Colloids and Surfaces A 590 (2020) 124518

Contents lists available at ScienceDirect

Colloids and Surfaces A

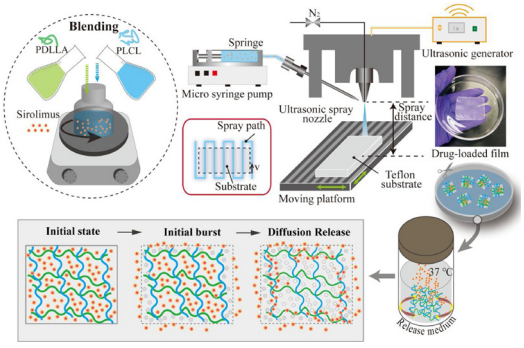
journal homepage: www.elsevier.com/locate/colsurfa

Preparation and evaluation of poly(D, L-lactic acid)/poly(L-lactide-co-ε-caprolactone) blends for tunable sirolimus release

Fengqin Li, Xin Li, Rongxin He, Jie Cheng, Zhonghua Ni*, Gutian Zhao*

School of Mechanical Engineering, Jiangsu Key Laboratory for Design and Manufacture of Micro-Nano Biomedical Instruments, Southeast University, Nanjing, 211189, Jiangsu, China

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Polymer blends
Ultrasonic spray coating
Controlled release
Poly (D, L-lactic acid)
Poly(L-lactide-co-ε-caprolactone)

ABSTRACT

Biodegradable materials are widely used in drug delivery at present. Blending polymers with complementary properties has become a promising strategy to tune drug release. In this study, the effects of poly(D, L-lactic acid) (PDLLA) and poly(L-lactide-co-ε-caprolactone) (PLCL) blend films on the *in vitro* release kinetics of sirolimus were investigated. Herein, a series of PDLLA/PLCL blend films with different ratios were prepared by the ultrasonic spray technology and *in vitro* release tests of these polymer films were carried out in phosphate buffered saline (PBS). Release profiles showed biphasic release pattern: the initial rapid release (phase I) and stable release (phase II) and more PLCL resulted in earlier and faster sirolimus release, with more cumulative drug release observed. The release rate could be tuned by adjusting the ratio of PLCL to PDLLA in blend films, but they may not be a simple linear proportional relationship. Moreover, *in vitro* sirolimus release kinetics from these blend films were analyzed using mathematical models. This work can provide a feasible way for tuning drug release in polymer matrices under a blend strategy and improve the design of coating films in drug delivery systems.

1. Introduction

Tunable drug release is an important field in drug delivery and material research. The biodegradable polymers as release carriers have become the promising research focus due to their excellent comprehensive properties [1–3]. At present, the biodegradable polymers such as poly(L-lactic acid) (PLLA), poly(D, L-lactic acid) (PDLLA), poly (lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL) or poly(L-

* Corresponding authors at: 79 Suyuan Avenue, School of Mechanical Engineering, Southeast University, Nanjing, 211189, China.
E-mail addresses: nzh2003@seu.edu.cn (Z. Ni), zhaogutian@seu.edu.cn (G. Zhao).

https://doi.org/10.1016/j.colsurfa.2020.124518
Received 7 November 2019; Received in revised form 26 January 2020; Accepted 28 January 2020
Available online 30 January 2020

Table 1
Compositions of the polymer blends used in this study.

Polymer blend (percentage polymer)	Drug-free film	Drug-loaded film		
	Sample name	Polymer :Sirolimus(w/w)	Sample name	Film weight (μg)
100 % PDLLA	100DL	2:1	100DLd	1443.5 ± 36
80%PDLLA + 20 %PLCL	8020	2:1	8020d	1573.5 ± 32
70%PDLLA + 30 %PLCL	7030	2:1	7030d	1511.5 ± 62
60 %PDLLA + 40 %PLCL	6040	2:1	6040d	1623.0 ± 21
50 %PDLLA + 50 %PLCL	5050	2:1	5050d	1692.9 ± 15
100 % PLCL	100CL	2:1	100CLd	1470.0 ± 41

lactide-co-ε-caprolactone) (PLCL) are widely applied in commercial medical equipment or scientific research [4–6]. There are many methods to modulate the drug release pattern, including the increase of surface area by using nano-patterned polymer [7], drug-loaded microparticles or nano-particles [8,9], the modification of crystallinity of drug on polymeric matrix [10], synthesis of new polymer materials [11], incorporation of hydrophilic additives [12,13]. The methods described above alter the release kinetics of drug delivery systems by modifying certain property of the drug or polymer. Compared to these methods, the blend is simple and reproducible which can obtain better physicochemical properties from the newly generated matrices. Previous reports have shown that polymer blend is a feasible strategy for tuning materials properties [14,15]. However, there are few studies on the controlled-release properties of blend polymer materials as drug carriers.

Regarding the optional blending materials, the PDLLA material can be selected as drug carriers for targeted treatment of cancer [16], cardiovascular diseases [17] and wound healing [18]. However, single PDLLA material belongs to brittle material, resulting in weak toughness. In the application of drug-eluting stents, the peeling and cracking of drug-loaded PDLLA coatings are still problems to be overcome [19]. Some reports showed that one polymer blended with PCL or PLCL could have better comprehensive properties [20,21]. PCL is prone to permanent deformation and is a polymer with high crystallinity and very slow degradation. Therefore, PLCL material may be a more suitable choice as the drug carrier compared with PCL. PLCL material is obtained from the ring-opening polymerization of PLLA and PCL. It is a semi-crystalline polymer with high flexibility and short degradation time. To our knowledge, some reports have only studied the physical properties of PDLLA or PLCL blended with other polymers, such as morphology, structure and mechanics [20,22]. However, less attention has been paid to drug delivery performance. Therefore, it is also necessary to study the release mechanism and regularity of PDLLA/PLCL blends used as drug carriers. In this context, sirolimus, an anti-proliferative hydrophobic agent commonly used in drug-eluting stents (DESs), drug-eluting balloons (DEBs) or cancer therapy [23,24], was selected to study its release from polymer blends.

There are many preparation techniques of polymer blends, such as spin coating technique [25], solvent evaporation technique [26], melting technique [27], ultrasonic spray atomization technique [28], *etc.* Ultrasonic spray technology has more obvious advantages in surface morphology, preparation size and thickness accuracy of three-dimensional microstructures [29,30]. Moreover, there is no degradation compared to the melting method. Bose et al. have shown the advantage of ultrasonic spray coating to achieve a continuous film with uniform thickness and low roughness [31]. Sharma et al. [5] have coated biodegradable polymers to fabricate bioresorbable composite implants with high mechanical strength.

In this paper, a series of degradable drug-free and drug-loaded PDLLA/PLCL blend films with different ratios were prepared by ultrasonic spray technology. The properties of these films were characterized by water contact angle (WCA), scanning electron microscopy (SEM) and X-ray diffraction (XRD). The effect of PLCL content on the sirolimus release from blend films was studied. It is found that sirolimus release from blend films showed biphasic release pattern: the initial rapid release (phase I) and stable release (phase II) and modulation of drug release can be achieved by altering the ratio of PLCL to PDLLA. Herein, this study could provide a feasible way to tunable release profiles for hydrophobic drug and might contribute to the design of drug delivery systems such as drug-eluting stents.

