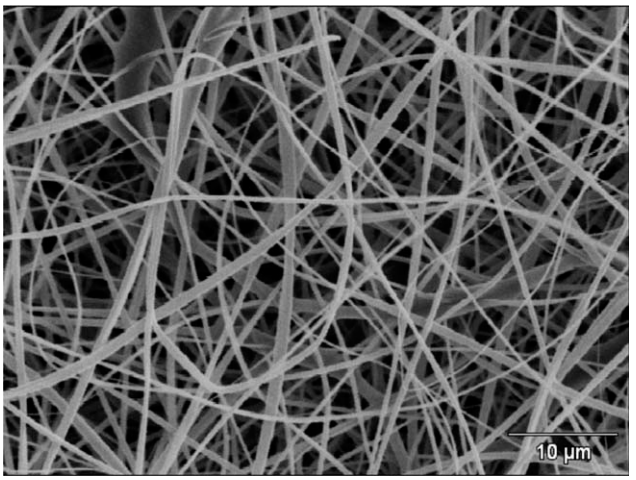

Figure 7 MEV images for the electrospun membrane of CA solution 17% (CA), with a 2000 magnitude, obtained under the following conditions: DMAc : Acetone (1 : 2) as solvent; 10 cm distance between needle and collector; applied voltage of 25 kV and flow rate of 1 mL/h.

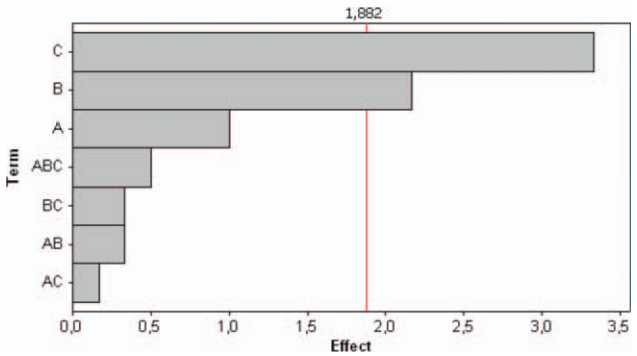

Figure 8 Pareto chart of each effect A, B, or C and their interaction for the membrane aspect using DMAc : acetone : water (32 : 63 : 5 w/w) as solvent system: (A) needle/collector distance, (B) potential, and (C) concentration. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the effects. The indication is given by the slope of the two lines in each quadrant. If the lines are parallel to each other, there is no interaction, while crossing lines means some interaction. One can observe that the highest slope of the curves corresponds to concentration and voltage, which are the determining factors for fiber diameter and have a greatest influence over the distance between the tip of the needle and the collector.

Using the DOE results, the Minitab software generated a new optimized condition for the process, providing the value for the membrane aspect within the desired range, with a smaller fiber diameter. An intermediate concentration of CA (15%) should be used, with a distance between the needle and collector of 10 cm, applied voltage of 15 kV and flow rate of 1 mL/h. For this reason, an experiment was performed considering this optimum condition indicated by the software as shown in Table I. Figure 10(a) shows the SEM image for the best condition obtained in the round of experiments (run 2, see Table I) and Figure 10(b) shows the image of the optimized condition.

Comparing the results for the two concentrations tested, a significant reduction of 37% (from 575 to 360 nm) is noted in the fiber diameter with the concentration decreasing from 17 to 15%. However, the score 8.5 was maintained for the membrane aspect, indicating that the optimum point was reached for this solvent system.

The results obtained for average fibers diameter and membrane aspect were 360 and 8.5 nm, respectively, which are already being used for the production of membranes loaded with gentamicin sulfate, propolis, and silver nanoparticles for extracorporeal treatment of injuries.[24]

CONCLUSIONS

In all conditions, it was possible to obtain fibers as observed in SEM images, but with different diameters and shapes, as ribbons and cylinders.

The smallest fiber diameters and the best aspects of nanostructured membranes were obtained with DMAc : Acetone (1 : 2) and DMAc : acetone : water (32 : 63 : 5) solutions. These membranes showed lower conductivity indicating that, for the range of parameters studied, lower conductivity provided better results relating to the fiber diameter and membrane aspect. The surface tension and viscosity were not significant in these results when compared with the different systems.

