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Drug release behavior of electrospun twisted yarns as implantable medical devices

Biofabrication

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RECEIVED
2 May 2016

REVISED
29 August 2016

ACCEPTED FOR PUBLICATION
31 August 2016

PUBLISHED
16 September 2016

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Keywords: electrospinning, twist, yarn, drug release

Abstract

In this study, twisted drug-loaded poly(L-lactide) (PLLA) and hybrid poly(L-lactide)/poly(vinyl alcohol) (PLLA/PVA) yarns were produced using an electrospinning technique based on two oppositely charged nozzles. Cefazolin, an antibiotic drug was incorporated in the yarn fibers by addition to the PLLA electrospinning solution. Morphological studies showed that independent of the twist rate, uniform and smooth fibers were formed. The diameter of the electrospun fibers in the yarns decreased at higher twist rates but produced yarns with larger diameters. At increasing twist rates the crystallinity of the fibers in the yarns increased. In the presence of cefazolin the fiber diameter, yarn diameter and crystallinity were always lower than in the non-drug loaded yarns. In addition the yarn mechanical properties revealed a slightly lower strength, modulus and elongation at break upon drug loading. The effect of the twist rate on the cefazolin *in vitro* release behavior from both PLLA and hybrid yarns revealed similar profiles for both types of drug-loaded yarns. However, the total amount of drug released from the hybrid PLLA/PVA yarns was significantly higher. The release kinetics over a period of 30 d were fitted to different mathematical models. Cefazolin release from electrospun PLLA yarns was governed by a diffusion mechanism and could best be fitted by Peppas and Higuchi models. The models that were found best to describe the drug release mechanism from the hybrid PLLA/PVA yarns were a first-order model and the Higuchi model.

Introduction

Electrospinning is an efficient method to produce ultrafine fibers. This method involves drawing a droplet of a polymer solution or melt under a strong electrostatic field into fine fibers, which deposit randomly on a collector to form a nonwoven web [1, 2]. In biomedical engineering initial research in the field of electrospinning focused on the preparation of randomly oriented fibrous mats useful as membranes, wound dressings, tissue engineering scaffolds and drug delivery systems. However, random fibrous matrices exhibit relatively low mechanical strength limiting their applications. Therefore in recent years the production of aligned structures of electrospun fibers, such as yarns, providing improved mechanical properties was taken into consideration. Compared to nanofiber webs, the increased lateral interaction, cohesion and friction between fibers in twisted yarns leads to structures with highly improved mechanical properties [3, 4]. Therefore electrospun yarns recently gained increased attention and found advanced applications in the medical field in the form of sutures [5], artificial blood vessels [6], drug delivery carriers and tissue scaffolding materials [7, 8].

Electrospinning is recently considered an appropriate method to prepare drug delivery systems. Drug delivery systems improve the effectiveness of drug therapy and reduce toxic side effects of drugs by controlling the rate, time, and site of release within the body [2, 9, 10]. Electrospun fibrous mats (or nanowebs) show interesting characteristics such as large surface area to volume ratio and afford high drug encapsulation efficiency. Moreover electrospinning

provides different choices by controlling the fiber properties such as morphology, diameter and porosity by adjusting the process variables and type of materials. This allows the regulation of drug release behavior and modulates the release kinetics [10–13]. Up to now, most of the reported studies have focused on the preparation and drug release from randomly oriented fibrous webs. However, fabricating yarns from electrospun fibers with improved mechanical properties is essential for some applications such as sutures and woven wound dressings. Moreover, depending on the properties of the polymers applied and process parameters, the properties of electrospun fibers, including fiber diameter, fiber crystallinity, and molecular orientation will differ. These properties will also influence drug release kinetics and the release mechanism which is rarely investigated for drug loaded yarns [14].

In this study, an electrospinning set-up consisting of two oppositely charged nozzles was applied to produce fibers which were drawn to a twister unit. Continuous twisted drug-loaded yarns were made in this way of poly(L-lactide) (PLLA) and hybrid poly(L-lactide)/poly(vinyl alcohol) (PLLA/PVA). PLLA, a biodegradable thermoplastic polymer has been investigated for many biomedical applications especially due to its biocompatibility and suitable chemical, biological and mechanical properties [6, 15, 16]. PVA is a biocompatible hydrophilic polymer with good chemical and mechanical properties, and has been proposed for different biomedical applications [17, 18]. The influence of the twist rate on the release behavior of cefazolin from electrospun yarns was investigated. Cefazolin is known as an antibiotic and is mainly used to treat bacterial infections [19, 20]. The morphology of drug-loaded yarns, thermal properties and crystallinity was related to the release properties of the drug. The mechanical properties of the electrospun yarns were investigated by tensile experiments. The release kinetics of cefazolin from the yarns was determined and related to existing models.

Experimental

Materials

PLLA (inherent viscosity 2.51 dl g^{-1}) was a gift from Purac Biomaterials (the Netherlands). PVA (Mw ~ 195.000, degree of polymerization ~4300 and degree of hydrolysis 98.0–98.8 mol%) was purchased from Sigma Aldrich. Cefazolin (sodium salt) was obtained from ACS DOBFAR SPA (Italy). 2, 2, 2-Trifluoroethanol (TFE) was purchased from Merck and used without further purification.

Polymer solutions

PLLA was dissolved in TFE at a concentration of 7 wt% and was stirred at 50 °C for at least 12 h to provide a homogeneous solution. PVA was dissolved in distilled water at a concentration of 7 wt% and stirred at 50 °C for 12 h. To prepare drug containing solutions, cefazolin was added (5% of polymer weight) and the resulting solutions were stirred at room temperature for 1 h. The viscosity and conductivity of the prepared solutions were determined using a MCR 301 Physical Rheometer (Anton Paar), and an Orion 160 conductivity meter, respectively.

Electrospinning

To produce neat and drug-loaded yarns, a previously described electrospinning set up consisting of oppositely charged nozzles and take-up/twister unit was used [6, 21]. In brief, using digitally controlled syringe pumps, two polymer solutions were transferred to needles (22-gauge, ID = 0.4 mm, OD = 0.7 mm) at a feeding rate of 0.3 ml h^{-1}. The needles were placed oppositely to each other at a distance of 30 cm. Using a DC high voltage-power supply the needles were oppositely charged with an applied voltage of 13.5 kV. The distance of the needles to a grounded cylinder was 2 cm. Electrospinning provides a triangle of fibers diverging from the center of the needles to the grounded cylinder. At the center of the triangle the formed yarn was drawn to a take-up unit with a rotating twister unit at a take-up speed of 2.4 m h^{-1}. The distance of the center of the needles to the take-up unit was always 30 cm. The twister rotation speed could be varied up to 440 rpm. In experiments a rotational rate of the twister plate of 80, 160, 240 or 320 rpm was applied. In case of hybrid PLLA/PVA yarns the PVA solution was spun from the positively charged needle and the PLLA solution from the negatively charged needle. The weight ratio of the PLLA and PVA in the hybrid yarns was determined by immersion of the yarns in distilled water at 50 °C for at least 2 h to dissolve the PVA and subsequent drying and weighing.

