Electrospun Poly(D,L-lactide) Fibers for Drug Delivery: The Influence of Cosolvent and the Mechanism of Drug Release

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ABSTRACT: Controlled-drug release from electrospun fibers has found important biomedical applications in wound healing, transdermal delivery, and tissue engineering. In this study, poly(D,L-lactide) (PDLLA) was electrospun into ultrafine fibers and loaded with tetracycline (TC) or chlorotetracycline (CTC) as model drugs. The influence of a cosolvent (methanol) at various concentrations was studied regarding physical properties, morphology, and *in vitro* release profiles of the drugs from the PDLLA nanofibers. Swelling tests in a physiological buffer solution were performed to determine the extent and rate of swelling of the fiber mats. The results showed that for both drugs electrospun fiber diameters decreased with increasing amounts of cosolvent, whereas water contact angles and drug-loading efficiency increased. However, similar in chemical structure, the two drugs exhibited considerably different release mechanisms. The results indicated that the concentration of methanol changed the release profiles mainly based on the morphology of the resultant nanofibers and the polymer/drug/solvent interaction during the electrospinning and drug release process. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 115: 1–8, 2010

Key words: electrospinning; poly(D,L-lactide); drug delivery; diffusion; case-II transport

INTRODUCTION

In the past several years, polymer-based controlled-drug delivery systems have gained great attention due to the improvement of therapeutic efficacy and reduction of toxic side effects.[1,2] Different types of drugs have been encapsulated into polymer micro/nanoparticles, hydrogels, films, and other specific devices to deliver a particular medicine to a designated part of the body with a designed release pattern.[2–5]

The formation of ultrafine fibers with diameters in submicron to nanometer range by electrospinning has increasingly become important in recent years. Ultrafine polymer fibers can be produced by using the electrostatic force between a spinneret and a grounded collector. It has been acknowledged that the jet instability is the main driving force for their formation.[6,7] Electrospun nonwoven fiber mats with a very large surface area to volume ratio find a wide range of biomedical applications in different areas, including tissue engineering, wound healing, and drug release.[8–10]

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A variety of research has been reported in literature in regard to delivery systems, using model pharmaceutical compounds. For example, in an early study Kenawy et al.[11] first successfully electrospun poly(ethylene-*co*-vinylacetate), poly (lactic acid) (PLA), and blends thereof with tetracycline hydrochloride (TC). In other studies, the hydrophilic antibiotic drug Mefoxin was included in electrospun PLA (Zong et al.[12]) and in poly(lactide-*co*-glycolide) (PLGA) matrices (Kim et al.[13]). However, a reoccurring problem seemed to have been the relatively fast initial release of the pharmaceuticals. Later, model drugs have been encapsulated in core-shell nanofibers by Huang et al.[14] and Liao et al.[15] with a more sustained release profile. Chunder et al.[16] successfully electrospun two weakly electrolytic polymers, poly(acrylic acid) (PAA) and poly(allylamine hydrochloride), containing methylene blue. Temperature sensitive PAA/poly(*N*-isopropylacrylamide) multilayers were deposited onto the drug-loaded nanofibers to control the release of drugs.[16] Moreover, electrospun fibers were fabricated as a delivery medium for proteins by Chew et al.[17] as well as Zeng et al.[18] Recently, electrospun blend polymer fibers were also fabricated as carriers for paracetanol and ketoprofen, respectively, by Peng et al.,[19] and Kenawy et al.,[20] Xie and Wang[21] used electrospun PGLA fibers with different diameters for the delivery of Paclitaxel which is used to treat C6 Glioma. In their study, a

cytotoxicity test was performed to confirm the safe use of drug-loaded nanofibers.

