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Processes taking place during the preparation and use of electrospun PLA fibers and their effect on controlled drug release

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Abstract

PLA fibers containing metronidazole as the active component were produced by electrospinning from a solvent mixture of dichloromethane (DCM) and dimethyl sulfoxide (DMSO). The DMSO content of the spinning solution changed between 0 and 25 vol% in 5 vol% steps. The fibers were dried at different temperatures, and processes taking place during fiber production and drying were followed by thermogravimetric analysis and differential scanning calorimetry. The morphology and structure of the fibers were studied by microscopy and X-ray diffraction. The mechanical properties of fiber mats and the release of the drug were also determined as a function of processing and drying parameters. The results showed that several processes take place during the production and subsequent handling of the fibers including the evaporation of the solvent (DMSO), the crystallization of the polymer, the changing of composition, phase separation and the consequent partitioning of the drug. The crystalline structure of the fibers changes considerably during drying which determines their mechanical properties. The rate of evaporation and crystallization is in the same order of magnitude. The rate of both processes increases considerably with temperature, but does not depend strongly on the amount of DMSO in the spinning solution. Both the amount of the drug released and the rate of release cover a wide range depending on the parameters of the preparation technology. The large range of mechanical and functional properties obtained allows the control of the kinetics of drug release to some extent.

Keywords Evaporation · Crystallization · Phase separation · Morphology · Mechanical properties · Drug release

Introduction

Because of environmental concerns, the demand for new solutions replacing commodity plastics increases continuously [1]. Although the application of bioplastics is in its infancy yet, biopolymers offer a viable alternative in many areas [2]. Biopolymers are used in increasing quantities in packaging [3] and agriculture [4] and they find their way more and more also into engineering applications [5, 6]. Biopolymers have many advantages including their natural raw material source, advantageous carbon footprint and often also biodegradability. One important additional advantage of biopolymers is their biocompatibility which is often utilized in medical applications to prepare scaffolds or controlled release devices [7, 8]. These latter can be prepared in many forms like spheres [9], films [10], membranes [11] or fibers [12], but one of the preferable technology to prepare such devices is electrospinning [13, 14].

Electrospinning is a versatile technique to produce fibers, fiber mats or formulated devices with or without one or more active components from biopolymers. The technology is relatively simple, and the characteristics of the fibers can be adjusted in many ways [15, 16]. The productivity of the method and the properties of the fibers depend on many factors including the polymer [17], the solvent [18], concentration [19], viscosity [20], interfacial tension [21] and dielectric constant [22], but besides component properties also on technological parameters like voltage, the distance to the

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collector, spinning rate and the type of the syringe used [23], which all can be adjusted to influence fiber properties. The characteristics of the polymer and/or the active component put limitations on the adjustable range of the parameters and often a combination of solvents must be used to facilitate the dissolution of the drug or modify the dipole moment of the solution to make spinning possible [24].

Poly(lactic acid) (PLA) is the biopolymer produced and used in the largest quantity presently [25]. It is produced from lactic acid which is obtained by the fermentation of starch. PLA is a true biopolymer, because it is also biodegradable under the conditions of composting. Many studies [26, 27] are carried out to investigate the possibility of using it as a carrier for some active component applied for the therapy of various diseases. PLA fibers can be easily spun from DCM, but this solvent does not dissolve drugs with high polarity. Consequently, a co-solvent is added before spinning to assist the dissolution of the drug. DMF [28] and DMSO [29] are the most often used co-solvents having sufficient polarity to help the dissolution of the drug, but also to change the dielectric constant of the solution. Moreover, these solvents are also approved by FDA to use them in medicine [30].

However, the application of DMF and DMSO as co-solvent in the electrospinning of PLA raises several new questions. The boiling point of these solvents, and especially that of DMSO, is high (189 °C), and thus, their removal is difficult. The solvents dissolve in the polymer to smaller or larger extent and thus plasticize it [31], changing the mobility of the molecules and thus modifying their crystallization. Plasticizers, but also solvents, accelerate the crystallization of PLA considerably [32], often more efficiently than traditional heterogeneous nucleating agents. The evaporation of the solvents results in the change of composition along the production technology, thus resulting in the partitioning of the active component between the polymer fiber and the surrounding space [33]; some of the drug is located within the fiber and a considerable amount among them [33, 34]. Changing crystallinity due to the evaporation of the solvent with high boiling point results in phase separation and further in the change of composition, which influences considerably also the efficiency of the device, the amount of the released drug and the kinetics of drug release.