Characterization

Morphology

The morphology of the electrospun yarns was determined using a scanning electron microscope (SEM; XL 30, Philips) at an accelerating voltage of 25 kV. Prior to analysis, samples were sputtered with a thin layer of gold. From at least six SEM images of every yarn prepared yarn diameters were determined at five different locations using Digimizer 4.1.1.0 software. At least ten high magnification images were used for determining the fiber diameter at three different locations.

Differential scanning calorimetry (DSC)

A differential scanning calorimeter (TA Instrument DSC SW 9.01 calorimeter) was used to determine the thermal properties of the electrospun yarns and the cefazolin. Heating scans were run from 25 °C to 250 °C at a scanning rate of 10 °C min^{-1} under a

nitrogen atmosphere. From the DSC curves the glass transition temperature (T_g), melting temperature (T_m) and cold crystallization temperature (T_{cc}) were obtained. The degree of crystallinity (χ_c) of PLLA fibers was calculated from the enthalpy of melting and cold crystallization according equation (1)

$$\chi_c(\%) = \frac{\Delta H_m - \Delta H_{cc}}{\Delta H_m^0 \times w_f} \times 100, \quad (1)$$

where, ΔH_m is the melting enthalpy and ΔH_{cc} is the cold crystallization enthalpy and w_f is the PLLA weight fraction. $\Delta H^0{}_m$ is the melting enthalpy of PLLA with a crystallinity of 100% (93.7 J g^{-1}) [6, 22].

Mechanical properties

Mechanical properties of the electrospun yarns were measured using a tensile tester (Instron Elima EMT-3050). The twisted fibrous yarns were randomly cut into pieces with a length of 50 cm and weighted to obtain the linear mass density (Tex) of the yarns. The yarn strength and Young's modulus were reported in cN per Tex (cN/Tex). At least 15 pieces of every yarn were tested and values determined were averaged. The applied gauge length and cross head speed were 20 mm and 10 mm min^{-1}, respectively.

In vitro release

The cefazolin release profiles from drug-loaded PLLA and hybrid PLLA/PVA electrospun yarns were determined by immersion dried and weighted pieces of yarns in 10 ml of a phosphate buffer solution (PBS, pH = 7.4). Samples were placed in a shaking incubator at 37 °C. At predetermined time points, 2 ml samples of the buffer solution were taken and replaced by an equal volume of fresh buffer (sink conditions). The absorbance of released cefazolin was determined using a UV–Visible spectrophotometer (UV-Mecasys) at a wave length of 271 nm. The concentration of cefazolin released was determined according a calibration curve prepared from cefazolin dissolved in PBS at concentrations ranging from 0.02 to 0.6 mg ml^{-1}. Three samples of each yarn were tested and the results were averaged. To compare the release behavior of drug-loaded PLLA and hybrid PLLA/PVA yarns prepared at different twist rates, a statistical analysis of ANOVA was performed. All statistical tests were carried out within 95% significance level ($\alpha = 5\%$).

Results and discussion

PLLA yarns were prepared by electrospinning cefazolin loaded PLLA 2, 2, 2-trifluoroethanol (TFE) solutions from both the positively and negatively charged needles. Drug loaded PLLA/PVA hybrid yarns were prepared by electrospinning the PLLA solution (TFE) from the positively charged needle and the aqueous PVA solution from the negatively charged needle. Due to the different properties of the solutions the PLLA fibers were produced at a faster rate and with larger diameter than PVA fibers. The ratio of PLLA and PVA in the hybrid yarns was 89/11 (wt/wt) and was determined after dissolution of the PVA from the yarns.

Characterization

Morphology

SEM images of the electrospun drug-loaded PLLA and hybrid PLLA/PVA hybrid yarns prepared at different twist rates are presented in figures 1 and 2. The corresponding fiber diameter distributions are presented in the inserts. The mean diameters of the yarns and fibers in the yarn structure in the absence and presence of cefazolin are presented in tables 1 and 2.

Electrospinning afforded uniform drug-loaded yarns composed of fibers with smooth surfaces without any bead formation. The SEM images as shown in figures 1 and 2 reveal that no larger drug crystals were present on the surface of the fibers implying that the cefazolin was dispersed in the electrospun fibers. Whereas the PLLA yarns were composed of fibers with a single diameter distribution (figure 2), drug-loaded hybrid yarns show a bimodal distribution due to the considerable difference in diameters of the electrospun PLLA and PVA fibers. In independent electrospinning experiments of only PVA applying the same process conditions afforded fibers with much smaller diameters compared to PLLA fibers (data not shown).

Electrospinning of PLLA solutions afforded nanofibers with average diameters of 789 and 480 nm at low and high twist rates, respectively. The decrease in the fiber diameter at higher twist rates likely results from extended drawing of the fibers. A similar decrease of the average fiber diameter at higher twist rates was observed in electrospinning cefazolin loaded polymer solutions. As an example, PLLA solutions containing cefazolin afforded fibers with diameters of 385 and 258 nm at twist rates of 80 and 320 rpm, respectively. In the case of hybrid yarns, in the presence of cefazolin, the mean diameter values decreased from 353 to 256 nm at increasing twist rates. The overall decrease in the fiber diameters upon electrospinning drug loaded polymer solutions can be attributed to the increased conductivity and decreased viscosity of the solutions [23–26]. Whereas a 7 wt% PLLA solution has a viscosity of 0.59 Pa s a cefazolin loaded PLLA solution has a viscosity of 0.28 Pa s. The conductivity of a drug loaded PLLA solution in TFE (1.15 μs cm^{-1}) was markedly higher than that of a PLLA solution in TFE (0.46 μs cm^{-1}). The considerable increase in the conductivity in the presence of cefazolin resulted in an increase in the charge density on the surface of the ejected polymer jet and thus a larger elongation of the jet, resulting in smaller fiber diameters [27, 28].

