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Nanostructured Membranes Based on Cellulose Acetate Obtained by Electrospinning. Part II. Controlled Release Profile and Microbiological Behavior

Silvia Vaz Guerra Nista,[1] Marcos Akira D'Ávila,[2] Elizabeth Ferreira Martinez,[3] Almenara de Souza Fonseca Silva,[3] Lucia Helena Innocentini Mei[1]

[1]Faculdade de Engenharia Química, UNICAMP (University of Campinas), Av. Albert Einstein, 500, CEP 13083-852 Campinas, São Paulo, Brazil

[2]Faculdade de Engenharia Mecânica, UNICAMP (University of Campinas), Rua Mendeleyev, 200 CEP 13083-860 Campinas, São Paulo, Brazil

[3]Instituto e Centro de Pesquisas São Leopoldo Mandic, Rua Doutor José Rocha Junqueira, 13 CEP 13045-755, Campinas, São Paulo, Brazil

Correspondence to: L. H. I. Mei (E-mail: lumei@feq.unicamp.br)

ABSTRACT: Nanofiber membranes of cellulose acetate (CA) were produced with four mixtures of solvents, that is, acetic acid/water, acetone/water, dimethylacetamide (DMAc)/acetone, and DMAc/acetone/water, with the incorporation of the drug gentamicin sulfate at two concentrations. We evaluated the influence of the drug concentration in the electrospinning process. The best membrane produced in this stage was the membrane electrospun with the DMAc/acetone/water solvent mixture, whose process was shown to be viable and did not alter the membrane diameter or aspect with the variation of the drug concentration. Membranes prepared in this way and loaded with 50% of the drug were used for the studies of the release kinetics. Comparisons between the release profiles of the same membranes coated with hydroxypropyl methylcellulose, Eudragit L100, and electrospun CA nanofibers were carried out. The best results on the drug-release profile were obtained with the membrane coated with nanofibers of CA, which caused a decrease of 9 h in the burst effect. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2013

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INTRODUCTION

Currently, medical practice is mainly based on the treatment of diseases;[1] however, the medicine of the future will be based on early detection and preventive treatment. Along with nanotechnology, new modalities of treatment are showing significant reductions in medical costs. Because of recent developments in the process of electrospinning, nanofibers of natural and synthetic polymers have been produced with controlled morphology and functionality for applications in the medical field. Major potential applications of these electrospun nanofibers have been observed in healthcare[2,3] and the pharmaceutical[4,5] and cosmetic industries.[6]

The technology of the controlled release of drugs presents itself as an interdisciplinary challenge for pharmacists, engineers, chemical engineers, and the medical community.[7]

Polymer systems with the controlled release of drugs have numerous advantages compared to the normal forms of dosing.[5] In these systems, the drug levels in plasma are continuously maintained in a desired therapeutic range, and the harmful side effects observed in conventional administration can be reduced or eliminated by local administration.

Nanofibers as drugs carriers show a promising future in biomedical applications. Compared with other pharmaceutical forms, there are several advantages of using electrospun nanofibers. Drugs may be conveniently incorporated into the polymers before or during electrospinning and manufacturers can control the geometry of the device, the operational conditions, and the solvents used, and the composition of the polymer solution and drug can be used to design the profile of drug release.[8]

Supaphol et al.[6] electrospun a solution of 16% ethyl cellulose with solvent systems such as acetone/dimethylacetamide (DMAc) with vitamins A or E incorporated for cosmetic application. Thereafter, Supaphol et al.[4] also electrospun cellulose

Table I. Electrospinning Parameters Used for Each Solvent Mixture

Polymer solution (w/w)	CA concentration (%)	Voltage (kV)	Distance between the needle and the collector (cm)
Acetic acid/water (75:25)	18	25	7
Acetone/water (80:30)	17	25	7
DMAc/acetone (1:2)	17	25	10
DMAc/acetone/water (63:32:5)	15	15	10

acetate (CA) and functionalized it for the topical delivery of drugs. In four solutions of CA, four nonsteroidal anti-inflammatory drugs were added, fibers with a diameter of 200 nm were obtained, and the drug release was compared to films containing the same drugs.

Kenawy et al.[9] studied the release of tetracycline hydrochloride 5% in poly(lactic acid) and poly(vinyl alcohol) blends. The initial release rates of all formulations were high (having a burst effect) during the first 10–12 h. In turn, Zong et al.[10] electrospun poly(D,L-lactide) containing Mefoxin, but the burst effect was observed after 3 h, and the complete release occurred in 48 h. Others, such as Zeng et al.,[11] electrospun poly(lactic acid) (PLLA) and added to the solution various surfactants and Rifampin (a drug used for tuberculosis). It was found that the drug was encapsulated inside the fiber, a continuous release was observed during the process of fiber degradation, and the burst effect was not observed. Another very interesting work was done by Rodrigues Filho et al.,[12] who developed cellulose triacetate membranes produced from sugarcane bagasse as a matrix for the controlled release of doxycycline for enteral and topical use. The results show that the membranes produced from sugarcane bagasse were adequate for producing matrices for drug-controlled release, both for enteric and topic use.