Taking into account all these considerations, the goal of this study was to investigate the effect of a co-solvent, DMSO, on the structure and properties of PLA electrospun fibers containing an active component, metronidazole, an efficient and common antibiotic widely used among others in the therapy of periodontitis. The malady is caused by anaerobic pathogen bacteria affecting the tissues responsible for fixing the tooth in the mandibles and according to dentist the use of a device prepared from electrospun fibers could help the local administration of the drug. The kinetics of both evaporation and crystallization were followed as a function of the DMSO content of the spinning solution and the temperature of solvent evaporation. The kinetics of drug release were also determined for selected compositions, and the amount of released drug as well as the rate of drug release was related to the parameters of processing and drying. The practical consequences of the two processes taking place during the fabrication and use of the fibers are also discussed briefly in the final section of the paper. By investigating the effect of solvent and temperature on the structure and properties of fibers during the whole processing, the potential electrospun PLA scaffolds containing metronidazole for dental treatment are able to achieve controlled release with easier and more flexible operations, while providing different release protocols upon various purposes in biomedical use.

Experimental

Materials

PLA granules (Ingeo 4032D, density of 1.24 g cm^{-1}) were supplied by NatureWorks (USA). Dichloromethane (DCM) and dimethyl sulfoxide (DMSO) were purchased from Molar Chemicals Kft. (Hungary). Spinning solutions contained 0, 5, 10, 15, 20 and 25 vol% DMSO. Distilled water was used for the preparation of water-based buffers in the drug release tests. The active agent used was metronidazole (Ph. Eur. 8., Hungaropharma Plc., Budapest, Hungary), and it was dissolved in some of the solvent mixtures at 2.5 mass% calculated for the amount of PLA in the fibers.

Sample preparation, fiber spinning

In order to prepare the spinning solution, 1.24 g PLA was dissolved in 10 mL of the solvent mixture. PLA fibers were prepared by electrospinning at ambient temperature, 22 kV voltage, 15 cm collector distance and a feeding rate of 2 μL s^{-1} using the Spinsplit apparatus, an integrated syringe pump-type electrospinning device (Spinsplit, Hungary). The aluminum foils supporting the collected fibers were put into an air circulating oven (Venti-Line VWR VL115, VWR International, UK) for various times to determine the evaporation of DMSO and the crystallization of the polymer. Drying temperatures of 23, 30, 35, 40 and 50 °C were used in the study. Electrospun fiber mats taken directly from the foils and round, compressed disks were used for characterization, as well as the analysis of release kinetics. The disks of about 0.46 mm thickness were obtained by compressing approximately 50 mg fibers under 5 MPa pressure for 2 min in a pellet die of 13 mm diameter (Specac Atlas Manual

Hydraulic Press 25 T and Specac 13 mm Pellet Press Die, Specac Ltd., Orpington, Kent, UK).

Characterization, measurements

Thermal analysis was used for the study of the kinetics of DMSO evaporation and crystallization. The evaporation of the solvent was followed by thermogravimetric analysis (TGA) using a PerkinElmer TGA apparatus. Fibers of 5–10 mg were filled into the ceramic pan and heated up from 30 to 500 °C under nitrogen purge with the heating rate of 10 °C min^{-1}. About 3 mg fibers were used to determine the effect of DMSO content, temperature and time on the crystallinity of the PLA fibers by differential scanning calorimetry (DSC). The measurements were taken using a PerkinElmer DSC IC. The samples were heated up from 30 to 200 °C with the heating rate of 10 °C min^{-1} under nitrogen atmosphere.