Although numerous reports are published concerning the incorporation of pharmaceutical compounds in nanofibers, only few studies focus on the mechanism of controlled-drug release and the corresponding release profile. Zeng et al.[22] primarily investigated the solubility and compatibility of drugs in poly(L-lactide) (PLLA) ultrafine fibers. It was found that by choosing compatible drugs with PLLA, burst release could be avoided. Various drugs were also incorporated into nanofibers by Taepaiboon et al.[23] Their research indicated that with increasing molecular weight of the drug, the overall rate and the total amount of liberated drug decreased. Most recently, Srikar et al.[24] performed a study to describe the release mechanism of a water-soluble compound from electrospun polymer fibers. The authors suggested that only the small molecules attached to the fiber surface could be released. The mechanism could then be described as a desorption-limited rather than a simple diffusion controlled process. However, there has been no report on the influence of drug solubility, the choice of the solvent for the electrospinning system, or the polymer/drug interaction in relation to the drug release profile from nanofibers.

In this study, the controlled delivery of two structurally similar model drugs, tetracycline hydrochloride (TC) and chlorotetracycline hydrochloride (CTC), from electrospun poly(D,L-lactide) (PDLLA) nanofibers was investigated. An effort was made to control the availability of the embedded drugs, and thus the fiber properties, by the solvent system used for electrospinning. The impact of the solvent system on changes in morphology and physical properties of the nanofibers was studied to get a better understanding of the release mechanism. Finally, a possible mechanism of the drug release from electrospun fibers is suggested, considering drug/polymer/solvent interactions.

EXPERIMENTAL

Materials

Poly(D,L-lactide) (PDLLA, M_w = 75,000–120,000), chlorotetracycline hydrochloride (CTC), and tetracycline hydrochloride (TC) were obtained from Sigma-Aldrich and used as received. The solubility of CTC and TC in methanol is 17.4 mg/mL and 50.0 mg/mL, respectively. Chloroform (analytical grade) was obtained from Fisher Scientific and methanol (HPLC grade) from Sigma-Aldrich. Tris buffer solution (0.05*M*) was prepared from tris(hydroxymethyl)aminomethane hydrochloride (Trizma™ HCl; Sigma-Aldrich) and adjusted to pH 7.35.

Electrospinning process

To prepare polymer solutions containing different concentrations of drugs, PDLLA (10 wt %) was dissolved in chloroform. For each sample, 2 wt % (based on polymer) CTC or TC were predissolved in methanol; for TC drug solutions, samples were prepared at a ratio of methanol : chloroform of 1 : 16, 1 : 8, and 1 : 4, respectively. For CTC drug solutions, the ratio was 1 : 16, 1 : 12, 1 : 8, and 1 : 4. Polymer-drug solutions were gently stirred at room temperature for at least 12 h. For the electrospinning process, a horizontal experimental setup was used, consisting of a syringe, an 18 gauge needle, an aluminum collecting board, and a high-voltage supply. A syringe pump connected to the syringe controlled the flow rate to 1 mL/h. PDLLA/drug mix solution was electrospun at a voltage of 18 kV with a tip-to-collector distance of 15 cm.

Characterization of product fibers

Morphology

The morphology of the electrospun fibers was investigated using a Zeiss DMS 940 scanning electron microscope (SEM) at 15 kV. Electrospun mats were sputter-coated with gold for 2 min to minimize charging effects. The diameters of the fibers were estimated from SEM images.

Contact angle tests

A DCA-322 (Cahn Instruments) was used to determine the contact angle of electrospun fiber mats to Tris buffer based on the Wilhelmy plate method. Fiber mats were first cut into squares of 10 mm × 10 mm width. To avoid effects caused by fiber swelling, the advancing distance was set to 2 mm with a speed of 80 μm/s, and all tests were conducted at room temperature. All tests were done in triplicate and results averaged.

Determination of swelling rates

The swelling behavior was evaluated by incubating electrospun mats (20 mm × 20 mm, initial weight W_i) in 20 mL Tris buffer at 37°C in a thermostated water bath. At each time interval, wet weights of samples (W_s) were measured after gently tapping the sample on filter paper to remove surface water. The degree of swelling (S_w) was calculated as follows:

$$S_w = (W_s - W_i)/W_i$$

All tests were performed in triplicate and the values averaged.