At similar twist rates the diameter of drug loaded yarns are slightly lower. As an example, the average diameter of the PLLA yarn at a twist rates of 80 rpm

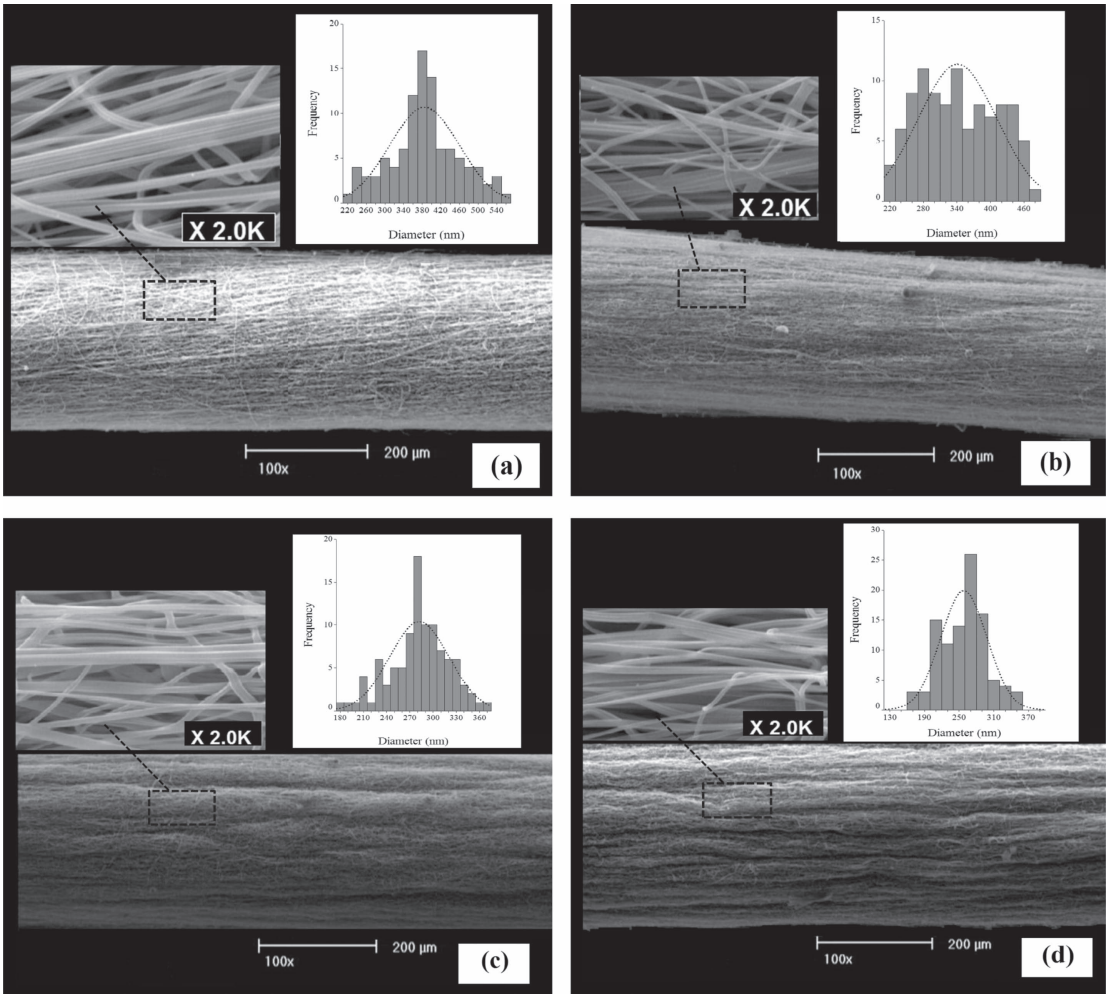

Figure 1. SEM images of cefazolin-loaded electrospun PLLA yarns prepared at different twist rates: (a) 80 rpm, (b) 160 rpm, (c) 240 rpm and (d) 320 rpm.

was 358 μm and when loaded with cefazolin 311 μm (table 1). Oppositely to the decrease in fiber diameters at higher twist rates, yarn diameters increased because more fibers are present per unit length. Similarly, in the case of hybrid yarns the fiber diameters decreased and the yarn diameters increased at higher twist rates.

Thermal properties

DSC was performed to study the thermal properties of neat and cefazolin loaded electrospun yarns, prepared at different twist rates. The DSC thermograms of cefazolin, PVA and PLLA are depicted in figure 3 and those of cefazolin loaded electrospun PLLA and hybrid PLLA/PVA yarns in figures 4 and 5, respectively.

The melting temperature (T_m), glass transition temperature (T_g), cold crystallization temperature (T_{cc}), cold crystallization enthalpy (ΔH_{cc}), melting enthalpy (ΔH_m) and degree of crystallinity (χ_c) of electrospun PLLA and hybrid (PLLA/PVA) yarns obtained from the DSC studies are summarized in tables 3 and 4, respectively. From the melting enthalpy and cold crystallization enthalpy, the crystallinity of PLLA was estimated using equation (1).

The thermograms of the electrospun PLLA yarns show a glass transition (T_g) followed by cold crystallization (T_{cc}) and a polymer melting transition (T_m) [29]. The rapid solidification and high elongation rates during electrospinning are known to result in a reduction in the glass transition temperature and melting temperature of PLLA [30]. Also here the electrospun fibers exhibited a lower glass transition temperature around 62 °C–65 °C as compared to neat PLLA (74 °C). The exothermic cold crystallization around 81 °C–84 °C was observed for both neat and drug-loaded electrospun yarns [31–33]. Electrospinning results in a partial alignment of polymer chains but the fast evaporation of solvent during fiber formation prevents adequate PLLA crystallization leading to the observed cold crystallization [34–36]. The melting temperature of the electrospun PLLA yarns (T_m) and the enthalpy of melting (ΔH_m) appeared somewhat lower than those of neat PLLA. The degree of crystallinity, an important characteristic of a semicrystalline polymer like PLLA, may affect the physical properties, mechanical properties, degradability and drug release rate [29, 35, 37, 38]. Significantly lower values of PLLA