2. Materials and methods

2.1. Materials and reagents

The PDLLA used in the study was a medical grade (RESOMER R203S) obtained from Evonik Industries (Essen, Germany). It has the inherent viscosity of 0.25-0.35 dl/g and average molecular weight of 24,600 g/mol. PLCL (IV = 0.8 dl/g) was purchased from Jinan Daigang Biomaterial. Sirolimus (purity ≥ 98 %) was supplied from Shanghai Yuan Ye Biological Co., Ltd. China. Phosphate buffered saline (PBS, pH = 7.4) and surfactant Brij58 (M_n, 1124) were purchased from Sigma. Acetonitrile and methanol of chromatographic grade were purchased from USA Tedia. All of the other reagents were of analytical grade if not otherwise specified. Ultra-pure water with a specific resistivity greater than 18.25 MΩ cm was used in these experiments.

2.2. Fabrication of polymer film

Fabrication of drug-free and drug-loaded blend films were realized by ultrasonic spray atomization technology. The PDLLA and PLCL were weighed and grouped into multiple blend ratios to prepare polymer solutions with different formulations. They were co-dissolved in dichloromethane by the oscillator (IKA, 640 rpm, 1 h) at room temperature, to obtain clear and homogenous solutions with concentration of 2 % w/w. Sirolimus was added to the prepared polymer solution. The ratio of polymer to drug was 2:1. The specific formulations are shown in Table 1.

The prepared solution was filtered and loaded into a glass syringe. The schematic diagram of the spray system is shown in Fig. 1.

The ultrasonic spray setup was equipped with the ultrasonic spray system (Sono-Tek; 120 kHz), a syringe pump (KD Scientific, MA, USA), an ultrasonic generator and a custom-built X–Y movable motor platform. The flow rate of polymer solution was controlled by the syringe pump, while nitrogen was used as a carrier gas. Major spray parameters including flow rate, nozzle-to-substrate distance and X–Y moving speed were tested and adjusted in order to obtain optimized spray characteristics. And the platform was moved along the X and Y axis to spray the needed area in a pre-programmed zig-zag pattern. The ultrasonic spray films were allowed to dry under vacuum at 37 ℃ for 48 h to completely eliminate residual solvents and stored in a desiccator for further analysis.

All of the coating procedures were performed in a Class-10,000 clean room within temperature range of 20 ℃–25 ℃ and relative humidity of 40 %–50 %.

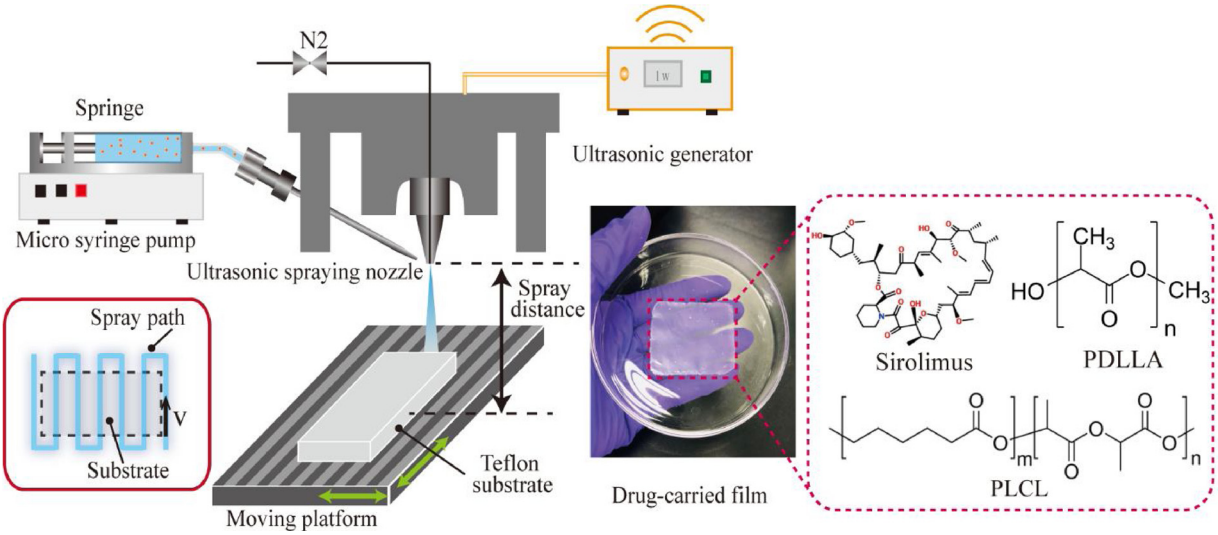


Fig. 1. Schematic diagram of film preparation.

2.3. Sample characterization

The surface morphology of films and sirolimus particles were studied by scanning electron microscopy (SEM; FEI, Inspect F50, USA) at an accelerating voltage of 10 kV and a working distance of 10 mm. Prior to scanning, dried samples were mounted on copper stubs and sputter coated by gold palladium for 120 s at 5 Pa to make them electrically conductive.

The hydrophilic property of drug-free and drug-loaded films was evaluated by water contact angle measurement. A droplet of deionized water (5 μL) was added on the surface using micropipette at room temperature and the contact angle was determined using optical bench-type contact angle goniometry (OCA 15 plus, Data Physical Instruments, Germany). All data were measured from 3 measured areas of the films and the average values were recorded.

The crystallinity of samples was analyzed by X-ray diffraction. Pure PDLLA, PLCL and blend films placed on the glass sheet were exposed to Cu radiation (40 kV, 30 mA) in X-ray diffractometer (SmartLab, Japan). The analysis conditions were scan speed of 5°/min and 2θ range of 5°-50°.

2.4. In-vitro drug release study

For the *in vitro* drug release study, PBS (pH 7.4) solution was selected as the release medium [32–35]. In order to increase the solubility of sirolimus and maintain sink conditions, 0.1 % Brij 58 was added in PBS solution.

The drug-loaded films were cut into rectangular samples of about 6 mm x 6 mm for drug release study. Prepared samples were incubated at 37 °C in 10 mL buffer solution in brown glass vials at a stirring speed of 120 rpm. At predetermined time points, the media were completely removed for analysis and replaced with fresh media. The drug release media were analyzed by reverse-phase HPLC on a C-18 column with a mobile phase consisting of water and acetonitrile (35:65, v/v). Sample solution (20 μL) was injected into the HPLC system (Agilent, 1200). Before injection, the solution was filtered with organic nylon filter head of 0.22 μm in order to make the chromatographic column run more stably.

An isocratic mode at a flow rate of 1.0 mL/min was set and the C-18 column was kept at a temperature of 50 °C throughout the separation. The detector wave length was set to 278 nm using UV spectrophotometry to obtain the best sirolimus response. The retention time of sirolimus was 10.9 min. Calibration curves were prepared in a concentration range of 1 − 50 μg/mL for sirolimus (R^2 = 0.999).