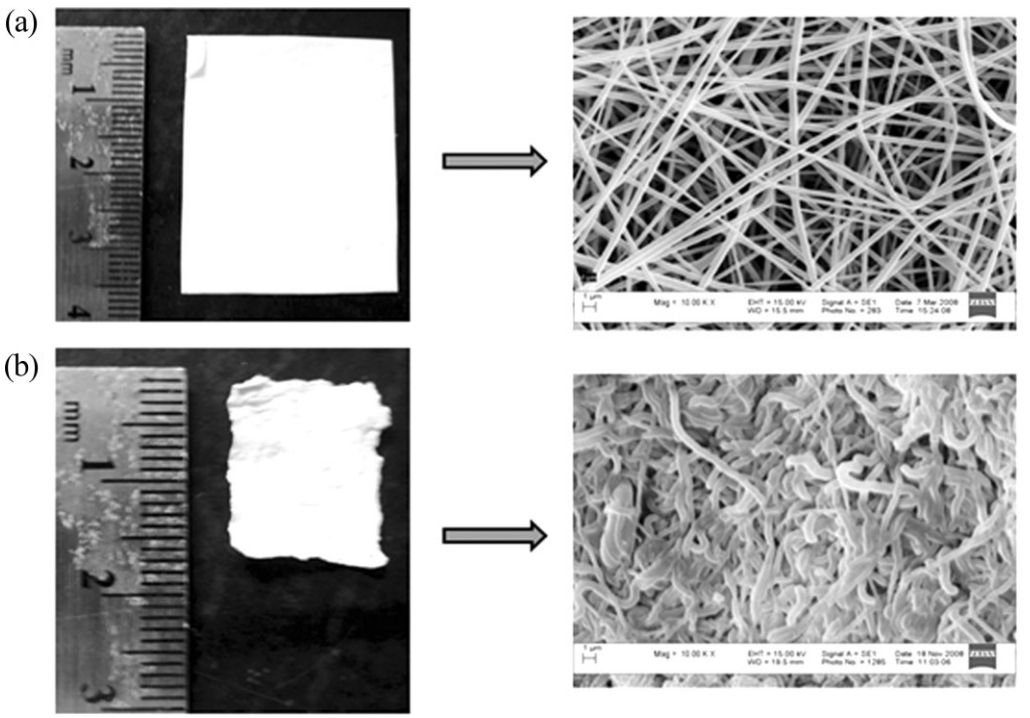

Figure 1 Optical (left-hand side) and scanning electron microscopic images (right-hand side) of electrospun TC-loaded PDLLA fibers with a methanol–chloroform ratio of 1 : 8: (a) directly after electrospinning and (b) after exposure to Tris buffer for 48 h.

Drug release assessment

Dried electrospun fiber mats with a thickness of $\sim$ 0.2 mm were weighed and placed into 20 mL Tris buffer, incubated at 37°C for a specified time interval and shaken at 100 rpm. At every time interval, a fiber mat was removed and placed into 20 mL fresh Tris buffer. Solution absorbance was assayed by a UV-vis spectrophotometer at 368 nm for TC and 377 nm for CTC, and the solution concentration determined from the absorbance standard curves. Each measurement was performed in triplicate and the values averaged. To determine the actual amount of drug loaded on nanofibers, a piece of fiber mat was weighed and hydrolyzed in 1*N* sodium hydroxide solution, then the solution was diluted and assayed by a UV-vis spectrophotometer. The drug-loading efficiency was determined as the actual amount of drug contained in the fiber divided by the original amount of the drug added to the polymer solution. All data were analyzed and fitted by Origin 8.0, OriginLab Corporation.