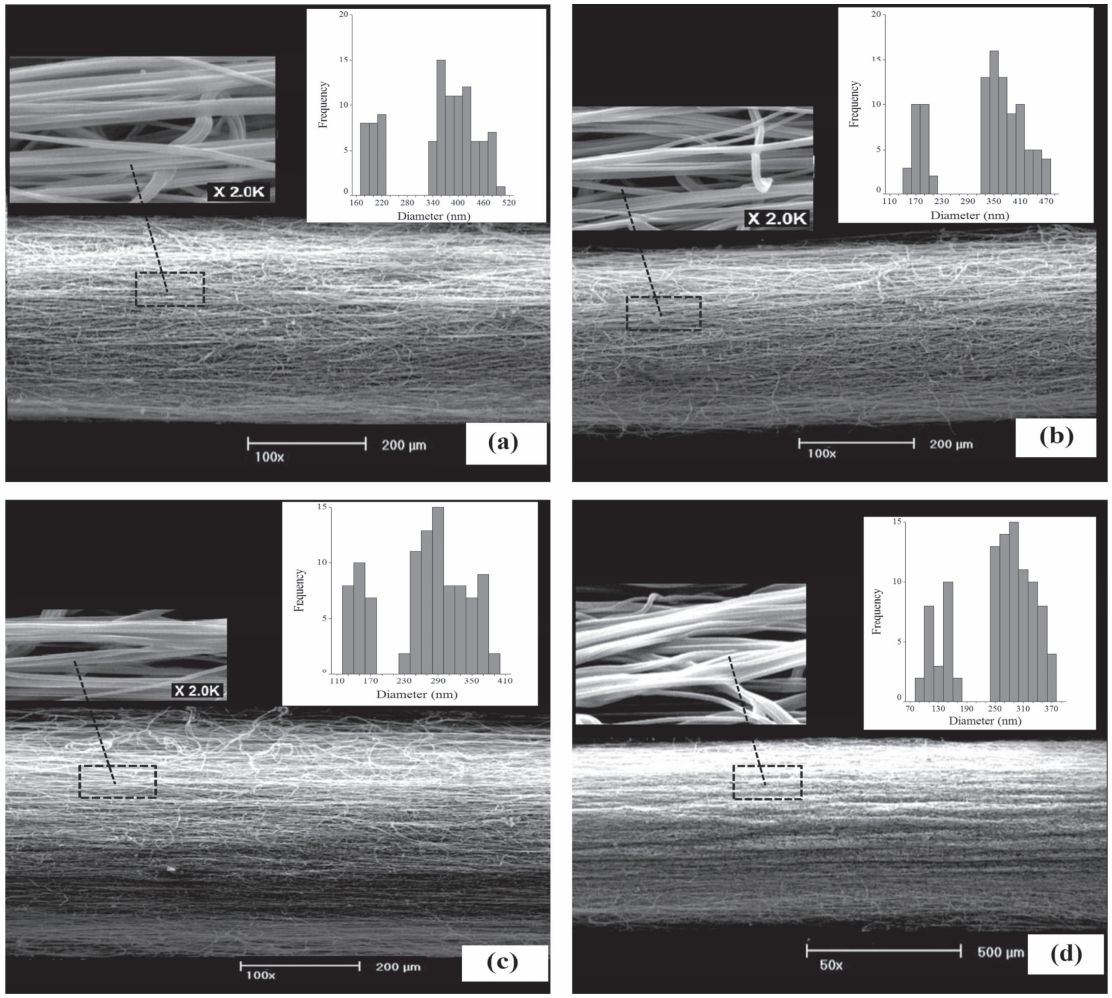

Figure 2. SEM images of cefazolin-loaded electrospun hybrid PLLA/PVA yarns prepared at different twist rates: (a) 80 rpm, (b) 160 rpm, (c) 240 rpm and (d) 320 rpm.

Table 1. Mean diameters of neat and cefazolin loaded electrospun PLLA fibers and corresponding yarns prepared at different twist rates.

Sample	Twist rate (rpm)	Fiber diameter (nm)	Yarn diameter (μm)
Neat PLLA yarns	80	789 ± 114	358 ± 74
	160	762 ± 119	381 ± 65
	240	595 ± 129	435 ± 74
	320	480 ± 48	471 ± 80
Cefazolin-loaded PLLA yarns	80	385 ± 75	311 ± 24
	160	341 ± 70	325 ± 34
	240	282 ± 38	354 ± 34
	320	258 ± 40	411 ± 68

crystallinity were found for electrospun yarns which are likely due to the fast evaporation of solvent during the electrospinning process hampering crystal growth [39–41].

As depicted in figures 4 and 5, DSC thermograms of drug-loaded samples did not show any characteristic thermal transitions of cefazolin. In the DSC thermograms of the drug-loaded electrospun yarns the cefazolin melting transition at 169 °C did not appear suggesting that cefazolin is in an amorphous state, similar to that reported in other studies [32, 38, 42, 43]. The data reported in tables 3 and 4 revealed that the presence of drug and twist rate did not significantly affect the melting temperature (T_m), glass transition temperature (T_g) and cold crystallization temperature (T_{cc}) of electrospun yarns. However, the DSC results revealed that the melting enthalpy (ΔH_m) of PLLA in the presence of cefazolin was lower, indicating that the presence of cefazolin hindered PLLA crystallization.

Increasing the twist rate caused an increase in ΔH_m and crystallinity of electrospun PLLA and hybrid

Table 2. Mean diameters of neat and cefazolin loaded electrospun PLLA/PVA fibers and corresponding hybrid yarns prepared at different twist rates.

Sample	Twist rate (rpm)	Fiber diameter (nm)	Yarn diameter (μm)
Neat hybrid (PLLA/PVA) yarns	80	547 ± 178	320 ± 40
	160	507 ± 183	335 ± 30
	240	433 ± 173	529 ± 74
	320	428 ± 166	595 ± 69
Cefazolin-loaded hybrid (PLLA/PVA) yarns	80	353 ± 97	275 ± 27
	160	330 ± 96	293 ± 34
	240	264 ± 77	467 ± 55
	320	256 ± 79	558 ± 50

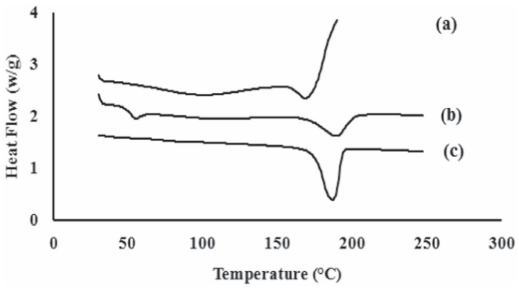

Figure 3. DSC first heating scans of (a) cefazolin, (b) PVA and (c) PLLA.

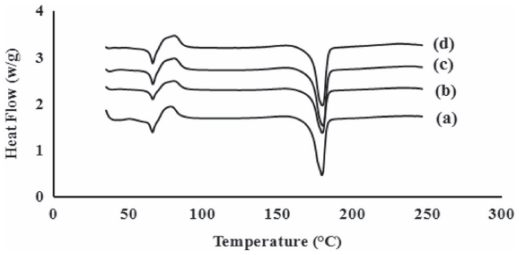

Figure 4. DSC first heating scans of cefazolin-loaded electrospun PLLA yarns prepared at twist rates of (a) 80 rpm, (b) 160 rpm, (c) 240 rpm and (d) 320 rpm.