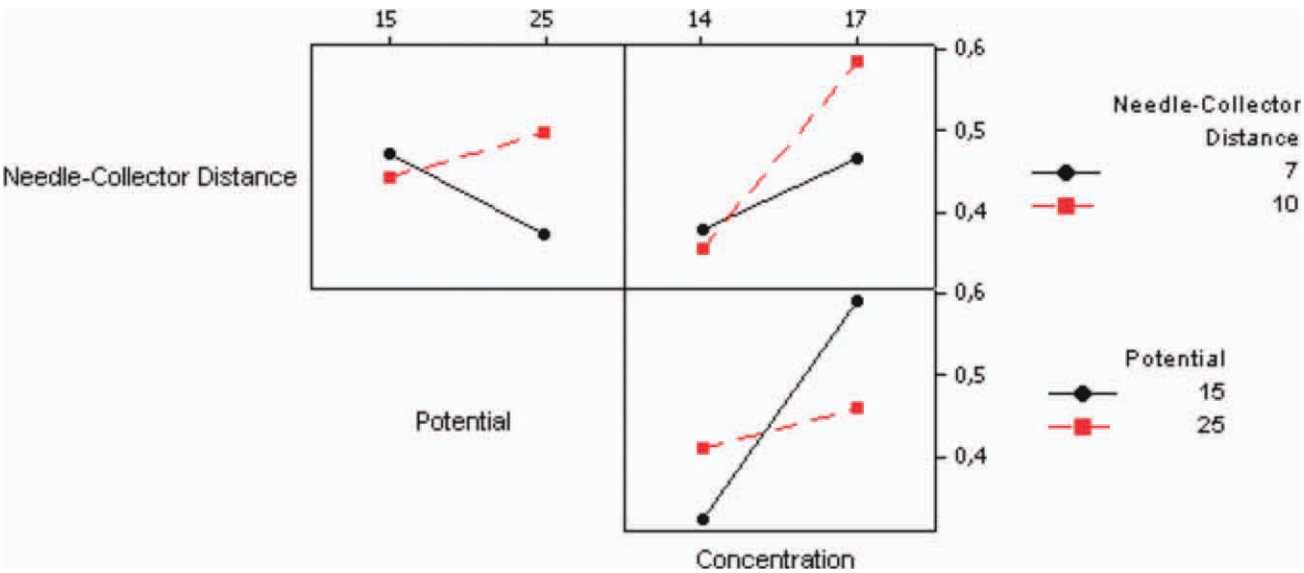

Figure 9 Interaction plot for the average fiber diameter using DMAc : acetone : water (32 : 63 : 5 w/w) as solvent system. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

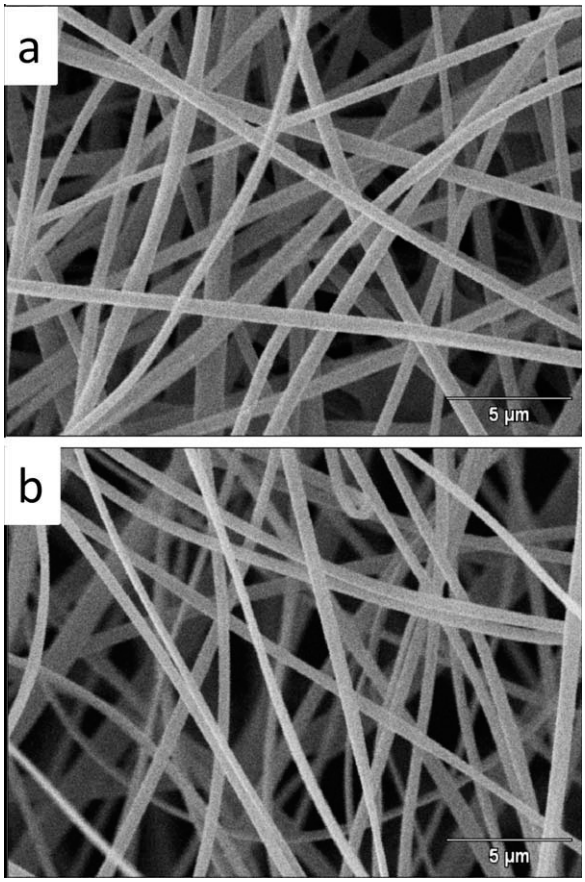

Figure 10 MEV images for the electrospun membrane of CA solution 15% (CA) in DMAc : acetone : water (32 : 63 : 5), with magnitude 5000, obtained under the following conditions: (A) best conditions obtained in the series of experiments number 2 and (B) optimized conditions.

The concentration of the solutions was highly significant in comparison to the other factors studied, in each solvent system. In some cases, the extrapolation of the results to values outside the range studied was possible, giving better results.

This work provided a greater understanding of CA nanostructured membranes obtained by electrospinning technique, using several solvents. With the set of data collected, it will become possible to choose the solvent system for CA polymer to produce nanostructured membranes, which will act as drug carriers in controlled delivery systems.

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