RESULTS AND DISCUSSION

Morphology of drug-loaded ultrafine fibers

PDLLA ultrafine fibers were electrospun from chloroform with methanol as the cosolvent and loaded with TC or CTC as model antibiotic compounds. Their surface morphology was characterized by scanning electron microscopy (SEM). All electrospun-drug-loaded ultrafine PDLLA fibers exhibited a well-formed smooth fibrous structure. None of the samples showed visible micropores on their surface and almost no traces of a bead-and-string structure were observed in any of the samples. Figure 1 shows the morphology of fibers containing TC obtained from a methanol–chloroform ratio of 1 : 8. The appearance of these fibers is representative for the fiber morphology generally observed before and after drug release of all samples prepared from different methanol–chloroform ratios.

Average fiber diameters of samples from different systems are listed in Table I. With increasing amount of methanol as cosolvent, the average diameters significantly decreased for all PDLLA systems. In earlier electrospinning studies of Doshi and Reneker[6] and Deitzel et al.,[25] evidence were presented that the polymer concentration is the dominant factor for the fiber diameter. Most likely, the main reason for the smaller diameter is due to the lower actual concentration of polymer solution with increasing amounts of methanol.

In regard to the type of drug incorporated, TC-charged fibers showed smaller diameters than CTC-loaded fibers. This effect might be the result of higher solubility of TC in methanol, leading to TC's better salt effect, which has a significant influence on the morphology of electrospun fibers.[12,13]

TABLE I
Average Diameters, Drug Loading Efficiency, and Contact Angles of Electrospun PDLLA Fibers

Samples	Methanol : chloroform ratio	Diameter (nm)	Drug-loading efficiency (%)	Contact angle (°)
PDLLA + TC	1 : 16	830 ± 280	62.1 ± 14.65	91.8 ± 0.29
	1 : 8	360 ± 70	84.1 ± 2.59	92.8 ± 0.91
	1 : 4	220 ± 60	98.8 ± 0.93	102.2 ± 0.87
PDLLA + CTC	1 : 16	1550 ± 330	53.4 ± 18.22	91.7 ± 0.24
	1 : 12	558 ± 134	88.8 ± 6.49	99.6 ± 2.18
	1 : 8	515 ± 190	98.9 ± 0.97	101.6 ± 1.01
	1 : 4	220 ± 50	99.5 ± 2.88	107.9 ± 1.53

It is important to note that electrospun PDLLA fiber mats showed considerable shrinkage under physiological conditions. As illustrated in Figure 1(a), immediately after electrospinning, the fibers looked fairly straight, detached from each other and with ample space in-between individual fibers; they evenly overlapped to form a nonwoven network structure. Within 120 min in Tris buffer, all PDLLA samples had decreased in size by ~ 70–80% of their original area [Fig. 1(b)]. At a temperature of 37°C, close the glass transition temperature of PDLLA, the nanofibers appeared bulkier and considerably closer together. As a result, with the elimination of space between the fibers, the size of the nonwoven sample was significantly reduced. Similar phenomena had also been observed for membranes made from electrospun poly(lactide-*co*-glycolide) (PLGA).[26]

Swelling behavior and contact angle of electrospun ultrafine fibers

As shown in Table I, PDLLA fibers loaded with either TC or CTC exhibited hydrophobic properties in Tris buffer with contact angles higher than 90°. It is possible that the hydrophobicity occurred as a consequence of the rough surfaces and the air trapped in-between the nanofibers.[27,28] Furthermore, with increasing amounts of methanol added to the electrospinning solution, the contact angle of resultant nonwoven fiber mats increased. As discussed earlier, higher quantities of the cosolvent methanol impacted the average fiber diameter, which lead to more pronounced roughness of the surface of the fiber mats and thus further increased the observed hydrophobic effects.

The swelling behavior of the electrospun-drug-loaded fibers is shown in Figures 2 and 3. To the most part, the degree of swelling of the electrospun PDLLA membranes with incorporated drugs increased within 90–120 min. Their swelling tendency can be explained through the contribution of two effects: (1) the swelling caused by the actual liquid pick up and (2) the hydrophobicity of the membranes. During constant agitation in Tris buffer at 37°C, the PDLLA mats eventually absorbed water and expelled trapped air. As a result, the weight of the membranes increased. After 90–120 min, the electrospun mats began to become more compact with decreased space between fibers, and subsequently the degree of swelling decreased.