In order to evaluate the sirolimus loading efficiency in multiple films, sample films were placed in brown bottles containing 15 mL acetonitrile and ultrasonically shaken for 20 min. Then solutions were filtered and detected to obtain the drug mass at the initial time. And the drug loading efficiency (%) was determined by eq. (1).

$$\text{Drug loading efficiency}(\%,\text{w/w}) = \frac{\textit{Mass of the drug detected at the initial time}}{\textit{Mass of the drug in theory}} \times 100\% \quad (1)$$

2.5. Analysis of release kinetics and mechanisms

The application of models to the drug release profiles may help to understand the mechanisms. For this purpose, three common models (Zero-order, Higuchi and Korsmeyer-Peppas models) were chosen to fit experimental data by the OriginPro 8 software. Parameters obtained from these models include kinetic constant (k), diffusion release exponent (n) and adjusted coefficient (R^2). The equations for each model are shown as follow:

$$\text{Zero-order model: } M_t = M_0 + k_0 * t \quad (2)$$

$$\text{Higuchi model: } M_t/M_\infty = k_H * t^{1/2} \quad (3)$$

$$\text{Korsmeyer-peppas Model (KP) } M_t/M_\infty = k_{KP} * t^n \quad (4)$$

where M_0, M_t and M_∞ are defined as the amount of drug released at the initial time, at time t and time approaches infinity, respectively. k_0, k_H and k_{KP} are defined as kinetic constant of models. And M_t/M_∞ is the fraction of drug released at time t. For the n parameter in the KP model, it is the release exponent and allows identifying the mechanism of the first 60 % of drug release [36]. In the eq. (4), if the n value is 0.5 or less, the release mechanism follows Fickian diffusion, and high value $0.5 < n < 1$ for mass transfer follows a non-Fickian model (anomalous transport).When $n = 1$, the drug release rate corresponds to zero-order release kinetics. For the Higuchi model, it describes the drug release as a Fickian diffusion process [37]. The kinetic model that best fits the release data is evaluated by comparing the correlation coefficient (R^2) values obtained in the three models above.

These models are easy to use and the established empirical rules will help explain release mechanisms.

2.6. Statistical analysis

All of the data was obtained at least in triplicate and were expressed

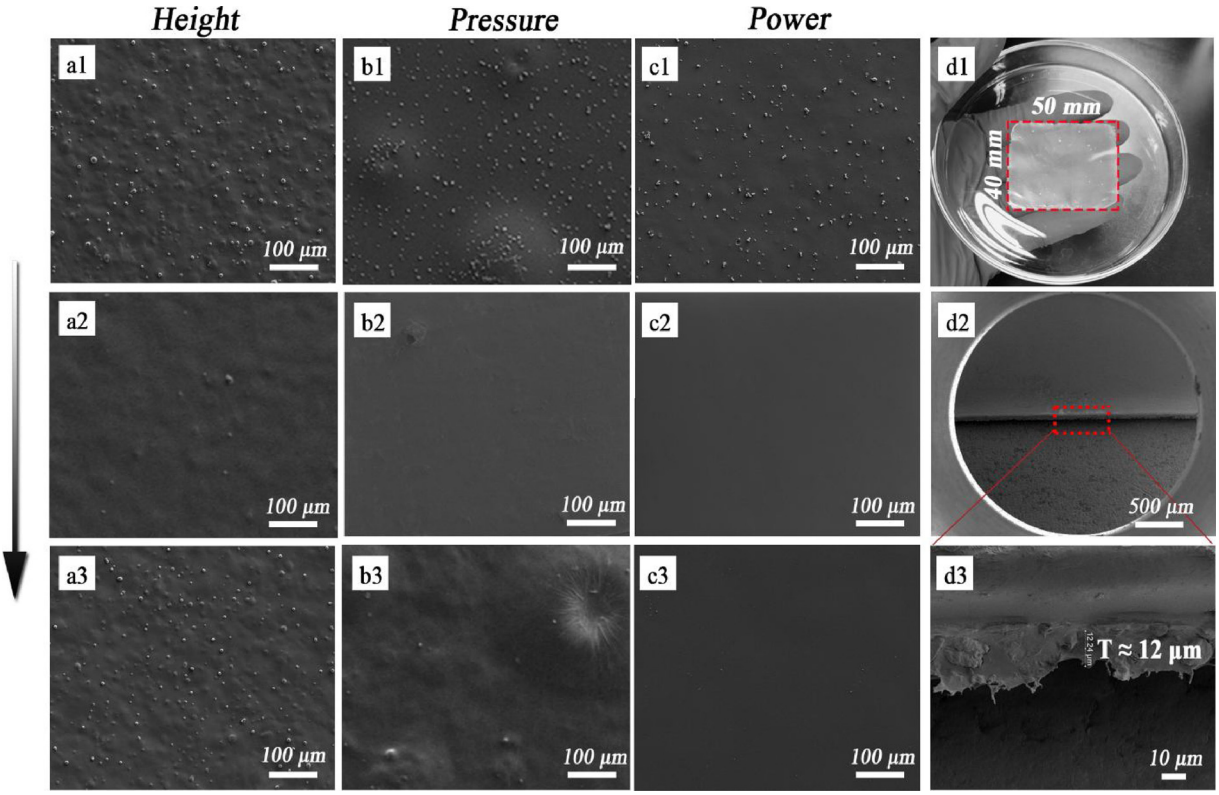


Fig. 2. The images of films morphology. By adjusting the preparation parameters: (a) height, (b) gas pressure, (c) ultrasonic power, (d) obtained film morphology and thickness.

as the mean ± standard deviation.

3. Results and discussion

3.1. Preparation and characterization of the blend films

3.1.1. Process optimization of ultrasonic spray coating

Fabrication process optimization of blend films became necessary as drug release characteristics were influenced by morphology, due to its thin configuration. So a preliminary investigation on process parameters was performed to obtain desired surface morphology. Fig. 2 shows the effect of process parameters such as height (Fig. 2a), gas pressure (Fig. 2b) and ultrasonic power (Fig. 2c) on morphology and homogeneity of blend films.

As shown in Fig. 2, before optimizing the fabrication conditions, a rough surface including granules, small pits was observed which are not recommended for a precise drug delivery system. The thin film showed a wet or dry deposition state at lower (Fig. 2a1) or higher (Fig. 2a3) height, because the drying rate of polymer solution was lower or higher than the deposition rate during the preparation process. Therefore, it is found that the surface was uniform at moderate height (Fig. 2a2) while numerous granules were observed in polymer film at lower or higher height. Similarly, lower (Fig. 2b1) or higher (Fig. 2b3) gas pressure resulted in uneven surface morphology. When the ultrasonic power was above the critical power (about 1.0 w), the surface was smooth and showed no significant morphological change with increasing ultrasonic power. These results indicated that the ultrasonic spray coating process used in this study was facile and versatile for polymer thin film fabricatetion. According to the optimized parameters, the macro material object picture of the prepared film is shown in the Fig. 2(d1), and the film size is approximately 50 mm x 40 mm. Furthermore, thickness of the film also plays a vital role in the eluting of drugs. It governs the diffusion of drug transfer within the films to the release media when exposed. Hence, it is necessary to maintain consistent thickness of films of different blend ratios in order to ensure the comparability of drug release in subsequent experiments. In the present study, all films were prepared to have a thickness of about 12 microns (Fig. 2d3) by controlling the number of spray cycles (5 times).