Among the available antimicrobial agents, gentamicin sulfate or gentamicin is an antibiotic belonging to the family of the aminoglycosides, produced by strains of *Micromonospora purpurea* and isolated in 1963; since then, it has been used in the treatment of infections because of its low cost and wide range of antibacterial activities by a protein synthesis inhibition mechanism. Many studies have been conducted to evaluate new forms of applications of gentamicin sulfate.[13–16] For the intended application, with a focus on skin problems caused by fungi and bacteria, gentamicin has topical application. Currently, it is applied in the form of an ointment three to four times daily. The advantages of using a nanofiber membrane for this application is increased patient comfort, the replacement of the ointment with a membrane (patch), and a reduction in the frequency to one application daily. Thus, a reduction in the side effects by use of lower doses over a longer period was expected. Another role of the membrane would be to act like a sponge to absorb the fluids released by injury and ensure oxygenation through its porous network of nanofibers.

On the basis of the information found in the literature and to continue the work previously developed,[17] the aim of this study was to evaluate the gentamicin loading in CA nanofibers and their coverage with different polymers to control the sustained release of the drug.

EXPERIMENTAL

Materials

We used CA (white powder, relative molecular mass (M_r) = 29,000, degree of substitution = 40%, Sigma-Aldrich), DMAc PA (Merck), acetone pro analysis (PA) (Synth), deionized water, gentamicin sulfate (Pharmaceutical Group Hualuan Co., Ltd.), phosphate buffer solution (0.1*M* pH 7.4, Dinâmica), Eudragit L100 (Evonik), hydroxypropyl methylcellulose (HPMC) PA (Dow Corning), and Ninhidrina PA (Sigma-Aldrich).

Preparation of CA Electrospun Membranes Loaded with Gentamicin Sulfate

Four polymeric solutions of CA were prepared [17% w/w CA in acetic acid/water (75:25), 18% w/w CA in acetone/water (85/15), 17% w/w CA in DMAC/acetone (1:2), and 15% w/w CA in DMAC/acetone/water (32:63:5)] according to our previous study.[17] Gentamicin sulfate at concentrations of 6 and 60% (w/w), on the basis of CA, were incorporated into membranes under stirring for 2 h to guarantee homogenization.

All polymer solutions were characterized with a conductivity meter (Analion, model C708 Plus, Ribeirão Preto, Brazil). All measurements were performed in triplicate at 25°C.

The electrospinning processing parameters used are summarized in Table I.

The CA solutions with gentamicin sulfate were electrospun at a temperature of 25°C and a humidity of 50% with 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 supply from a Hewlett-Packard model 3406A was connected to the metallic needle of the syringe, whereas the ground electrode was used to ground the copper plate collector with dimensions of 30×40 cm^2. A feed stream of 1 mL/h was controlled by a KdScientific model 100 pump, and the set was connected to a syringe. 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.

The CA nanostructured membranes loaded with gentamicin sulfate were analyzed by scanning electron microscopy (SEM), with a Leica LEO 440i scanning electron microscope. Eight images were obtained for each sample with different magnitudes and were analyzed with the software Image Tool to measure the average diameter from 50 measurements registered by each sample. The best membranes were chosen by comparative analysis of the images obtained; we focused on their appearance, morphology, and diameter uniformity.

Controlled Release Tests

For the controlled release tests, we chose only one membrane among all of the systems of solvents used, corresponding to the one obtained with the DMAC/acetone/water (32:63:5) solvent mixture with 15% (w/w) CA. This membrane was electrospun

Table II. Average Diameter of the CA Electrospun Nanofibers Loaded with Gentamicin Sulfate to Form Membranes

	Average diameter (nm)	
Solution	6% gentamicin	60% gentamicin
18% CA in acetic acid/water (75:25 w/w)	170 ± 50	400 ± 70
17% CA in acetone/water (85:15 w/w)	3400 ± 710[a]	920 ± 640[a]
17% CA in DMAc/acetone (1:2 w/w)	510 ± 140	410 ± 150
15% CA in DMAc/acetone/water (32:63:5 w/w)	490 ± 170	400 ± 120

[a] Average ribbon width.

with a solution flow rate of 1 mL/h, a voltage of 15 kV, a needle–collector distance of 10 cm, and 50% gentamicin sulfate based on the CA concentration. The samples were cut in circle forms 20 mm in diameter. The results of the drug-release test were compared to those obtained with the same membrane covered with Eudragit L100, HPMC, and drug-free CA nanofibers.