Wide-angle X-ray diffraction (XRD) was used to study the crystalline structure of PLA disks. Measurements were taken using a Philips PW 1830 instrument in the 2θ range of 5°–40° with 0.04° increments and 1 s per step rate at the accelerating voltage of 40 kV and 35 mA. In order to study the morphology of the fibers, a very thin layer of fibers was put on a Superfrost slide with a cover glass and then it was stored in an oven to follow the effect of evaporation on structure. Micrographs were recorded as function of time using a digital optical microscope (DOM, Keyence VHX-5000). The diameter of fibers was also determined using the software of the apparatus. Compressed fiber disks were fractured at the temperature of liquid nitrogen, and then, a thin gold layer was sputtered onto their surface. Scanning electron microscopy (SEM) was carried out using a Jeol JSM 6380LA (Jeol Ltd., Japan, Tokyo) apparatus.

Continuous spinning was done for 10 min to obtain a relatively thick layer of fiber mat. The mats were removed and cut into 40 × 10 mm strips, and then, they were attached to custom-made paper frames for the tensile test. The thickness of each specimen was measured, and uneven samples were discarded. Tensile tests were done on the mats using an Instron 5566 type universal testing machine at 25 mm gauge length and 5 mm min^{-1} in cross-head speed. Three to five parallel measurements were carried out on each sample. The thickness and mass were determined for each sample.

A water solution of 2 mg mL^{-1} metronidazole (Metro) was prepared in a volumetric bottle, and then, it was diluted to 0.0091, 0.01, 0.011, 0.0125, 0.0143, 0.0167, 0.02, 0.025 and 0.033 mg mL^{-1} to create a calibration curve by UV–Vis spectrophotometry. 2.5 mass% Metro calculated for the amount of PLA was dissolved in DMSO to produce PLA/Metro fibers by electrospinning. The spinning technology and disks preparation are described in "Sample preparation, fiber spinning" section. Subsequently, the fibers were stored at 23 or 50 °C for 3 days. The fiber disks with the drug were put into vials containing 10 mL water for 264 h, and then, the eluate was detected by UV–Vis spectrophotometry at the scan range of 200–350 nm and scan rate of 240 nm min^{-1} with lamp change at 325 nm. After 264 h, the disks were removed from the vials and washed with distilled water several times and then 3 mL DCM was added to dissolve the fibers. Subsequently, 10 mL water was added to extract Metro from the solution, the mixture was shaken by hand and stored until the two phases (DCM/PLA and water/Metro) totally separated. The amount of drug located in PLA was determined by UV–Vis spectrophotometry in the way described before.

Results and discussion

The results are discussed in several sections. The processes taking place during the preparation and drying of the fibers are discussed briefly first, and then, the structure of the resulting material is shown, followed by the mechanical properties of fiber mats. The kinetics of DMSO evaporation and crystallization are analyzed subsequently, and finally, drug release and consequences for practice are discussed in the last section of the paper.

Processes

The miscibility of DMSO and PLA is limited; approximately 30 mass% DMSO dissolves in the polymer [33]. DCM evaporates during electrospinning and more DMSO than this 30 mass% is left behind. Consequently, two phases form, PLA fibers containing DMSO, the drug, if present, and a DMSO phase also containing some drug. DMSO must be removed before the use of the fibers. The best way to remove DMSO is the evaporation of the solvent, but because of its high boiling point (189 °C) this can be done efficiently only in an oven at elevated temperature. The procedure seems to be simple, but it initiates several processes which all have considerable bearing on the structure, mechanical and functional properties of the fibers, including drug release.

PLA crystallizes quite slowly and the articles produced by melt processing, but also fibers prepared by electrospinning from a solvent which evaporates rapidly like DCM, have amorphous structure. Solvents, on the other hand, were shown to promote the crystallization of PLA [35, 36]. Practically, all solvents except hexane accelerated PLA crystallization [37]. A solvent which evaporates slowly, like DMSO, has even more pronounced effect on the kinetics of the crystallization of PLA; the amorphous polymer obtained after electrospinning transforms into a material with relatively large, 30–40% crystallinity in a fairly short time. DMSO evaporation is assisted by heating the fibers in an oven,

which accelerates crystallization even further. Accordingly, the composition and the structure of the electrospun PLA fibers change with time during processing and drying.