3.1.2. XRD and surface wettability analysis

XRD analysis was an important method to investigate the composition of the crystalline states in the films in many previous papers [38,39]. The physical states of sirolimus incorporated in the polymer films are shown in Fig. 3.

The result in Fig. 3a shows that sirolimus powder was highly crystalline and exhibited intense diffraction peaks at 7.16°, 10.14°,14.4°,16.12°,19.96° and 21.72° as also reported by Seong Min Kim et al. [12]. Meanwhile, pure PLCL and drug-loaded PLCL both showed the main diffraction peak at 16.58°, suggesting high crystallinity, while pure PDLLA films shown only amorphous halo patterns. After loading sirolimus into PDLLA or PLCL film, no diffraction peaks associated with sirolimus crystal molecules were observed, which indicated that sirolimus drug was in amorphous form in polymer films. The result is consistent with other studies about the state of hydrophobic drug such as sirolimus, paclitaxel (PTX) and progesterone in the polymeric matrix in literature. Choi et al. [40] have reported a similar result that sirolimus was amorphous in PLGA films. Zhang et al. [41] showed that crystalline progesterone turned into amorphous in the PLGA matrix. Lu et al. [10] also indicated that PTX granule existed in an amorphous state in the PVP matrix. Therefore, the explanation for XRD result is that sirolimus molecules were molecularly dispersed within the polymeric matrix and almost complete amorphization was achieved.

As shown in Fig. 3b, the XRD patterns of blend films including PDLLA and PLCL still exhibited the one characteristic peak at about 16.5° and intensity respectively decreased with the content of PDLLA, these results were also supported by the pure polymer diffraction patterns. The blue curve represented the XRD pattern of drug-free PDLLA/PLCL (70/30) blend film and its intensity was relatively highest. All

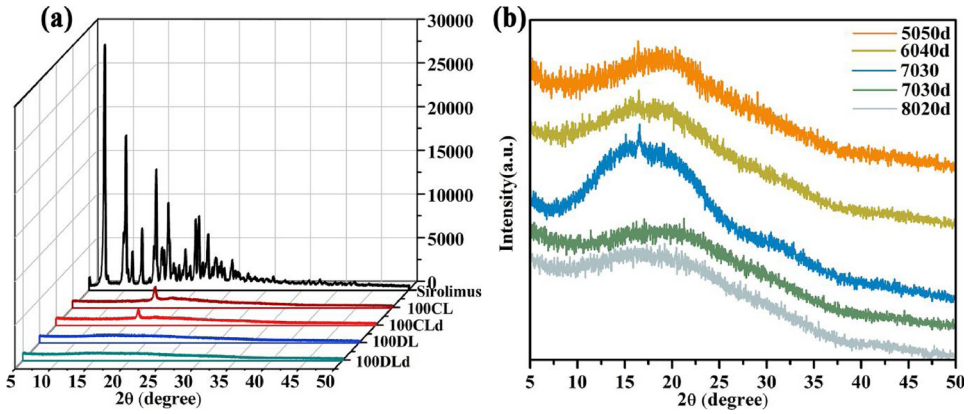


Fig. 3. X-ray diffraction patterns of (a) sirolimus powder and pure polymer films, (b) blend polymer films.

curves in Fig. 3b have shown no sirolimus diffraction peaks, which indicated sirolimus particles in blend films were amorphous.

Surface wettability, which is often characterized by the water contact angle, is determined using a sessile drop method. The water contact angle values of drug-free and drug-loaded polymer films are shown in Table 2.

Interestingly, we can see that the surface wettablity of the drug-loaded polymer films exhibits a lower value than that of the drug-free polymer films, indicating the loading of polymer films with hydrophobic sirolimus leads to more hydrophilic surface. We infer that the different surface roughness between drug-loaded film and drug-free film may affect the contact angle, and some literature also gave this explanation for the results [42]. Compared the results obtained by Xu et al., the difference in contact angles between drug-free films and drug-loaded films was relatively small in this work. Like 100 % PDLLA drug-free film (100DL), their water contact angles were 81.3° and 79.1°, respectively. Also for 100 % PLCL drug-free film (100CL), the values were 73.07° and 70.13°, respectively. This might be relative to preparation methods for films. Their group used the drop-coating method while we used ultrasonic spray technology, which may be more accurate and repeatable. But the contrast between two pure polymers, the drug-loaded PDLLA film (100DLd) was significantly more hydrophobic than the drug-loaded PLCL film (100CLd). Xu et al. [42] have reported similar results to ours. And the water contact angles of the four blend polymers decreased with the increase of PLCL content, which result was consistent with the value of pure polymer film. A more hydrophilic polymer surface may prevent non-specified protein adsorption and platelet adhesion [43]. Therefore, blending PLCL to PDLLA may have better biocompatibility than single PDLLA material.

3.1.3. Drug loading efficiency analysis

Drug-loading efficiency is a basic parameter of films. It reflects the utilization and accuracy of drug loading during the ultrasonic atomization spray-preparation process. Taking into account subsequent cumulative drug release studies of films, high and stable drug-loading efficiency is necessary. Table 2 shows the drug-loading efficiencies obtained for the six formula films using HPLC analysis. The results showed that the drug loading efficiencies of most samples were around 95 %. However, the efficiency of 5050d samples was the lowest (92.48 %), and that of 7030d samples was the highest (104 %). This phenomenon may be caused by weighing error and measurement error of chromatographic system.

3.2. In vitro release study

In order to better investigate the effect of blend ratio on sirolimus release pattern, firstly, a preliminary experiment about the cumulative release rates of sirolimus from pure PDLLA and PLCL drug-loaded films were performed for a period of 14 days.

As shown in Fig. 4, it is found that the sirolimus release behavior was completely different in the pure PDLLA and PLCL films. The sirolimus in PLCL films exhibits a trend of sustained release throughout 14 days while sirolimus was almost undetectable in pure PDLLA films after 1 day. Finally, up to 14 days, the cumulative release rate of PLCL-sirolimus films was 31.92 ± 1.24 % while that of PDLLA-sirolimus films was only 1.17 ± 0.34 %.