The coating of the CA membrane loaded with gentamicin sulfate was performed on both of its sides, with electrospun CA nanofibers from a solution of 15% CA in DMAC/acetone/water (32:63:5), according to the same processing conditions reported in Table I. This coating represented about 65% of the total weight of the resulting membrane.

In the case of those membranes coated with Eudragit L100 (20%), they were prepared by the dripping of a solution of this substance plus PEG (5%) in isopropyl alcohol over the membrane loaded with the drug. Here, the coating weight of the new device was about 75% of the total. The same coating procedure was done by the spraying of an aqueous solution made with 0.1 g of HPMC in 35 mL of water over the membrane loaded with gentamicin sulfate; this resulted in a final membrane whose coating was nearly 65% of the total weight.

Samples of each type of CA membrane loaded with gentamicin sulfate; that is, a noncoated membrane and membranes coated with CA nanofibers, HPMC, and Eudragit L100 were placed in test tubes.

A volume of 20 mL of a phosphate buffer solution (0.1*M*, pH 7.4) was added in each tube and left in a bacteriological oven (model 410N from Nova Ética, Brazil) at 37°C. At predetermined periods, an aliquot of 5 mL was removed and replaced by a new one. The gentamicin sulfate in each aliquot was analyzed quantitatively with the same method used by Frutos et al.[18] This analysis, which was done in triplicate, was based on an indirect measurement by the determination of the absorbance of gentamicin sulfate in an ultraviolet–visible spectrometer (model Cary 1G from Varian) and the evaluation of its concentration in a standard curve previously constructed with known concentrations of the drug.

Microbiological Analysis

All procedures were carried out in a laminar air flow instrument; in the diffusion test, CA nanofibers loaded with gentamicin sulfate at different concentrations (10, 20, and 50%) were prepared as 13-mm diameter disks and sterilized by ethylene oxide. As negative controls, membranes were prepared without the drug.

A suspension of brain–heart infusion broth containing approximately 1.5×10^8 microorganisms/mL (Factor 1 McFarland scale, Nefelobac, Brazil) from *Staphylococcus aureus* (ATCC 25923.2) and *Escherichia coli* (ATCC 25922), both obtained from American Type Culture Collection (ATCC, Manassas, VA). The strains were spread uniformly on Mueller–Hinton agar plates with a sterile cotton swab, and then, the membranes were plated. The agar plates were incubated at 37°C for 48 h. Then, the zones of inhibition were examined and measured as the maximum width from the edge of the well to the periphery of the inhibition zone with a digital ruler (Digitech, Campinas, Brazil).

All of the tests were performed in triplicate.

RESULTS AND DISCUSSION

Definition of the Best Membrane Loaded with Gentamicin Sulfate

Several tests were performed to change the concentration of gentamicin sulfate in polymer solutions to minimize its influence in the electrospinning process. The appearance (the absence of defects as drops and beads, good uniformity, and diameter distribution) of the membrane and the diameters of the nanofibers obtained were evaluated and compared with those of membranes produced under the same process conditions without the addition of drug.

Table II shows the best results obtained for the average diameter of nanofibers; these were loaded with the drug and prepared according to the conditions shown in Table I.

Evaluating the results of Table II, we observed that for solutions of acetic acid/water and acetone/water, the concentration of gentamicin had a great influence on the nanofiber average diameter compared with the results obtained for the DMAc/acetone and DMAc/acetone/water solutions. The scanning electron micrograph (SEM) pictures of the membranes obtained with the polymer solution of 18% CA in acetic acid/water loaded with 6 and 60% gentamicin sulfate are shown in Figure 1(a,b), respectively.

The images presented in Figure 1(a,b) show that an increase in the gentamicin sulfate concentration may have reduced the number of beads and defects on it. It was also clear that an increase in the drug concentration caused an increase in the fiber diameter but kept it lower than 500 nm, as desired.

To understand why an increase in the gentamicin sulfate produced fewer defects, the electrical conductivity of the solutions with 6 and 60% drug contents were measured. The values obtained are shown in Table III.