Not only the crystalline structure, but also the composition of the fibers changes during these steps. First, the product of the spinning process separates into the fibers and the DMSO rich solution. This latter contains a considerable amount of drug, which precipitates in the form of crystals among the fibers. The fibers themselves also contain Metro dissolved in DMSO. Since the solubility of the drug is relatively small in PLA (2.5 mass%), it also forms crystals within the fibers after the evaporation of DMSO. Crystallization promoted by the presence of the solvent and heating leads to further phase separation, since the drug can be located only in the amorphous phase of the polymer. Accordingly, the processes taking place during processing and drying determine the resulting structure and the location as well as the form of the drug and thus the amount of drug released, but also the kinetics of drug release.

Morphology

As discussed above, the evaporation of DMSO and heating results in changes in the morphology and the structure of the fibers. In order to demonstrate this statement, DOM micrographs recorded on neat fibers after the electrospinning procedure and on fibers from which DMSO completely evaporated are presented in Fig. 1. The micrograph in Fig. 1a clearly displays the separate DMSO phase among the fibers, and a more thorough scrutiny also shows that the diameter of the fibers is somewhat larger than that of the dry fibers shown in Fig. 1b. Drying removes DMSO completely from among the fibers, but also from within the fibers that is not visible in the micrographs and is indicated only by changing fiber diameter.

Drying, the removal of DMSO from the fibers after spinning, has several consequences as described above. The morphology of the fibers is shown in larger magnification in Fig. 2. The micrograph was recorded on the surface of a disk fractured at liquid nitrogen temperature. The evaporation of the solvent leaves behind voids, and a large number of cavities can be seen on the surface of the fibers. The effect of changing composition and phase separation is also demonstrated well by the SEM micrograph presented in Fig. 2. Phase separated crystalline drug particles can be seen at several places on the surface of the fibers in Fig. 2a. Dissolution and extraction experiments, as well as further SEM study, showed that crystalline drug particles are located within the fibers as well (see Fig. 2b).

Several phase separation processes take place during the drying of the fibers. The results of the separation of a DMSO phase as well as the phase separation of the drug are demonstrated in Figs. 1 and 2. Crystallization also occurs and a separate crystalline phase forms as the

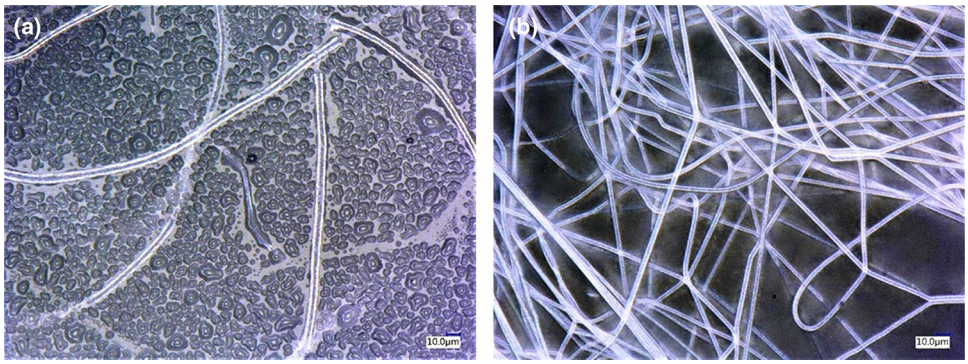

Fig. 1 DOM micrographs recorded on PLA fibers electrospun from a solvent mixture of DCM/DMSO and stored under different conditions; DMSO content: 20 vol%, **a** as prepared, **b** dried at 50 °C for 3 days