This result is consistent with the hypothesis that the PDLLA-sirolimus film is in a semi-glassy state while the PLCL-sirolimus film is in a rubber-like flexible state in the release medium with 37 °C. PLCL is a semi-crystalline polymer with a T_g of 22 °C while PDLLA is an amorphous polymer with a T_g of 48 °C. The PLCL backbone chain may be presumed to be in a highly flexible state with significant free volume in the PLCL-sirolimus matrix at 37 °C. The results reported by Xu et al. [42] about the release profiles of sirolimus from PDLLA and PLCL matrix were similar to ours. In their study, the cumulative percentages of released sirolimus from PDLLA and PLCL at 14 days were slightly higher, which might be related to the dipping preparation method of films. The surface of films prepared by ultrasonic spray atomization was relatively compact, which restrained the initial release of sirolimus.

To confirm that sirolimus release profiles were related to the state of PDLLA and PLCL, surface morphologies incubated in release buffer at 37 °C for a period of 0–14 days were investigated by SEM.

As shown in Fig. 5(a1) and (b1), the surface micrographs of PLCL and PDLLA are both smooth and uniform at the initial moment.

Table 2
Water contact angle of drug-free and drug-loaded polymer films, and drug loading stability.

Film formula	Drug-free film	Drug-loaded film	Drug-loading stability (%)
100 % PDLLA	81.3° ± 0.64°	79.1° ± 0.24°	95.81 ± 3.61
80%PDLLA + 20 %PLCL	80.5° ± 0.82°	77.43° ± 1.72°	101.43 ± 0.22
70%PDLLA + 30 %PLCL	80.15° ± 1.61°	76.43° ± 2.04°	104 ± 5.16
60 %PDLLA + 40 %PLCL	78.03° ± 1.05°	76.33° ± 2.40°	95.38 ± 0.22
50 %PDLLA + 50 %PLCL	77.6° ± 0.78°	72.8° ± 2.82°	92.48 ± 1.26
100 % PLCL	73.07° ± 2.37°	70.13° ± 5.76°	96.05 ± 1.62

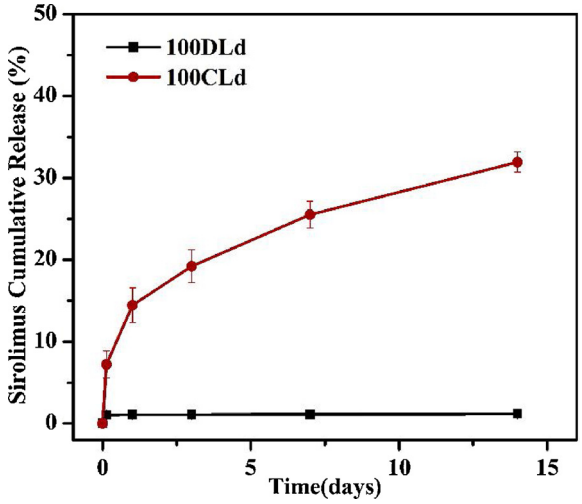


Fig. 4. *In vitro* release profiles of sirolimus from pure PDLLA and PLCL drug-loaded polymer films.

However, their surface morphologies changed and appeared different after 14 days. In Fig. 5(a2), there is no obvious change on PDLLA-sirolimus films except for rougher surface and few scattered holes, which was consistent with the little release of sirolimus in PDLLA films. In Fig. 5(b2), however, numerous micro holes were observed on the surface of the PLCL-sirolimus film. Furthermore, in order to confirm that the holes on the film were left by sirolimus release, the sizes of drug particles were characterized individually. We dissolved the sirolimus in dichloromethane, then a small amount of solution was dropped onto the silicon plate. And the silicon plate was then placed at room temperature to completely evaporate dichloromethane. The morphologies detected by SEM on the silicon plate were shown in Fig. 5(c). The size of sirolimus particles was observed about 1 μm or smaller, which matched the size of the holes.

In order to better understand the sirolimus release from PDLLA/PLCL blends, four different blend ratios were selected for research. In this paper, the cumulative release rates of sirolimus in 45 days from the films with four ratios were measured and the release results are shown in Fig. 6.

As shown in Fig. 6, the cumulative release percentage of these four samples were all released continuously and exhibited faster growth in the first 14 days period (phase I) than that in the later (phase II). Phase I is usually described as initial rapid release, which may be caused by the weak binding force of drugs on the surface of film and diffusion of drug particles from the nearer surface. Phase II is predominately governed by drug diffusion through water-filled pores on polymer matrix. Moreover, we can see that within a certain proportion, the increase in release rate was not as pronounced with increasing PLCL content. The sirolimus release curves of 8020d and 7030d samples, 6040d and 5050d samples were similar, respectively. Overall, the higher the content of PLCL in blend films, the greater the release rate of sirolimus. Mcdonald et al. [44] have reported results similar to ours whereby aspirin released from PDLLA/PCL films. This might be relative to the similar physical properties between PCL and PLCL. In the initial 1 day, with the increase of PLCL content from 20 % to 50 %, the cumulative release of sirolimus also increased continuously from 6.1 %, 8.72 %, 11.77 % and 13.82 % accordingly (Fig. 6b). This result was consistent with the decrease of water contact angle of the blend films with the increase of PLCL ratio. Water-uptake and polymer hydration occur immediately upon immersion in water or administration *in vivo* [45]. The buffer media can easily permeate into the surface of blend films with the increase of hydrophilicity [46]. This property has been found to be the process of pore-formation, leading to an increase in drug diffusion [47–49]. The sirolimus was continuously released in the release media. After 7 days, the cumulative release rates of these blend films were 19.84 %, 25.58 %, 33.1 % and 31.27 %, respectively. And by the 14th day, their cumulative release rates were about 30 % (sample: 8020d, 7030d) and 36 % (sample: 6040d, 5050d). During 14–45 days, the blend films released slowly and stably compared with the previous release and the highest release rate up to 44.16 % at 45 days. Overall the drug release period, the release curves of sirolimus showed biphase pattern and were not simple linear proportionate to the ratios of PLCL in the blend films. This result might provide us with more choices to adjust the release rate by