Differences in swelling were observed depending on whether the membranes contained TC or CTC.

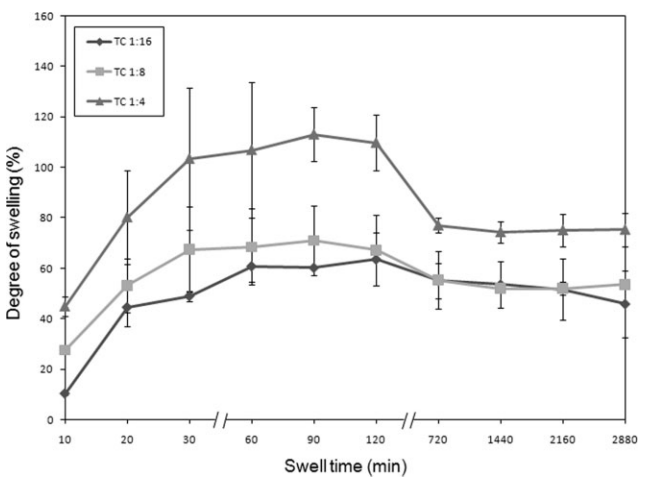

Figure 2 Degree of swelling of TC-containing PDLLA fiber mats, prepared at different ratios of methanol : chloroform, in Tris buffer at 37°C.

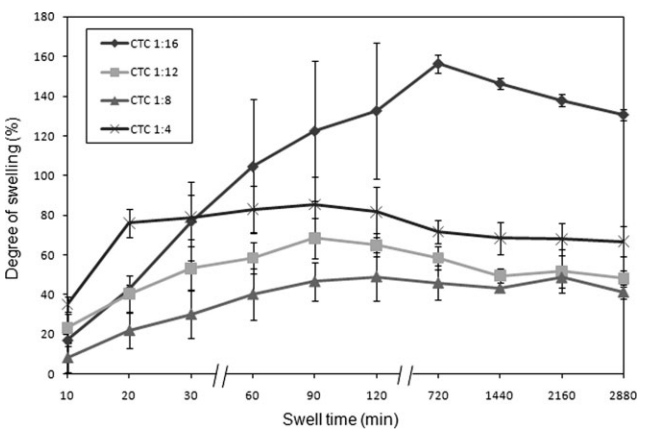

Figure 3 Degree of swelling of CTC-loaded PDLLA nano-fibers, prepared at different ratios of methanol : chloroform, in Tris buffer at 37°C.

For TC-loaded PDLLA, nanofibers prepared with higher methanol content, the degree of swelling increased (Fig. 2). In this case, it could be argued that the diameter of the nanofibers was smaller and thus the space between individual fibers had increased. In contrast, the swelling behavior of CTC-loaded nanofibers proved to be more complicated to explain. When the drug was completely dissolved in the electrospinning solution, a similar trend was observed as for TC samples (e.g., for CTC 1 : 8 and CTC 1 : 4 samples). However, in the case of the CTC 1 : 16 and 1 : 12 samples, the drug could not be entirely dissolved. Here, a significant and increasing amount of sorbed water was measured after a relatively low-initial uptake. A possible explanation of this phenomenon could be that a phase separation between drug and polymer occurred during electrospinning due to the low solubility of CTC under these conditions. An assumption is made that a higher amount of drug molecules is located on the surface of the nanofibers instead of being encapsulated in the fiber interior due to the polarity of the drugs. Thus, when immersed in buffer solution, drugs on the surface would be flushed out faster than those confined inside and more water might more easily penetrate via channels created by the released drugs. As a consequence, drug/polymer/water interactions would result in a strong increase in swelling of the PDLLA nanofibers. This assumption was confirmed by drug release experiments (see below).

Drug release studies

The weight of the fiber mats was measured before and after *in vitro* release, and no significant weight loss was observed for any of the samples after 48 h exposure in Tris buffer. Consequently, the effect of polymer hydrolysis and degradation has not been taken into consideration in this study.