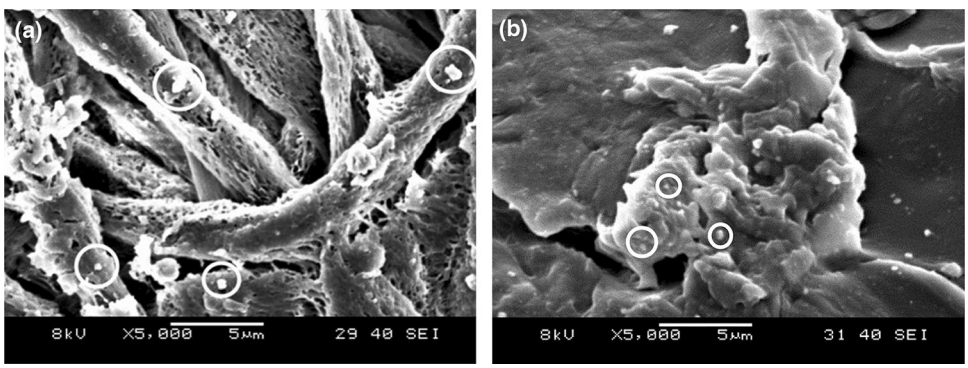

Fig. 2 SEM micrograph recorded on the fractured surface of a disk compressed from electrospun fiber mats. DMSO content: 5 vol%, stored at 23 °C for 3 days; **a** cross section of the mat, drug particles located among the fibers, **b** cross section of a fiber, drug particles located within the fiber

result, as demonstrated in Fig. 3. The XRD traces of fibers produced with different amounts of DMSO in the spinning solution are presented in Fig. 3a immediately after spinning. All the fibers are completely amorphous; they do not have any crystallinity at all. Drying initiates crystallization and a relatively large crystalline phase forms during the process in all materials (Fig. 3b). The beneficial or accelerating effect of the solvent is clearly shown by the comparison of the XRD traces in Fig. 3b; crystallinity is smaller and less perfect crystals form in the neat PLA not containing any solvent than in those spun from a solvent mixture. Obviously, several processes take place during drying and the morphology as well as the structure of the fibers change considerably, which must modify properties as well.

Tensile properties

The as-prepared fibers contain a relatively large amount of DMSO solvent, and they are completely amorphous, as Figs. 1 and 3a show. Accordingly, the mechanical properties of the fibers are determined mainly by their DMSO content. The tensile strength and the elongation-at-break values of fiber mats are plotted against the DMSO content of the spinning solution in Fig. 4a for the as-prepared fibers. Both properties decrease with increasing DMSO content quite considerably. Although only one correlation was drawn in the figure in order to guide the eye, the correlation of the two quantities plotted is dissimilar shown by the different scales on the vertical axes. DMSO molecules increase the mobility of the polymer molecules and disrupt interactions leading to the decrease of both tensile properties.

The characteristics of the completely dry fibers are quite different and depend dissimilarly on DMSO content as shown in Fig. 4b. Both quantities increase slightly with increasing DMSO content. The amount of DMSO in the spinning solution should not influence the mechanical properties of fiber mats, but it obviously does. The plausible explanation is that the mobility of the molecules becomes larger with increasing DMSO content resulting in faster crystallization and larger crystallinity and thus in stronger materials. Although the explanation is plausible, we must call the attention here to the difficulties of the determination of tensile properties for the fiber mats prepared. All efforts were done to always test the same amount of material, but the thickness of the mats, the number of the fibers

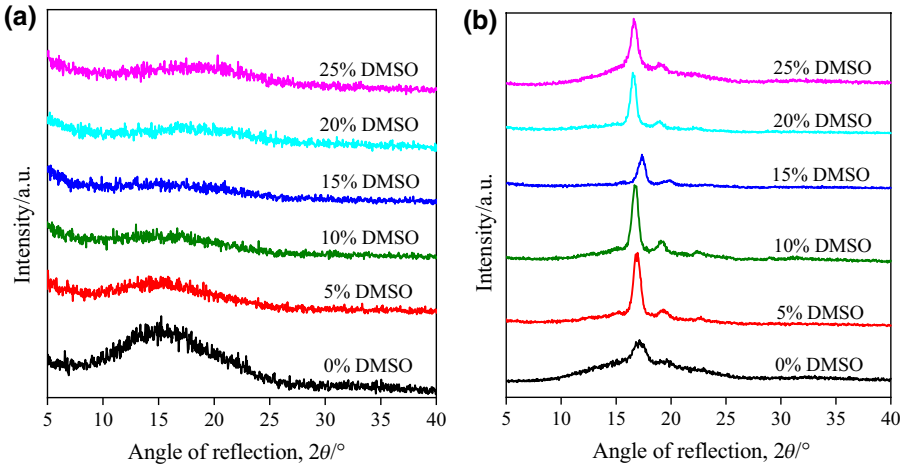

Fig. 3 XRD traces of PLA fibers produced by electrospinning and stored under different conditions. Effect of the DMSO content of the spinning solution. **a** As prepared, **b** stored at 50 °C for 3 days