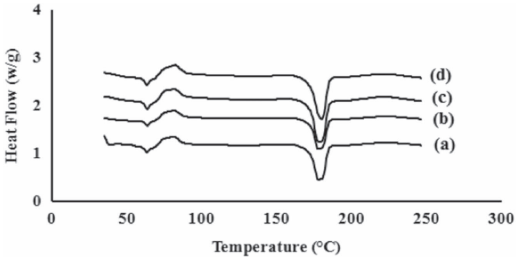

Figure 5. DSC first heating scans of cefazolin-loaded electrospun hybrid (PLLA/PVA) yarns prepared at twist rates of (a) 80 rpm, (b) 160 rpm, (c) 240 rpm and (d) 320 rpm.

PLLA/PVA yarns (with and without drug) ($p < 0.05$). At higher twist rates the crystallinity of neat PLLA yarns gradually increased from 40% to 59% and the crystallinity of drug-loaded PLLA yarns increased from 30% to 46%. Similarly, the crystallinity of drug-loaded PLLA fibers in the electrospun hybrid yarns increased from 32% to 50% with increasing twist rates (table 4). The higher crystallinity at higher twist rates could be attributed to a higher degree of molecular orientation resulting from fiber drawing upon twisting [44, 45].

Mechanical properties

The mechanical properties of both neat and cefazolin loaded electrospun yarns were evaluated by stress–strain measurements. Stress–strain curves of yarns at a twist rate of 80 rpm as presented in figure 6 show that the mechanical properties of drug loaded yarns were lower than those of non-drug loaded yarns. For example, at a twist rate of 80 rpm, a PLLA yarn had a tensile strength and modulus of 4.1 and 29.6 cN/Tex, respectively, and elongation at break of 187%. The cefazolin loaded PLLA yarn exhibited a relatively lower tensile strength and modulus of 2.12 and 9.64 cN/Tex and elongation at break of 65% (table 5). Similar results were observed at higher twist rates. In case of electrospun hybrid yarns, at all twist rates, a lower tensile strength, modulus and elongation at break was observed in the presence of cefazolin in comparison to neat PLLA/PVA yarns. The decrease in crystallinity upon drug loading likely led to the lower strength, modulus and elongation at break of the fibers and resulting yarns [46–48].

The tensile strength and modulus of the drug-loaded PLLA and hybrid yarns were higher at higher twist rates due to the generation of a more compact structure which leads to a higher interfacial adhesion between fibers. In case of drug-loaded hybrid yarns, increasing the twist rate from 80 to 320 rpm, the strength and modulus increased to a higher extend. In all cases, the elongation at break decreased slightly with increasing twist rates which can be ascribed to an increase in crystallinity at higher twist rates [5].

***In vitro* drug release**

The release of cefazolin from the electrospun PLLA and hybrid PLLA/PVA yarns was investigated by incubation 1 cm pieces of the yarns in PBS (pH 7.4) at

Table 3. Thermal properties of PLLA, non-loaded and cefazolin-loaded electrospun PLLA yarns prepared at different twist rates.

Sample	Twist rate rpm	T_g (°C)	T_{cc} (°C)	T_m (°C)	ΔH_m (J g^{-1})	ΔH_{cc} (J g^{-1})	χ%
PLLA		74	—	187	74	—	79
Electrospun PLLA yarns	80	64	84	179	57	20	40
	160	65	83	178	58	17	44
	240	65	83	178	70	21	52
	320	64	84	179	71	16	59
Cefazolin-loaded electrospun PLLA yarns	80	65	81	179	43	16	30
	160	65	82	179	53	19	38
	240	65	82	180	58	19	44
	320	65	82	179	62	21	46

Table 4. Thermal properties of non-loaded and cefazolin-loaded electrospun hybrid PLLA/PVA yarns prepared at different twist rates.

Sample	Twist rate rpm	T_g (°C)	T_{cc} (°C)	T_m (°C)	ΔH_m (J g^{-1})	ΔH_{cc} (J g^{-1})	χ%
Electrospun hybrid PLLA/PVA yarns	80	64	83	179	50	22	33
	160	64	84	179	56	24	38
	240	63	83	179	63	23	47
	320	63	84	179	66	20	54
Cefazolin-loaded electrospun hybrid PLLA/PVA yarns	80	62	82	178	41	16	32
	160	63	82	178	45	18	33
	240	63	83	178	52	20	40
	320	62	83	179	60	19	50

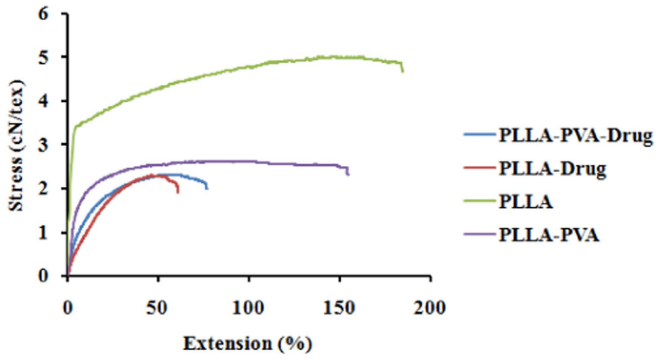

Figure 6. Stress–strain curves of electrospun yarns at twist rate of 80 rpm.

Table 5. Mechanical properties of cefazolin-loaded electrospun yarns.

Sample	Twist rate rpm	Strength (cN/Tex)	Young's modulus (cN/Tex)	Elongation at break (%)
Electrospun PLLA yarns	80	2.12	9.64	65
	160	2.40	14.42	65
	240	2.64	15.43	55
	320	3.00	19.77	53
Electrospun hybrid PLLA/PVA yarns	80	2.36	13.15	70
	160	2.06	12.13	69
	240	3.03	19.07	60
	320	3.17	19.95	55

37 °C. The concentration of released cefazolin was determined by UV measurements at 271 nm. The initial (5 h) and long term (90 d) cumulative cefazolin release profiles are presented in figure 7.