As shown in Table III, the addition of gentamicin sulfate significantly increased the CA conductivity of the solution in acetic acid/water. This increase in the conductivity explained the improvement in the aspect of the membrane reduction of the beads after incorporation of the drug. As mentioned in the literature by Ramakrishna et al.,[19] when the conductivity of the

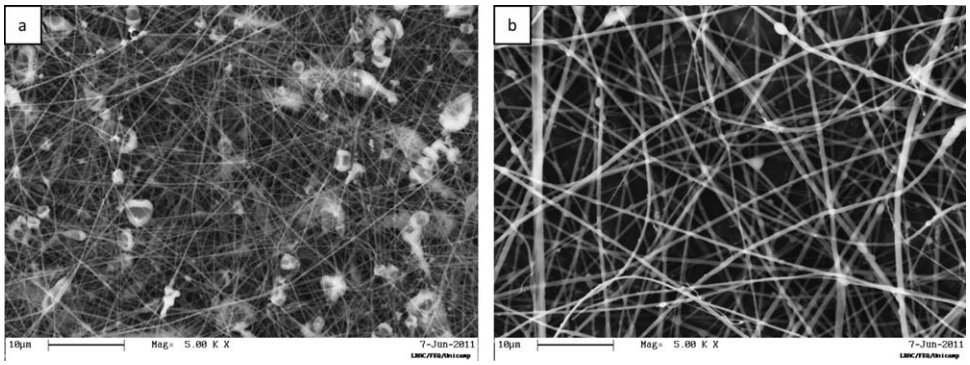

Figure 1. Nanostructural images of the electrospun membranes obtained from a polymeric solution of 18% CA in acetic acid/water loaded with (a) 6 and (b) 60% of gentamicin sulfate under ideal conditions (original magnification = 5000×).

polymer solution increases, more ions will be carried by the jet and, consequently, a greater stretching of the fiber will occur with fewer beads.

Figure 2(a,b) show the SEM micrographs of the membranes loaded with 6 and 60% gentamicin sulfate, respectively, and prepared from polymer solution of 17% CA in acetone/water. For this solvent mixture, with the conditions described in Table I, it was not possible to prepare electrospun membranes loaded with 6 and 60% of the drug. In the same way that was observed in our previous work,[17] electrospun fibers with this solvent mixture were preferably obtained in the form of ribbons. Because of this, we chose to show the values of width instead of diameter in Table II.

Thus, the CA concentration was kept constant, and minor adjustments to voltage applied and the distance between collector and needle were made until the nanofibers could be obtained.

As shown in Figure 2, when the concentration of gentamicin sulfate in the electrospun membrane was increased, it resulted in a significant reduction in the average width of the nanofibers, that is, from 3.14 to 0.92 μm; this corresponded to a reduction of 71%. However, the appearance of the membrane (the presence of defects) and the homogeneity in the fibers' width were not retained; this indicated a decrease in the quality of the material.

Table III. Electrical Conductivity of the CA Polymer Solutions Loaded with Gentamicin Sulfate

	Conductivity (μS/cm)		
Solution	0% gentamicin	6% gentamicin	60% gentamicin
18% CA in acetic acid/water (75:25 w/w)	56.1	101.4	306.0
17% CA in acetone/water (85:15 w/w)	12.9	17.9	20.8
17% CA in DMAc/acetone (1:2 w/w)	8.1	8.1	6.2
15% CA in DMAc/acetone/water (32:63:5 w/w)	8.7	8.0	7.6
Deionized water	1.8	1830.0	8510.0

As shown in Table III, the conductivity of the CA solution in acetone/water was increased after the addition of drug but not as much as for the CA solution in acetic acid/water; this was possibly due to the gentamicin sulfate ionization in this solvent mixture. This increase in the conductivity was due to the mixture of solvents, and the increase in the gentamicin sulfate concentration was a good combination for producing electrospun membranes with fewer defects, as shown in Figure 1(b).

Another effect caused by the increase of charges, also cited in the literature,[19] was the increase of the jet instability due to the higher solution conductivity; as a result, an increase in the area of the fibers deposited and the nonhomogeneity of their diameter were observed.

The membranes obtained with the polymer solution of 17% CA in DMAc/acetone are shown in Figure 3. In this case, it was also necessary to change the conditions presented in Table I because, under these conditions, it was not possible to obtain fibers. Thus, the solution concentration was kept at 17% CA, and the voltage and the needle–collector distance were changed until the formation of the membranes was observed.

As shown in Figure 3, with increasing drug concentration, there was a reduction in the nanofiber diameter of 19%, and the membrane was free from defects and had a good size uniformity.

Table III shows that the conductivity of the CA solution in DMAc/acetone decreased significantly with increasing drug amount. This decrease in the conductivity could have been the result of the physical barrier created by the higher concentration of gentamicin sulfate (60%) because this drug did not solubilize in this solution but preferentially dispersed. A reduction in the conductivity, promoted by the physical barrier, helped to obtain fibers with smaller diameters.