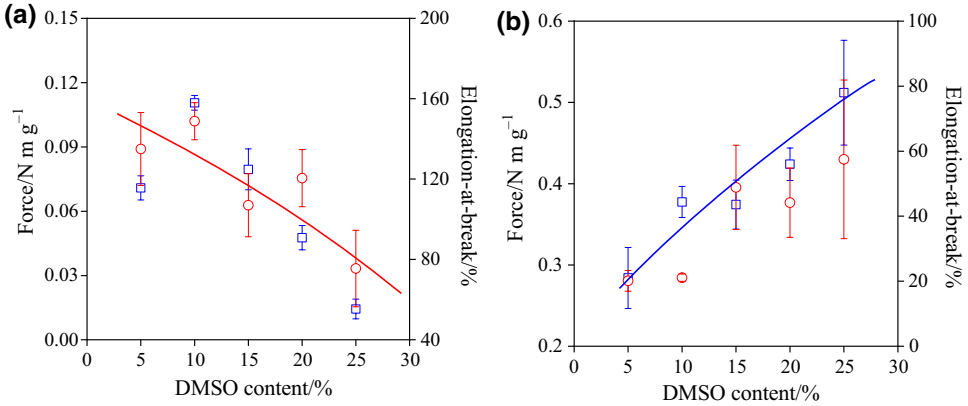

Fig. 4 Mechanical properties of fiber mats consisting of PLA fibers produced by electrospinning. Effect of DMSO content and storage conditions. **a** As prepared, **b** stored at 50 °C for 3 days. Symbols: (open square) relative force, (open circle) elongation-at-break

within them as well as their orientation changed from one mat to the other resulting in considerable standard deviation as shown also by the figure. Nevertheless, the tendencies are clear and we can state with certainty that the processes taking place during drying change the structure and properties of the fibers considerably.

Kinetics

Both processes, evaporation and crystallization, proceed simultaneously and must influence each other. One might assume that the rate of the two processes is different, but the assumption is not based on facts, no information whatsoever is available indicating their relative rate. Because of the interaction of the two processes, the determination of their rate is difficult, but hopefully not impossible. The time dependence of DMSO evaporation at two different temperatures is presented in Fig. 5 for fibers produced by the spinning of the solution containing 25 vol% DMSO. We can see that the rate of evaporation differs significantly at the two temperatures as expected. At room temperature, the removal of DMSO is slow and it is very fast at 50 °C. In spite of the slower rate, the total amount of DMSO disappears in 3–4 days even at the lower temperature. Rather surprisingly, the amount of DMSO in the spinning solution does not change the relative rate of evaporation very much. We must note here that DMSO evaporation is expressed in percentages, and it is related to the amount of the solvent present originally in the spinning solution.

The kinetics of crystallization is very similar to that of the evaporation as shown in Fig. 6 for the same material. Crystallinity could not be determined reliably at room temperature, because of its slow rate, but even more because of the presence of the solvent. The heat change resulting from the evaporation of the solvent overlapped with cold crystallization and melting, and thus, the determination of crystallinity was extremely difficult. Nevertheless, the effect of temperature on the rate of crystallization is clearly seen in the figure. Similarly to evaporation, the rate of crystallization depended on the amount of DMSO in the spinning solution only slightly. One reason for this independence is the fact that only a limited amount, around 30 mass%, DMSO dissolves in PLA. Accordingly, the amount of the solvent was always nearly the same during the crystallization of the polymer. This result apparently contradicts the conclusion drawn from the dependence of mechanical properties on DMSO content (see Fig. 4), but we must emphasize that the determination of all quantities was very difficult for various reasons.