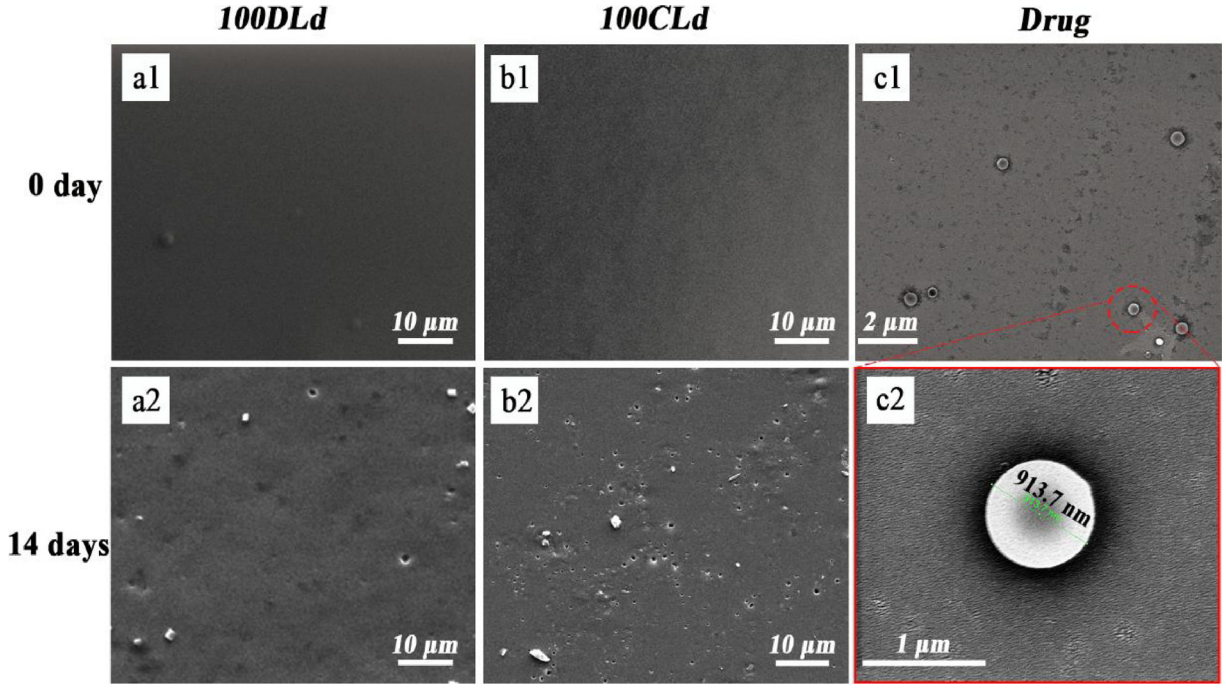


Fig. 5. Surface morphologies of (a) pure PDLLA drug-loaded films and (b) pure PLCL drug-loaded films after incubation in release media for 0 days and 14 days, respectively and (c) sirolimus particle size characterization.

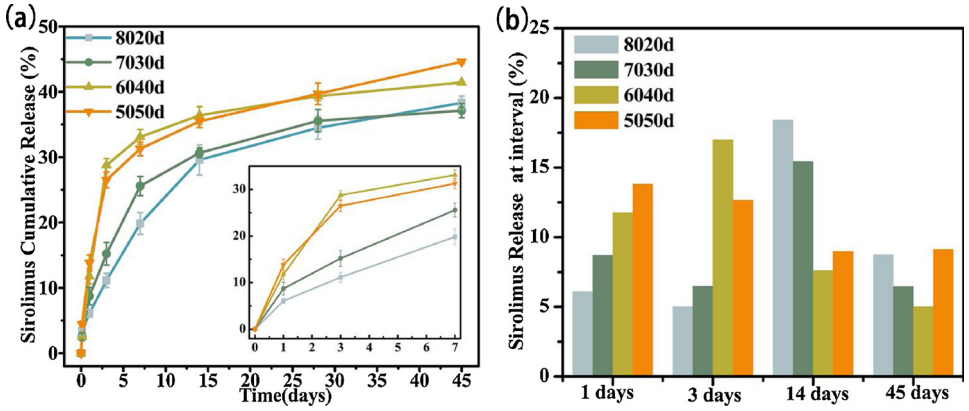


Fig. 6. (a) *In vitro* release profiles of sirolimus in PDLLA/PLCL blend drug-loaded films with different ratios, (b) sirolimus release at predetermined intervals.

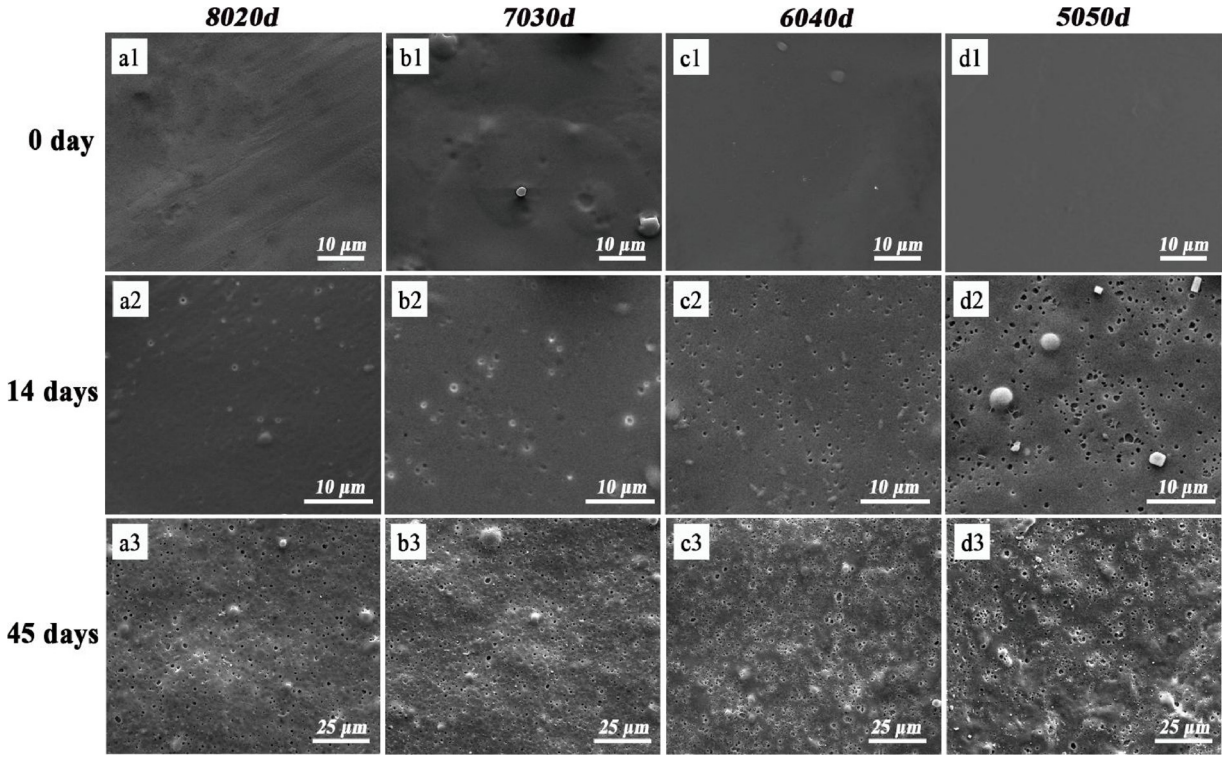


Fig. 7. Surface morphologies of PDLLA/PLCL blend films with different ratios exposed to the release medium (PBS solutions with 0.1 % Brij 58, pH = 7.4) after 0 day, 14 days and 45 days, (a) 80:20 radio, (b) 70:30 ratio, (c) 60:40 ratio and (d) 50:50 ratio.

Table 3
Parameters obtained from drug release models of blend polymer films.