When a solution of 15% CA was used in DMAc/acetone/water, fibrous membranes free of defects were obtained, as shown in Figure 4. In this case, it was possible to maintain the ideal conditions, presented in Table I, without any modification of the parameters.

By comparing the results shown in Table II with the images of Figure 4, we observed that when the drug concentration was

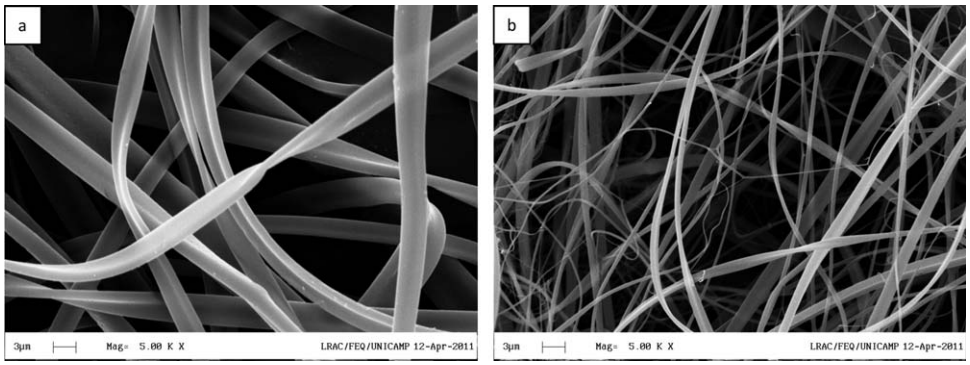

Figure 2. Nanostructural images of the electrospun nanofibers obtained from a polymeric solution of 17% CA in a mixture of acetone/water loaded with (a) 6% gentamicin sulfate at Voltage = 15 kV and Distance = 10 cm and (b) 60% gentamicin sulfate at Voltage = 15 kV and Distance = 7 cm (original magnification = 5000×).

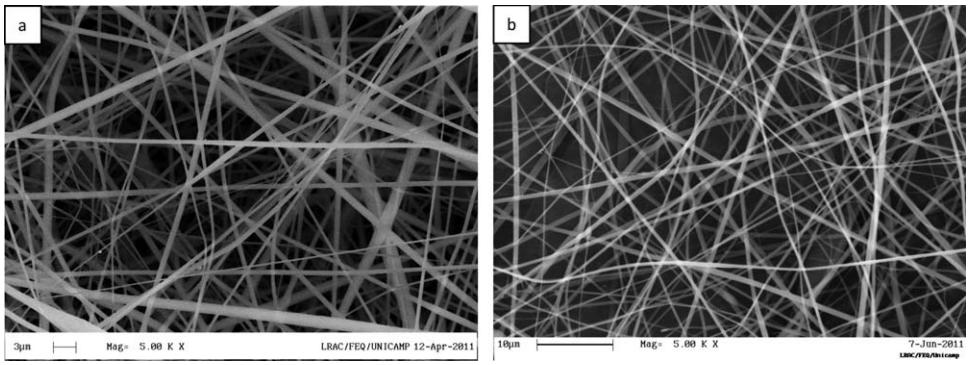

Figure 3. Nanostructural images of the electrospun nanofibers obtained from polymeric solutions of 17% CA in DMAc/acetone loaded with (a) 6% gentamicin sulfate at Voltage = 15 kV and Distance = 10 cm and (b) 60% gentamicin sulfate at Voltage = 10 kV and Distance = 7 cm (original magnification = 5000×).

increased, changes in the appearance of the membrane and their average diameter and uniformity were not observed. This was evidence that the system was stable and allowed variations in the drug concentration without losses in the quality of the final membrane.

The same behavior was detected after a comparison of these results with those obtained for the solution conductivity in Table III. We noted that the conductivity also decreased for gentamicin in DMAc/acetone/water with the addition of the drug, but the decrease was less than that obtained for the drug in DMAc/acetone solution.

This behavior of the conductivity suggested the formation of a physical barrier created by the fraction of gentamicin sulfate not solubilized in DMAc/acetone/water because this drug was not solubilized in organic solvents but was highly soluble in water. However, the effect on the conductivity was small in this case because of the small proportion of water in this solvent mixture (5%), which helped to partially solubilize the drug without affecting the membrane characteristics.