For the PLLA yarn, in the initial stage a burst release was observed followed by a sustained release (figure 7). The burst release could be related to drug dispersed at or close to the surface of the fibers. It is expected that part of the cefazolin, in the form of its sodium salt, is present at the surface of the fibers generated in the electrospinning process and diffuses out upon incubation. However, this burst release

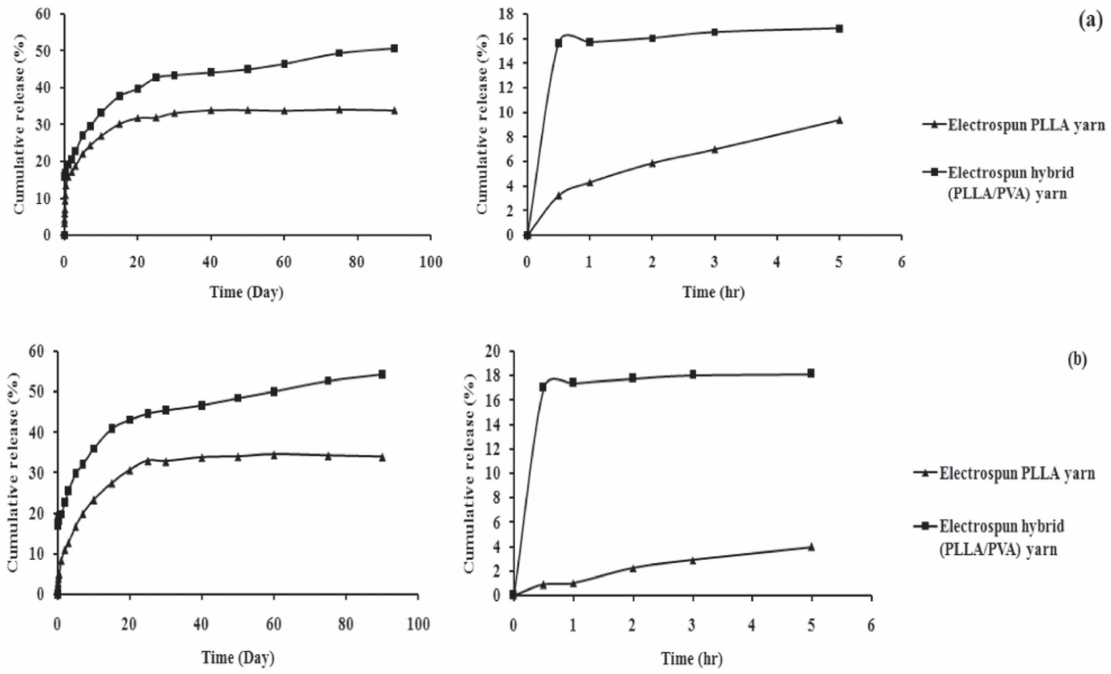

Figure 7. Cumulative release of cefazolin from electrospun PLLA and hybrid PLLA/PVA yarns: (a) 80 rpm, (b) 320 rpm.

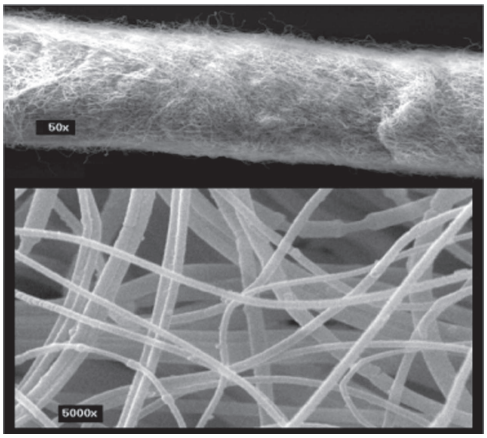

Figure 8. SEM image of a cefazolin-loaded electrospun PLLA yarn prepared at a twist rate of 240 rpm after 90 d incubation.

Table 6. Correlation coefficients (R^2) of the cefazolin release profiles from electrospun yarns fitted to mathematical models.

		R^2			
Sample		Zero-order	First-order	Higuchi	Peppas
PLLA	80 rpm	0.74	0.79	0.92	0.97
	160 rpm	0.77	0.85	0.91	0.99
	240 rpm	0.88	0.85	0.98	0.98
	320 rpm	0.87	0.83	0.99	0.99
PLLA/PVA	80 rpm	0.80	0.96	0.92	0.88
	160 rpm	0.79	0.94	0.91	0.88
	240 rpm	0.79	0.95	0.91	0.88
	320 rpm	0.77	0.95	0.91	0.89

decreased from 16% for the yarns prepared at a twist rate of 80 rpm to 8% for the yarns prepared at a twist rate of 320 rpm. This dependence on the twist rate could be related to both differences in fiber packing and crystallinity. The compact structure of the yarns prepared at the higher twist rates does not allow fast diffusion from the interior of the yarn to the surrounding solution [49–51]. Moreover, the higher crystallinity of the PLLA fibers prepared at higher twist rates will affect the drug release for this occurs firstly from the amorphous regions [52].

In the initial period of 15 d, a somewhat higher cumulative release of the drug from the PLLA yarns prepared at lower twist rates was observed which could be related to their lower crystallinity. At longer immersion times, no significant differences were observed between samples prepared at different twist rates. A total of approximately 30% was released. The partial release of the cefazolin from the yarns is likely a result of the slow degradation of the PLLA fibers and may be hampered by drug polymer interactions. SEM images of the yarns revealed that the PLLA electrospun fibers were relatively stable under the incubation conditions. As an example a SEM image of the drug-loaded PLLA yarn prepared at a twist rate of 240 rpm after 90 d immersion did not show changes in the yarn fiber morphology (figure 8). In addition the weight loss of the PLLA yarns after 90 d incubation was negligible. This may explain that most of the drug is trapped in the fibers and may only be released upon degradation of the polymer.

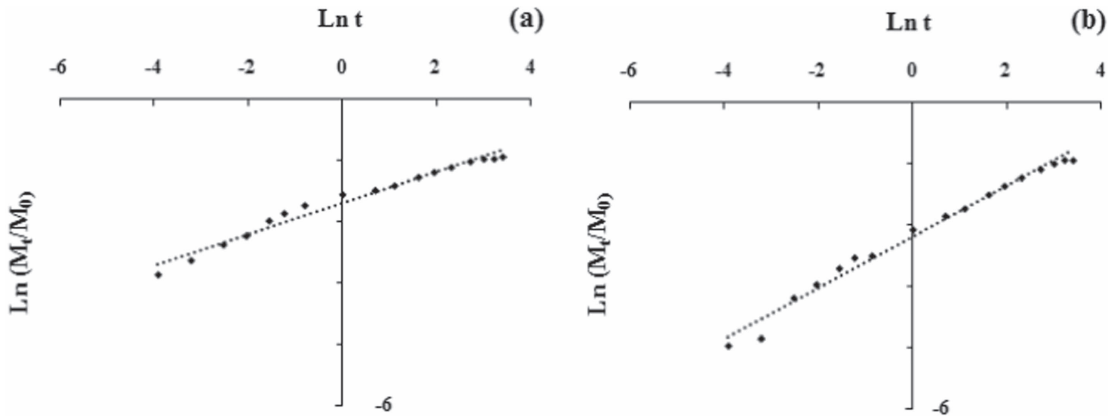

Figure 9. Cefazolin release from electrospun PLLA yarns prepared at twist rates of (a) 80 rpm, (b) 320 rpm, according the Peppas model.