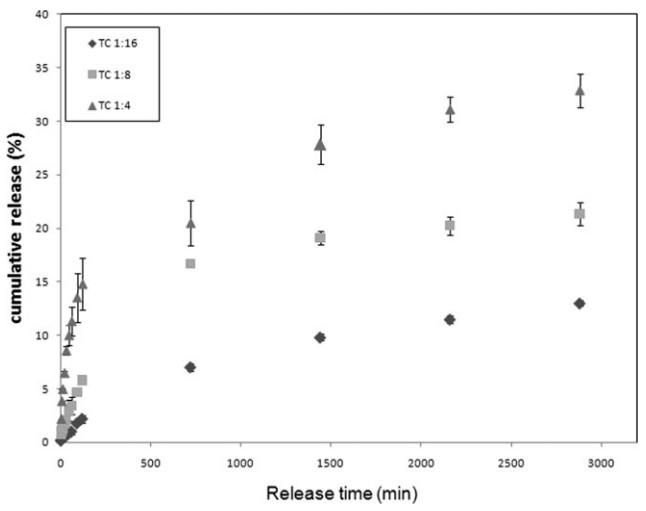

Figure 4 TC release from electrospun PDLLA fiber mats into Tris buffer solution at 37°C.

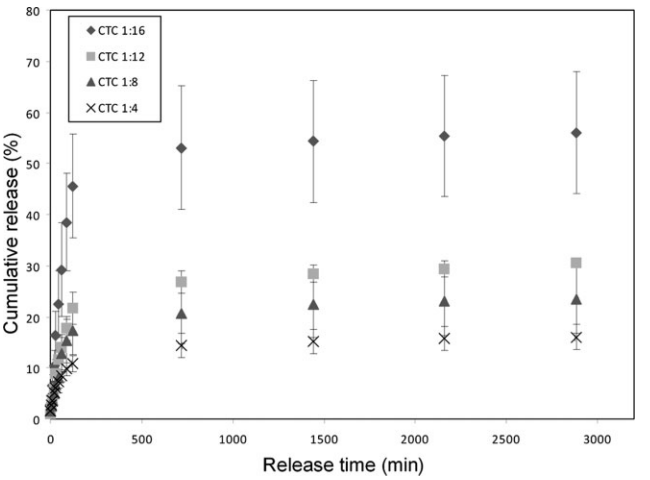

Figure 5 CTC release from electrospun PDLLA fiber mats into Tris buffer solution at 37°C.

Before investigating the drug release profile, the drug-loading efficiency was determined. As shown in Table I, the drug-loading efficiency of both CTC and TC, as defined as the actual amount of drug divided by the original amount of the drug added to the polymer solution, increased with higher methanol content. All samples except for CTC and TC 1 : 16 samples actually contained 85–100% of the drug loaded, suggesting that electrospinning could be a sufficiently effective method for encapsulation of drugs. The loading efficiency of CTC 1 : 16 and TC 1 : 16 samples was somewhat lower compared with the other samples, since very small amounts of solvent were used and traces of the active compound might have been lost due to experimental difficulties, such as the solution transfer and the actual electrospinning process.

The *in vitro* drug release profiles of PDLLA ultrafine fibers are shown in Figures 4 and 5. Interestingly, CTC and TC drugs exhibited an entirely different release behavior. In the case of fibers containing TC, the rate of drug delivery decreased with higher methanol content. Only ~ 13% were discharged from the TC 1 : 16 samples, whereas a release of about 33% was observed for TC 1 : 4 at comparable exposure times (Fig. 4). In contrast, CTC was released to almost 56% from 1 : 16 samples and to about 16% from 1 : 4 samples (Fig. 5). Overall, however, with lower methanol content in the electrospinning solution, CTC was released considerably faster and to a higher extent than TC. It can be speculated that the differences observed in discharge behavior are based on differences in the nature of molecular diffusion of TC and CTC and their solubility in methanol as well as in the release medium (aqueous Tris buffer at pH 7.35).