In order to estimate and compare the rate of the two processes, the results were evaluated quantitatively. An exponential process going to saturation was assumed in both cases and the corresponding equations were fitted to the time

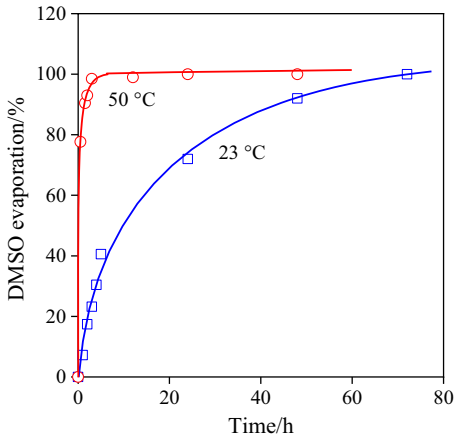

Fig. 5 Effect of the temperature of storage on the evaporation of DMSO prepared by electrospinning of PLA from a spinning solution containing 25 vol% DMSO. Symbols: (open square) 23 °C, (open circle) 50 °C

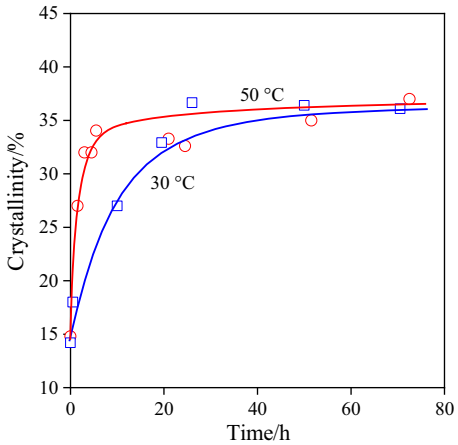

Fig. 6 Kinetics of crystallization in electrospun PLA fibers spun from a solution of 25 vol% DMSO content. Effect of temperature. Symbols: (open square) 30 °C, (open circle) 50 °C

dependence of the determined quantity, mass loss, in one case, and crystallinity, in the other. Accordingly, the time dependence of mass loss was evaluated by Eq. 1

$$\Delta G = \Delta G_{\infty}\left[1 - \exp\left(-\frac{t}{\tau_s}\right)\right] \tag{1}$$

where ΔG and ΔG_{∞} are mass loss at time t and at infinite time, respectively, t is time, and τ_s is a time constant related to the overall rate of solvent evaporation. Similarly, the time dependence of crystallization can be expressed as Eq. 2

$$\alpha = \alpha_{\infty}\left[1 - \exp\left(-\frac{t}{\tau_c}\right)\right] \tag{2}$$

where α is crystallinity and τ_c is the time constant of crystallization.

Equations 1 and 2 were fitted to the measured data, and the time constants were determined in order to estimate the relative rate of the two processes. Both occur on the same timescale expressed in hours. The dependence of the two time constants, τ_s and τ_c, on temperature is presented in Fig. 7 for the fibers spun from a solution containing 25 vol% DMSO. Time constants decrease with increasing temperature exponentially, as expected, indicating a faster process at higher temperature. The effect of the initial DMSO content of the rate of the two processes was negligible corroborating our earlier observation and conclusion. What is somewhat surprising is that the overall rate of the two processes is very similar, and they do not differ from each other considerably. The difficulties in the determination of the various quantities, especially in that of crystallinity, must be noted here again, but we can conclude that the magnitude of the two rates is the same.

Drug release, consequences

We proved in the previous sections that several processes take place during the preparation and subsequent drying of electrospun PLA fibers. These processes determine the final structure of the fibers, but also the encapsulation and partitioning of the drug between the separate DMSO phase and the fibers themselves. Conditions, i.e., the rate of evaporation and crystallization must determine also the distribution of the drug and thus both the amount and the rate of release. Drug release is presented as a function of time in Fig. 8 for fibers prepared from a spinning solution containing 20 vol% DMSO after drying for 3 days at room temperature (23 °C) and 50 °C, respectively. According to the figure, both the amount of the released drug related to the initial amount added to the spinning solution, as well as the rate of release differs considerably. Somewhat surprisingly, less drug is released and slower from fibers that were dried at 50 °C than from those stored at room temperature.