Samples	Higuchi model	(0–45 days)	Korsmeyer-Peppas model	(0–45 days)		Higuchi model	Zero-order model		
						(0–14 days)	(14–45 days)		
	k_H	R^2	k_{KP}	R^2	n	k_H	R^2	k_0	R^2
8020d	6.41	0.96	8.55	0.97	0.41	–	–	–	–
7030d	6.68	0.9	11.37	0.96	0.33	–	–	–	–
6040d	7.87	0.71	16.84	0.90	0.26	11.39	0.9	0.16	0.95
5050d	8.01	0.78	16.59	0.96	0.27	11.01	0.91	0.29	1

Unit of kinetic constant k : %/day.

changing the ratio of PLCL for tunable drug release.

The surface morphologies of PDLLA/PLCL blend films before and after sirolimus release were observed by SEM.

As shown in Fig. 7, the surfaces of these films were compact and smooth before drug release (0 day). It indicated that different proportions of above materials did not particularly affect appearance. After 14 days, some holes left by sirolimus release appeared on the surfaces of all blend films. Obviously, the number of holes on the surface of blend films with 40 % or 50 % PLCL content were more than that of 20 % or 30 % PLCL content. The results were consistent with the

faster release of sirolimus from the blend films with 40 % or 50 % PLCL content. After 45 days, surfaces of the four blend films turned to be rough and uneven and were covered with a large number of holes. There was no obvious difference except that the surface of films with 40 % or 50 % PLCL content had more surface erosions. The phenomenon about surface erosions was also observed by Raval et al. [50] on the PLCL/PVP coating. This indicated that at 45 days PLCL might have begun to degrade.

3.3. Analysis of release kinetics and mechanisms

The purpose of mathematical model of drug release is to predict drug release rates and diffusion behavior from the delivery systems. In this study, the experimental data were analyzed and fitted on three common theoretical models to understand the underlying release mechanisms. The fitting results are shown in Table 3.

For the drug release profiles of the blend films with PLCL content of 20 % and 30 % (8020d, 7030d), their fitting degrees obtained from Higuchi and Korsmeyer-Peppas model were higher than 0.9. This results suggested that drug release mechanisms from the above two blend films belonged to Fickian diffusion.

For drug release profiles from blend films with PLCL content of 40 % and 50 % (6040d, 5050d), the Higuchi model did not show good fitting degree, yielding the R^2 values of 0.71 and 0.78, respectively. In addition, although the corresponding plot of Korsmeyer-Peppas model yielded comparatively good fitting degree, the values of n were much smaller than 0.5. This may be related to other driving forces of drug release. In order to further analyze the release mechanism of sirolimus in the two blend films (6040d, 5050d), the piecewise fitting was carried out. As shown in Table 3, during the first 14 days, R^2 values obtained by Higuchi model fitting were 0.9 and 0.91, respectively, which indicated that the release mechanism was diffusion-based release. During the following 14–45 days, the release was linearly fitted by the Zero-order model, with the release constant k of 0.16 % and 0.29 %/day, respectively. As a preliminary result, the drug release mechanism of the two blend films (6040d, 5050d) was Fickian diffusion in the early stage and Zero-order release in the late stage. This result was consistent with the surface characterization in Fig. 7(c3), (d3) where surface erosion was found in films with 40 % or 50 % PLCL content. These results provided us with potential options to design drug delivery systems with different release mechanisms by blending PDLLA and PLCL. For example, on the drug-eluting coating, antiproliferative drug is required a fast release in the early state and follows by a slow release for more than a month [51]. Under these circumstances, blend films of 5050d or 6040d formulation may be more suitable and recommended.

4. Conclusion

In this study, the *in vitro* release profiles of sirolimus from PDLLA/PLCL blend films with different ratios were investigated. The morphologies of blend films were uniform with low roughness under optimizing process parameters. It is found that sirolimus release from blend films showed biphasic release pattern: the initial rapid release (phase I) and stable release (phase II) and modulation of drug release can be achieved by altering the ratio of PLCL to PDLLA. Moreover, the release rate of sirolimus was not a simple linear proportional relationship to the ratio of PLCL. In this work, three mathematical models were selected to describe the obtained release data, indicating that different mechanisms may be involved in drug release and the main one was the diffusion. This work could provide a feasible way to tunable release profiles for hydrophobic drug and might contribute to the design of drug delivery systems such as drug-eluting stents.

CRediT authorship contribution statement

Fengqin Li: Investigation, Formal analysis, Data curation, Visualization, Writing - original draft. **Xin Li:** Investigation, Formal analysis. **Rongxin He:** Investigation. **Jie Cheng:** Conceptualization, Supervision, Validation. **Zhonghua Ni:** Conceptualization, Funding acquisition, Supervision. **Gutian Zhao:** Conceptualization, Methodology, Writing - review & editing, Funding acquisition, Supervision.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China [grant number 51775107] and Postgraduate Research & Practice Innovation Program of Jiangsu Province [grant number 3202009703].