Srikar et al.[24] suggested a desorption-limited mechanism instead of a diffusion-limited mechanism for drug release from nanofibers with nanopores on the surface. Since no such nanoporous structure was observed in this study, a diffusion-limited mechanism was assumed. To explain the drug release mechanism from electrospun nanofibers, the Fickian diffusion model of swellable devices could be applied. According to Ritger and Peppas's research,[29] a Fickian diffusional release from a polymer matrix can be described by the following equation,

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t/M_∞ is the fraction of drug released, k is a constant related to the drug diffusion coefficient, n is the diffusional exponent, which is an indication for the drug release mechanism, and t is the drug release time. For TC-loaded electrospun PDLLA ultrafine fibers, the drug release data were fitted with eq. (1) as shown below in eqs. (2)–(4):

$$\text{TC } 1:16, \quad \frac{M_t}{M_\infty} = 0.0133t^{0.665} \quad r^2 = 0.992 \tag{2}$$

$$\text{TC } 1:8, \quad \frac{M_t}{M_\infty} = 0.0383t^{0.509} \quad r^2 = 0.984 \tag{3}$$

$$\text{TC } 1:4, \quad \frac{M_t}{M_\infty} = 0.1036t^{0.352} \quad r^2 = 0.966 \tag{4}$$

The value of n is depended on the geometry, as indicated by Ritger and Peppas,[29] and r^2 is the adjustment coefficient of determination. For example, for Fickian diffusion from a thin film, n is 0.5, whereas for a cylindrical sample, n is 0.45. Thus, for the case of larger fiber diameters as a result of lower methanol content in the spinning solution, the fiber mesh could be considered a film. On the other hand, at higher concentrations of methanol in the spinning solution and consequently smaller resultant fiber diameters, the electrospun fibers could be regarded as cylinders. However, for the TC 1 : 16 sample, n is higher than 0.5 because TC might not have been entirely dissolved in methanol and therefore might not have been homogeneously distributed. For the TC 1 : 4 sample, the deviation of n from 0.45 occurred because the electrospun fibers were not perfectly shaped cylinders and the existence of overlapping and entangled fibers reduced the effective surface for drug release. It was also noticed that k increased with increasing amount of methanol used, which suggests that with the smaller diameter of the fibers, a higher surface area was available for drug transport and as a consequence, the diffusion coefficient increased.

However, Fickian diffusion did not prove to be a good model for CTC release from PDLLA nanofibers, as indicated by the lower r^2 values of 0.7 to 0.8. Since CTC is barely soluble in water, it might be more difficult for this drug to diffuse through polymer chains. Here, a Case-II release (non-Fickian diffusion) mechanism was applied to interpret the release behavior. According to Ritger and Peppas[29] and Kosmidis et al.,[30] Case-II release is a solute transport based on polymer relaxation, and it can be described as follows,

$$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{k_0}{C_0\alpha'}t\right]^N \tag{5}$$

Here, α' is the diffusional length of the sample, and k_0 and C_0 are constants. N is the diffusional exponent, which is determined by sample geometry and ranges from 1 for films, to 2 for cylinders. Initially, the electrospun fibrous membranes were considered as a film. As $N = 1$, the equation can be formulated as shown in (6),

$$\frac{M_t}{M_\infty} = \frac{k_0}{C_0\alpha'}t \tag{6}$$

Based on eq. (6), CTC drug release data were linear-fitted until a saturation value was reached. The linear portion below saturation of each sample can be described as follows,

$$\text{CTC } 1:16, \quad \frac{M_t}{M_\infty} = 0.3753t \quad r^2 = 0.982 \tag{7}$$

$$\text{CTC } 1:12, \quad \frac{M_t}{M_\infty} = 0.1921t \quad r^2 = 0.958 \tag{8}$$

$$\text{CTC } 1:8, \quad \frac{M_t}{M_\infty} = 0.1380t \quad r^2 = 0.959 \tag{9}$$

$$\text{CTC } 1:4, \quad \frac{M_t}{M_\infty} = 0.0754t \quad r^2 = 0.900 \tag{10}$$