The results obviously corroborate the expectation that the structure of the fibers have a profound effect on their functional property, drug release. The determination of the location of the drug by washing, dissolution and extraction showed that only 10.4% of the drug added to the spinning solution is located within the fibers dried at room temperature, and the rest among them, or it is physically lost during the handling of the fiber mats and disks in preparation and the release study. In the case of the fibers dried at 50 °C, 45.6% of the drug is located within the fibers and much less outside. The reason for the large difference is the fast evaporation of the solvent which leaves more drug behind and does not seep out of the polymer with DMSO during its crystallization. As the results in Fig. 8 show, drug release might proceed in two stages: a fast initial stage during which crystalline Metro particles located among the fibers are dissolved and released into the dissolution medium, and a slower one, during which drug molecules located within the fibers diffuse out slowly. The control of the technology of fiber production determines structure and thus allows also the adjustment of the rate of drug release to some extent.

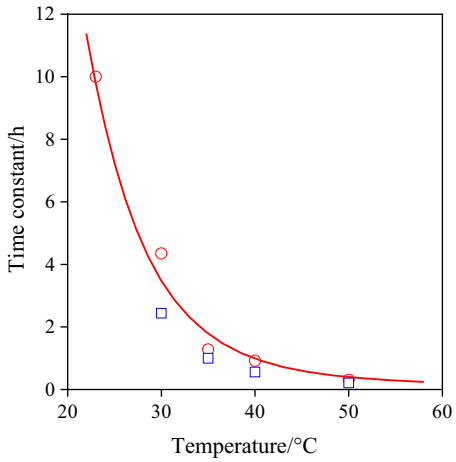

Fig. 7 Comparison of the rate of DMSO evaporation and PLA crystallization in electrospun PLA fibers produced from a spinning solution containing 25 vol% DMSO. Symbols: (open circle) evaporation, (open square) crystallization

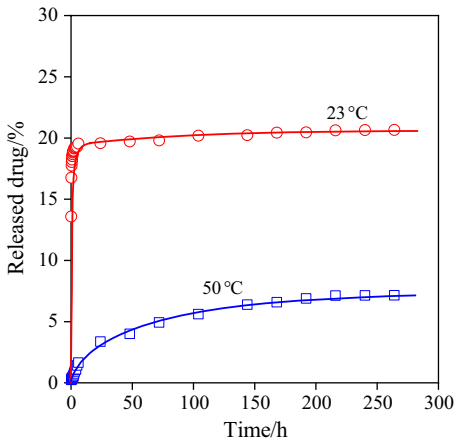

Fig. 8 Kinetics of drug release from electrospun PLA fibers spun form a solution with 20 vol% DMSO. Symbols: (open circle) 23 °C, (open square) 50 °C storage temperature

Conclusions

The study of PLA fibers produced by electrospinning from a solvent mixture showed that several processes take place during the production and subsequent handling of the fibers including the evaporation of the solvent (DMSO), the crystallization of the polymer, the changing of composition, phase separation and the consequent partitioning of the drug. The combination of these processes determines the morphology and the structure of the fibers, as well as the distribution of the drug within and among the PLA fibers. The crystalline structure of the fibers changes considerably during drying which determines their mechanical properties. The rate of evaporation and crystallization is in the same order of magnitude, and the two processes take place simultaneously on the same time scale. The rate of both processes increases considerably with temperature, but does not depend strongly on the amount of DMSO in the spinning solution. The processes and the resulting structure determine also the functional property of the device prepared, both the amount of drug released and the rate of release cover a wide range depending on the parameters of the preparation technology. The large range of mechanical and functional properties obtained allows the control of the kinetics of drug release to some extent. The results and their analysis offer a clear view on the complex processes taking place during the preparation of electrons fibers containing an active component for the first time. The knowledge obtained allows the development of devices with controlled drug release for periodontal therapy. The approach can be extended to the preparation of other drug delivery systems for different biomedical applications.

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Authors' contribution LY: Data curation, Visualization, Formal analysis. SL: Measurement. LC: Project Administration, Conceptualization. MB-S: Resources. JM: Investigation. BP: Writing- Original draft preparation, Supervision, Validation.

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