On the basis of the results obtained, the system of 15% CA in DMAc/acetone/water was chosen to prepare membranes loaded

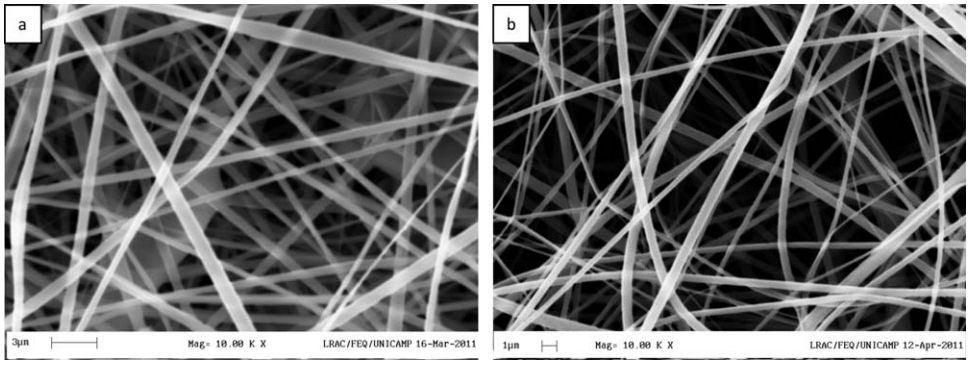

Figure 4. Nanostructural images of the electrospun nanofibers obtained from the polymeric solution of 18% CA in DMAc/acetone/water loaded with (a) 6 and (b) 60% gentamicin sulfate under ideal conditions (original magnification = 10,000×).

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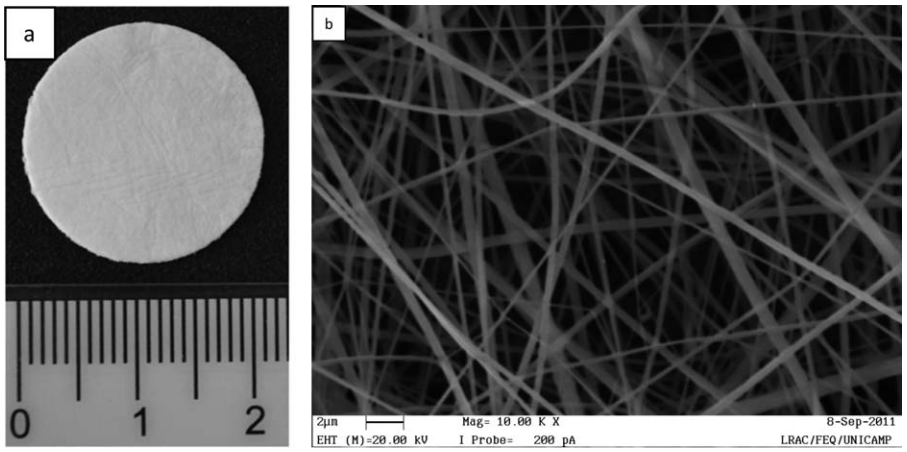

Figure 5. Images of the electrospun membranes from a solution of 15% CA loaded with 50% gentamicin sulfate: (a) membrane and (b) membrane SEM nanostructural conditions (original magnification = 10,000×).

with gentamicin sulfate and to study the profile of the drug-controlled release. This system was the most reproducible and did not affect the electrospinning process after the great increase in drug concentration. This system also produced nanofibers with an average diameter value smaller than 500 nm, as desired, and the produced membranes were easy to handle.

Testing for the Controlled Release of Gentamicin Sulfate

A picture of the electrospun membrane with 50% gentamicin sulfate prepared with a 15% CA solution in DMAC/acetone/water and used in the drug-release tests is shown in Figure 5(a), whereas the SEM image of this membrane is shown in Figure 5(b). As shown in this image, a good fiber distribution and no defects were observed. The average fiber diameter measured was 260 nm, which was within the expected range.

Figure 6 shows the images of the coated membrane. For the membrane coated with HPMC, we observed that the fiber structure was maintained, but the membrane was more compact than the uncoated one. In the SEM image of the membrane coated with