It was noticed that the $k_0/C_0\alpha'$ number decreased with increasing amount of methanol used, which is inconsistent with the experimentally observed TC drug release profile. Therefore, polymer chain relaxation seems to be the major driving force of the CTC release from PDLLA fibers. This result is in agreement with data of fiber mat shrinkage and swelling tests of CTC-loaded nanofibers. In the initial phase, the polymer relaxation probably leads to the shrinkage of the membrane. Subsequently, as discussed earlier, with less methanol used in the electrospinning solution, more drugs may be located on the surface of the electrospun fibers and faster water uptake may occur in these systems. This polymer/drug/water interaction at 37°C could then have lead

to a polymer chain movement that allowed the solution release from the fibrous matrix.

Equation (6), however, did not accurately describe the release of CTC from the 1 : 4 sample, since $r^2 = 0.900$. Analogous to the TC 1 : 4 sample, CTC 1 : 4 sample was treated as a cylindrical matrix for drug release, and eq. (5) with $N = 2$ was applied, leading to eq. (11),

$$\frac{M_t}{M_\infty} = \frac{2k_0}{C_0\alpha'}t - \left[\frac{k_0}{C_0\alpha'}t\right]^2 \quad (11)$$

Using a polynomial form to fit CTC 1 : 4 data,

$$\frac{M_t}{M_\infty} = 0.1505t - 0.00065t^2 + 1.9013\,, \quad r^2 = 0.984 \quad (12)$$

However, the parameters in eq. (12) do not match the requirement of eq. (11). Thus, the drug release from the CTC 1 : 4 sample could not simply be described as a Case-II relaxational release. According to Peppas and Sahlin's model,[31] eq. (13) can be formulated as follows:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \quad (13)$$

On the right-hand side of eq. (13), the first term is the contribution of Fickian diffusion, whereas the second term is the contribution of Case-II diffusion, and m is a geometrical parameter. Considering the CTC 1 : 4 sample as a cylindrical specimen, m is equal to 0.89. Therefore, a nonlinear fitting curve could be developed based on the following:

$$\frac{M_t}{M_\infty} = 0.2190t^{0.89} - 0.0005104t^{1.78}\,, \quad r^2 = 0.959 \quad (14)$$

Equation (14) suggests that with a cylindrical geometric shape, CTC release from the electrospun fibers prepared with a methanol to chloroform ratio of 1 : 4 was driven by both Fickian and relaxational contributions. The reason is that in this case, CTC dissolved very well, which leads to a lower amount of the drug being located on the nanofiber surface. Thus, the influence of Case-II relaxational release was less prominent in CTC 1 : 4 sample.

CONCLUSIONS

Tetracycline (TC) or chlorotetracycline (CTC) containing ultrafine PDLLA fibers were successfully fabricated by electrospinning. The influence of methanol as a cosolvent in the electrospinning solution was discussed in regard to physical fiber properties and drug release behavior. With increasing amounts of methanol, fiber diameters decreased and contact angle and drug-loading efficiency increased. The nanofiber mats showed considerable area shrinkage and swelling under simulated physiological conditions. Differences in *in vitro* release profiles and swelling behaviors showed that different drug release mechanisms for TC and CTC occurred. A Fickian diffusional release mechanism could be applied to interpret TC drug release from electrospun fibers. However, CTC-loaded PDLLA fibers displayed a more complex swelling and release pattern due to the influence of lower drug solubility in the spinning solution and release medium, and as a result of the involved polymer/drug/solvent interactions. In this case, the main driving force of release was proposed to be a Case-II relaxation mechanism for lower methanol ratios and a combination of Fickian diffusion and Case-II mechanism for higher methanol content. The choice of solvent system might, therefore, be used to control the drug release from nanofibrous materials.

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