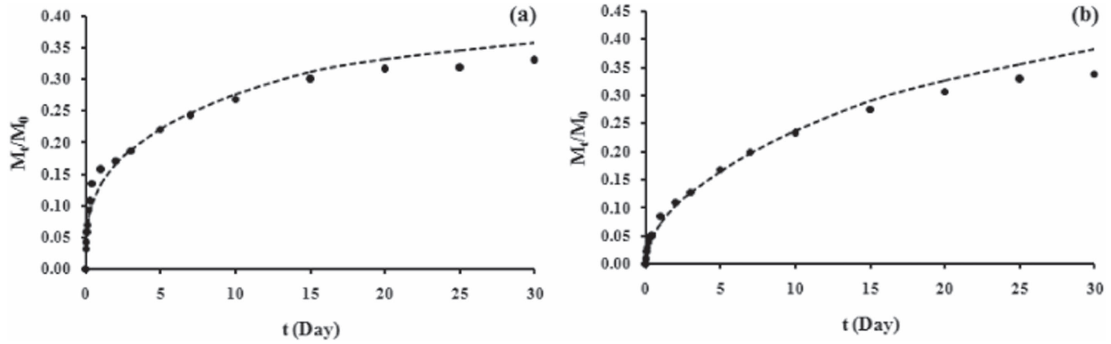

Figure 10. Drug release profiles of electrospun yarns based on the Peppas model: (a) 80 rpm, (b) 320 rpm. Dots correspond to experimental data and the dashed lines to the fitting.

Table 7. Drug release kinetic parameters according the Peppas model.

Twist rate (rpm)	K	n	R^2
80	0.135	0.31	0.97
160	0.136	0.30	0.99
240	0.069	0.49	0.98
320	0.074	0.48	0.99

A burst release of 15%–18% of total drug loaded from the hybrid PLLA/PVA yarns was observed during the first 30 min independent of the twist rate applied. This fast initial release of drug can be ascribed to the swelling of PVA fibers immediately upon contact with buffer. These fibers consecutively dissolve creating an increase in porosity of the yarn

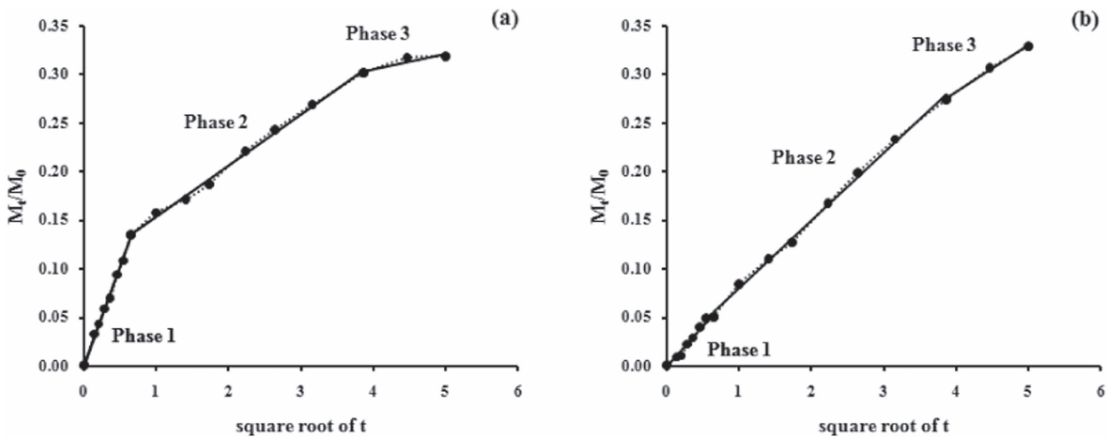

Figure 11. Cefazolin release profiles from electrospun PLLA yarns prepared at twist rates of: (a) 80 rpm and (b) 320 rpm, according the Higuchi model.

Table 8. Correlation coefficients (R^2) and release rate constants (k) for the Higuchi approximation of the cefazolin release profiles from electrospun PLLA and hybrid PLLA/PVA yarns prepared at different twist rates.

Twist rate (rpm)	Phase 1				Phase 2				Phase 3			
	PLLA		PLLA/PVA		PLLA		PLLA/PVA		PLLA		PLLA/PVA	
	R^2	k	R^2	k	R^2	k	R^2	k	R^2	K	R^2	k
80	0.99	0.20	0.47	—	0.99	0.05	0.99	0.07	0.96	0.02	0.98	0.04
160	0.95	0.21	0.45	—	0.99	0.05	0.99	0.07	0.99	0.02	0.99	0.03
240	0.95	0.08	0.50	—	0.99	0.06	0.99	0.07	0.94	0.03	0.99	0.03
320	0.97	0.08	0.48	—	0.99	0.06	0.99	0.07	0.99	0.05	0.99	0.03

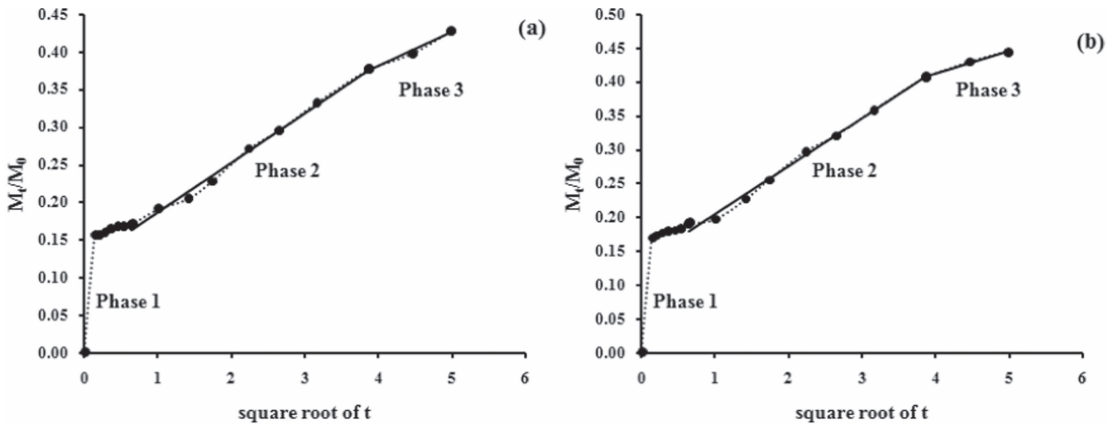

Figure 12. Cefazolin release profiles from electrospun hybrid PLLA/PVA yarns prepared at twist rates of: (a) 80 rpm and (b) 320 rpm, according the Higuchi model.