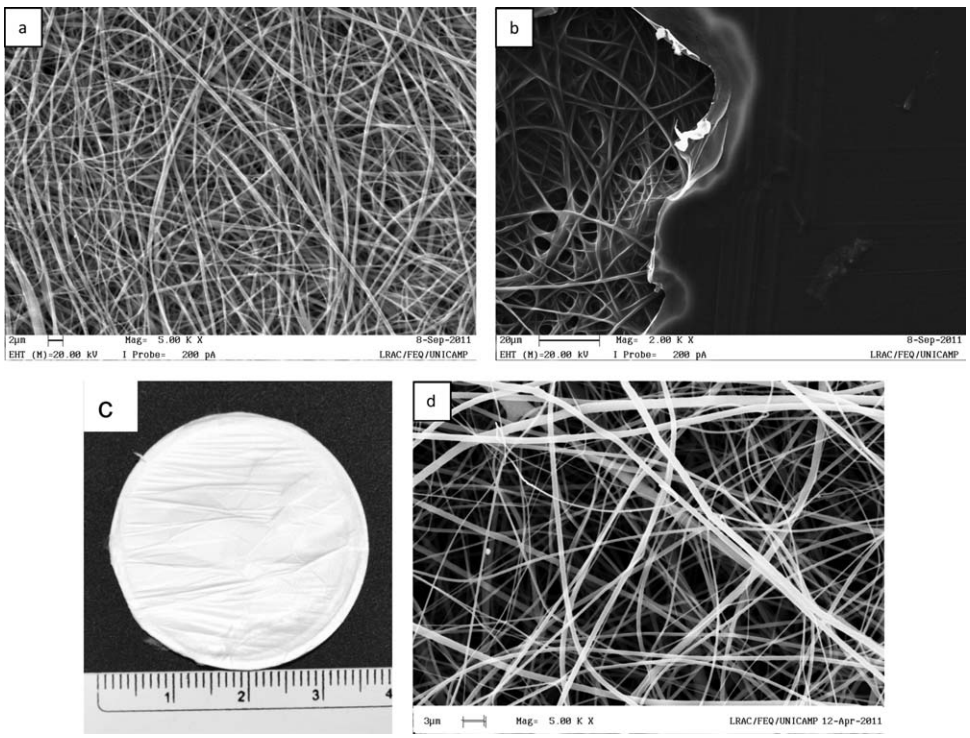

Figure 6. Nanostructural images of the electrospun nanofibers membranes loaded with 50% gentamicin sulfate: (a) SEM image of the HPMC-coated membranes (original magnification = 5000×), (b) SEM image of the Eudragit L100 coated membranes (original magnification = 2000×), (c) nanofiber membrane coated membranes, and (d) uncoated membrane (original magnification = 5000×).

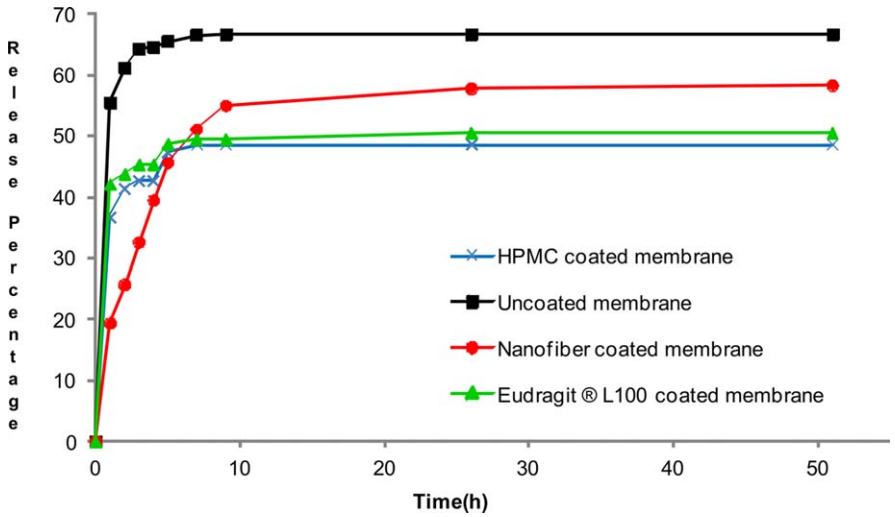

Figure 7. Release kinetics profile of gentamicin sulfate contained in the coated and uncoated membranes based on CA nanofibers. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Eudragit L100, we found a thicker and more complete covering, with the formation of a homogeneous layer on its surface without changes in the nanoscale of the fibers.

The drug-release profile with the different coatings on the nanofibrous membranes are shown in Figure 7.

As shown in Figure 7, the uncoated membrane had the greatest burst effect compared to the others, with a release of approximately 55% of the total drug in the 1st h of the test. In turn, those membranes coated with HPMC and Eudragit L100 presented a smaller burst effect and showed a drug release near 40% in the 1st h of the test. Finally, a very interesting release profile was obtained with the membrane coated with CA nanofibers without drug, which released only 20% of the total drug in the 1st h of the experiment. The release of 50% of the drug occurred during the first 10 h, whereas for the other membranes, this value was reached in the first 2 h of testing. This result, which was considered excellent, showed that it was possible to reduce the burst effect according to the coating type and open an opportunity to develop controlled release devices scheduled for each case.

The best result for drug release obtained with the membrane coated with CA nanofibers without drug could be attributed to the good physical barrier formed by this cover; this delayed the drug diffusion to the medium. Because this coverage was more efficient than the others used, it was chosen for the continuation of this research.

With respect to HPMC, which was soluble in water at 80°C, the test was performed at 37°C, below its complete solubilization; thus, we believe that its partial solubilization was responsible for the low efficiency of the system. The burst effect delay in the 1st h of the test (ca. 10%) compared to the uncoated membrane was probably due to the range of time in which HPMC acted before its complete dissolution. Similarly, the physical barrier expected for Eudragit L100 was not efficient because this coating dissolved at pH values higher than 6, and the test was carried

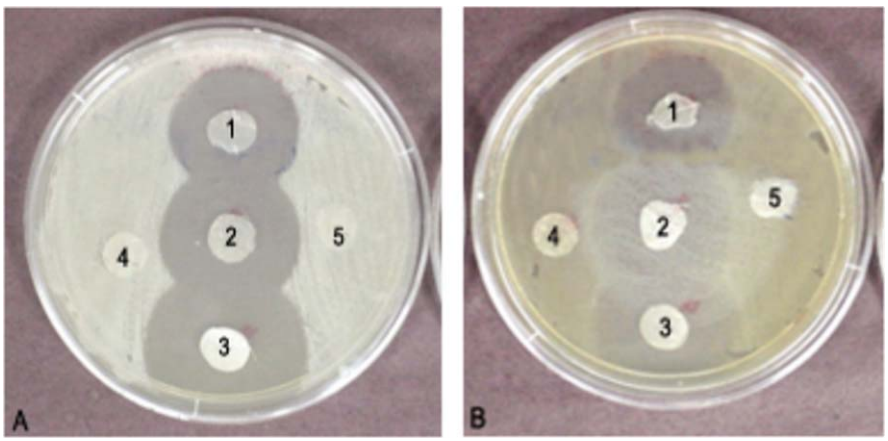

Figure 8. Inhibition zone formed around 15% CA nanofiber membrane loaded with (1) 10, (2) 25, and (3) 50% of gentamicin sulfate compared to the controls (4 and 5) on (a) *S. aureus* and (b) *E. coli* strains. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table IV. Average Size of the Inhibition Zone Obtained on Antimicrobial Tests as a Function of the Drug Concentration

Gentamicin sulfate (%)	Average size of Inhibition zone (mm)	
	S. aureus	*E. coli*
10	29.38 ± 0,51	20.26 ± 1,55
25	30.96 ± 1,25	23.07 ± 2,82
50	34.48 ± 0,03	25.17 ± 0,90

out at pH 7,4. The values of drug release registered for this kind of coating were very near of those obtained for HPMC.

From the results obtained, it was clear that the membrane coated with CA nanofibers was the best barrier for controlling the burst effect of the studied system; this resulted in a versatile material, which could be modulated to produce membranes with different drug time releases. This could be done by controlling the thickness of the electrospun nanofibers deposited over the membrane loaded with drug.

Microbiological Analysis

The results obtained for bacterial growth inhibition are demonstrated in Figure 8 for *S. aureus* [Figure 8(a)] and *E. coli* [Figure 8(b)]. After an incubation period of 48 h, the effects of different concentrations of gentamicin sulfate were clearly observed, and the inhibition zones were measured (Table IV).

The results show a significant increase in the inhibition zone with increasing gentamicin sulfate concentration for both bacterial strains.

On the basis of these results, we verified that the CA membranes incorporated with gentamicin sulfate showed the antibacterial action expected. The electrospinning process did not affect the performance of the drug because it remained effective even after high voltages were used in the process.

CONCLUSIONS

The membranes loaded with gentamicin sulfate and obtained by electrospinning from a solution of 15% CA in DMAc/acetone/water with a solution flow rate of 1 mL/h, a voltage 15 kV, and a distance of 10 cm between the needle and collector was shown to be a promising drug-delivery system.

In this system, the drug concentration did not influence the electrospinning process but rather produced membranes with good homogeneity and nanofibers with diameters smaller than 500 nm, as desired.

The electrospinning process did not inhibit the efficiency of the drug, as demonstrated in the antimicrobial tests with the presence of a halo against *S. aureus* and *E. coli*.

After 10 h of testing the controlled-release drug, we found that membranes coated with nanofibers were more effective than the other coatings tested; they reduced the burst effect during the 1st h, from 50 to 20% of the drug release.

The multipurpose material obtained in this study was shown to be efficient as a gentamicin-release device and opens many possibilities of use because it can be projected according to the applications needed. Different drugs and concentrations could be used, and the thickness of the coating nanofibers could be modulated to control the kinetics of drug release.

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