Table 9. Correlation coefficients (R^2) and release rate constants (k) for the first order release profiles from electrospun hybrid PLLA/PVA yarns prepared at different twist rates.

Twist rate (rpm)	K	R^2
80	0.014	0.96
160	0.014	0.94
240	0.015	0.95
320	0.015	0.95

[17, 18, 47, 53, 54]. In addition the total amount of drug released from the hybrid PLLA/PVA yarns was much higher (figure 7). Changing the twist rate demonstrated no significant differences in the total release of cefazolin from hybrid yarns and a total of approximately 52% of drug was released.

Release kinetics

In order to determine the mechanism of drug release, the results of the *in vitro* drug release over a period of 30 d were fitted to various mathematical models. A zero order and first order model, and the Peppas and Higuchi models were evaluated.

For the zero-order model the release rate is given by equation (2) [27, 55, 56]

$$\frac{M_t}{M_0} = k_0 t. \quad (2)$$

In which M_t is the amount of drug released at time t, k_0 is the zero-order release constant, and M_0 is the amount of the total drug in the sample.

A first-order release rate can be described by equation (3) [57, 58]

$$\frac{M_t}{M_0} = \exp(-k_1 t). \quad (3)$$

In which k_1 is the first-order release constant.

Equation (4) is based on the release model described by Peppas [26, 59, 60]

$$\frac{M_t}{M_0} = k_P t^n, \quad (4)$$

where k_P is the Peppas constant.

A model developed by Higuchi is presented by equation (5) [61, 62]

$$\frac{M_t}{M_0} = k_H t^{0.5}, \quad (5)$$

where k_H is the Higuchi release rate.

The results of a regression analysis, R^2, were applied to correlate the fit to different models, and results were summarized in table 6.

The data presented in table 6 show that the *in vitro* release behavior of cefazolin from electrospun PLLA

yarns prepared at different twist rates could be best described by the Peppas and Higuchi model.

When the logarithm of the cumulative release (i.e. Ln (M_t/M_0)) was plotted as a function of Ln t, a linear relationship is obtained (figure 9). This shows that the cefazolin release from electrospun PLLA yarns was controlled by a Fickian diffusion mechanism. The Peppas parameter n, related to the geometrical shape of the matrix and the Peppas rate constant k were determined from this plot and are presented in figure 10 and table 7 [60]. The results indicated that the Peppas parameters are dependent on the twist rates. By increasing the twist rate from 80 to 320 rpm, the release rate constant k decreased from 0.135 to 0.074.

According the Higuchi model a plot of the released fraction of cefazolin (M_t/M_0) against the square root of time should give a straight line [50, 60]. For the PLLA electrospun yarns prepared at twist rates of 80 and 320 rpm three different stages were found (figure 11). The slope of the line at each stage provided the release rate constant (k) and R^2 provided a correlation of the fit (table 8).

In the first stage (10 h), the release from the PLLA yarns prepared at a twist rate of 80 and 160 rpm show the highest release rate, while the samples with twist of 240 and 320 rpm exhibited the lowest release rate. As mentioned above these results can be due to the compact structure and higher crystallinity of the yarns prepared at twist rates of 240 and 320 rpm. In the second stage of 15 d, the release rate constants for the PLLA yarns did not significantly depended on the twist rate (0.05–0.06). A relative higher release rate was found in the third stage especially for PLLA yarns prepared at a twist rate of 320 rpm. Probably, the small fiber diameter and corresponding larger surface area present increased the drug release rate [55, 60].

In the case of hybrid yarns, approximately, linear relationships ($R^2 > 0.98$) between M_t/M_1 and $t^{1/2}$ were found except for the large burst release during the first hour as presented in figure 12. In the initial hours the dominant mechanism of release is the dissolution of the PVA fibers. Thus, in the first stage, for these hybrid yarns prepared a fit of the data was not observed ($R^2 < 0.50$). For the second phase and third stages, at all twist rates straight lines were obtained (figure 12).

The release of cefazolin from electrospun hybrid (PLLA/PVA) yarns could also be fitted to a first-order model (table 6).

The fit afforded the rate constants k were determined (table 9) and showed that the release rate constant (k) did not significantly depended on the twist rate applied.

Conclusion

Drug-loaded continuous twisted PLLA or hybrid PLLA/PVA yarns were fabricated by electrospinning and studied for their use as materials for medical textiles. Cefazolin, an antibiotic drug was selected, for its main applications in wound healing and prevention of implant infections. In this work it was shown that besides the composition the physical and mechanical properties of the yarns, the applied twist rate of the electrospun fibers enabled control of the release rate. SEM images showed that a smooth and bead-free fiber morphology was obtained for all drug-loaded yarns and that the fiber and yarn diameters were significantly smaller when cefazolin was added to the spinning solutions. DSC analysis and mechanical properties investigations of the yarns revealed that the addition of drug decreased the crystallinity, strength, modulus and elongation at break.

In vitro release profiles revealed that the drug was released in a controlled manner with prolonged duration depending on the composition and twist rate. An initial burst release was followed by a sustained release over longer immersion times.

The PLLA fibrous yarns were stable in aqueous solutions with negligible weight loss during the test time. In the presence of PVA, the increased hydrophilicity of the matrix resulted in a higher initial release rate and the total release of cefazolin from these hybrid yarns was higher compared to PLLA yarns. The high water solubility of the incorporated PVA fibers in the yarns thus allowed tuning the drug release from the yarn matrix. At higher twist rates the burst release of cefazolin was reduced and prolonged its release due to a lower porosity of the structure and higher crystallinity of fibers. The release kinetics was evaluated by fitting the release data with various empirical models. Cefazolin release from electrospun PLLA yarns was governed by a diffusion mechanism and could best be fitted by the Peppas and Higuchi models. The models that were found best to describe the drug release mechanism from the hybrid PLLA/PVA yarns were a first-order model and the Higuchi model.

These cefazolin-loaded electrospun yarns prevent implant infections and may find main applications in wound healing. The methodology presented also enables incorporation of a wide range of pharmaceutical drugs into the fibers. Overall the twisted electrospun yarns developed opens possibilities for producing a new generation of medical textiles in various wound healing applications e.g. scaffolds for tissue regeneration, surgical sutures and woven wound dressings.

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