References

[1] M. Bernard, E. Jubeli, M.D. Pungente, N. Yagoubi, Biocompatibility of polymer-based biomaterials and medical devices - regulations, in vitro screening and risk-management, Biomater. Sci. 6 (2018) 2015–2053, https://doi.org/10.1039/c8bm00518d.
[2] P. Davoodi, L.Y. Lee, Q. Xu, V. Sunil, Y. Sun, S. Soh, C.-H. Wang, Drug delivery systems for programmed and on-demand release, Adv. Drug Deliv. Rev. 132 (2018) 104–138, https://doi.org/10.1016/j.addr.2018.07.002.
[3] N. Kamaly, B. Yameen, J. Wu, O.C. Farokhzad, Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release, Chem. Rev. 116 (2016) 2602–2663, https://doi.org/10.1021/acs.chemrev.5b00346.
[4] X. Qi, Y.W. Ren, X. Wang, New advances in the biodegradation of poly(lactic) acid, Int. Biodeterior. Biodegrad. 117 (2017) 215–223, https://doi.org/10.1016/j.ibiod.2017.01.010.
[5] U. Sharma, D. Concagh, L. Core, Y. Kuang, C. You, Q. Pham, G. Zugates, R. Busold, S. Webber, J. Merlo, R. Langer, G.M. Whitesides, M. Palasis, The development of bioresorbable composite polymeric implants with high mechanical strength, Nat. Mater. 17 (2018) 96–103, https://doi.org/10.1038/nmat5016.
[6] J.-M. Lü, X.W. Wang, C. Marin-Muller, H. Wang, P.H. Lin, Q.Z. Yao, C.Y. Chen, Current advances in research and clinical applications of PLGA-based nanotechnology, Expert Rev. Mol. Diagn. 9 (2009) 325–341, https://doi.org/10.1586/erm.09.15.
[7] A. Peer, R. Dhakal, R. Biswas, J. Kim, Nanoscale patterning of biopolymers for functional biosurfaces and controlled drug release, Nanoscale 8 (2016) 18654–18664, https://doi.org/10.1039/c6nr05197a.
[8] H. Gasmi, F. Siepmann, M.C. Hamoudi, F. Danede, J. Verin, J.F. Willart, J. Siepmann, Towards a better understanding of the different release phases from PLGA microparticles: dexamethasone-loaded systems, Int. J. Pharm. 514 (2016) 189–199, https://doi.org/10.1016/j.ijpharm.2016.08.032.
[9] Y.Q. Kang, G.F. Yin, P. Ouyang, Z.B. Huang, Y.D. Yao, X.M. Liao, A.Z. Chen, X.M. Pu, Preparation of PLLA/PLGA microparticles using solution enhanced dispersion by supercritical fluids (SEDS), J. Colloid Interface Sci. 322 (2008) 87–94, https://doi.org/10.1016/j.jcis.2008.02.031.
[10] F. Lu, Y.Y. Shen, Y.Q. Shen, J.W. Hou, Z.M. Wang, S.R. Guo, Treatments of paclitaxel with poly(vinyl pyrrolidone) to improve drug release from poly(varepsilon-caprolactone) matrix for film-based stent, Int. J. Pharm. 434 (2012) 161–168, https://doi.org/10.1016/j.ijpharm.2012.05.043.
[11] G. Vergnol, H. Sow, E. Renard, F. Haroun, V. Langlois, Multilayer approach for tuning the drug delivery from poly(3-hydroxyalkanaoate)s coatings, React. Funct. Polym. 72 (2012) 260–267, https://doi.org/10.1016/j.reactfunctpolym.2012.02.004.
[12] S.M. Kim, S.B. Park, T.M. Bedair, M.H. Kim, B.J. Park, Y.K. Joung, D.K. Han, The effect of solvents and hydrophilic additive on stable coating and controllable sirolimus release system for drug-eluting stent, Mater. Sci. Eng. C Mater. Biol. Appl. 78 (2017) 39–46, https://doi.org/10.1016/j.msec.2017.04.024.
[13] L. Navarro, D.E. Mogosanu, N. Ceaglio, J. Luna, P. Dubruel, I. Rintoul, Novel poly (diol sebacate)s as additives to modify paclitaxel release from poly(lactic-co-glycolic acid) thin films, J. Pharm. Sci. 106 (2017) 2106–2114, https://doi.org/10.1016/j.xphs.2017.05.012.
[14] S. Petisco-Ferrero, A. Etxeberria, J.R. Sarasua, Mechanical properties and state of miscibility in poly(racD,L-lactide-co-glycolide)/(L-lactide-co-epsilon-caprolactone) blends, J. Mech. Behav. Biomed. Mater. 71 (2017) 372–382, https://doi.org/10.1016/j.jmbbm.2017.04.003.
[15] H.B. Zhao, G.Q. Zhao, Mechanical and thermal properties of conventional and microcellular injection molded poly (lactic acid)/poly (epsilon-caprolactone) blends, J. Mech. Behav. Biomed. Mater. 53 (2016) 59–67, https://doi.org/10.1016/j.jmbbm.2015.08.002.
[16] Q. Ding, Z. Li, Y. Yang, G. Guo, F. Luo, Z. Chen, Y. Yang, Z. Qian, S. Shi, Preparation and therapeutic application of docetaxel-loaded poly(d,l-lactide) nanofibers in preventing breast cancer recurrence, Drug Deliv. 23 (2016) 2677–2685, https://doi.

org/10.3109/10717544.2015.1048490.
[17] T.M. Bedair, S.J. Yu, S.G. Im, B.J. Park, Y.K. Joung, D.K. Han, Effects of interfacial layer wettability and thickness on the coating morphology and sirolimus release for drug-eluting stent, J. Colloid Interface Sci. 460 (2015) 189–199, https://doi.org/10.1016/j.jcis.2015.08.051.
[18] M. Dzikowski, N. Castanie, A. Guedon, B. Verrier, C. Primard, J. Sohier, Antibiotic incorporation in jet-sprayed nanofibrillar biodegradable scaffolds for wound healing, Int. J. Pharm. 532 (2017) 802–812, https://doi.org/10.1016/j.ijpharm.2017.08.117.
[19] S.K. Yazdani, M. Vorpahl, M. Nakano, S.-H. Su, F.D. Kolodgie, R. Virmani, In vitro and in vivo characterisation of biodegradable polymer-based drug-eluting stent, EuroIntervention 7 (2011) 835–843, https://doi.org/10.4244/EIJV7I7A131.
[20] J. Esmaeilzadeh, S. Hesaraki, S.M. Hadavi, M. Esfandeh, M.H. Ebrahimzadeh, Microstructure and mechanical properties of biodegradable poly (D/L) lactic acid/polycaprolactone blends processed from the solvent-evaporation technique, Mater. Sci. Eng. C Mater. Biol. Appl. 71 (2017) 807–819, https://doi.org/10.1016/j.msec.2016.10.070.
[21] H.Y. Ang, J. Chan, D. Toong, S.S. Venkatraman, S.J. Chia, Y.Y. Huang, Tailoring the mechanical and biodegradable properties of binary blends of biomedical thermoplastic elastomer, J. Mech. Behav. Biomed. Mater. 79 (2018) 64–72, https://doi.org/10.1016/j.jmbbm.2017.12.013.
[22] J.M. Ugartemendia, A. Larrañaga, H. Amestoy, A. Etxeberria, J.R. Sarasua, Tougher biodegradable polylactide system for bone fracture fixations: miscibility study, phase morphology and mechanical properties, Eur. Polym. J. 98 (2018) 411–419, https://doi.org/10.1016/j.eurpolymj.2017.11.040.
[23] G.G. Camici, J. Steffel, I. Amanovic, A. Breitenstein, J. Baldinger, S. Keller, T.F. Luscher, F.C. Tanner, Rapamycin promotes arterial thrombosis in vivo: implications for everolimus and zotarolimus eluting stents, Eur. Heart J. 31 (2010) 236–242, https://doi.org/10.1093/eurheartj/ehp259.
[24] S.N. Kang, S.-E. Kim, J. Choi, K. Park, J.H. Goo, D.S. Sim, Y.J. Hong, J.H. Kim, Y.K. Joung, J. Lee, M.H. Jeong, D.K. Han, Comparison of phytoncide with sirolimus as a novel drug candidate for drug-eluting stent, Biomaterials 44 (2015) 1–10, https://doi.org/10.1016/j.biomaterials.2014.12.015.
[25] E. Albarahmieh, M. Albarahmieh, B.A. Alkhalidi, Fabrication of hierarchical polymeric thin films by spin coating toward production of amorphous solid dispersion for buccal drug delivery system: preparation, characterization, and in vitro release investigations, J. Pharm. Sci. 107 (2018) 3112–3122, https://doi.org/10.1016/j.xphs.2018.08.019.
[26] T. Nardo, V. Chiono, P. Gentile, M. Tabrizian, G. Ciardelli, Poly(DL-lactide-co-ε-caprolactone) and poly(DL-lactide-co-glycolide) blends for biomedical application: physical properties, cell compatibility, andin vitrodegradation behavior, Int. J. Polym. Mater. 65 (2016) 741–750, https://doi.org/10.1080/00914037.2016.1163566.
[27] A.Q. Low, J. Parmentier, Y.M. Khong, C.C. Chai, T.Y. Tun, J.E. Berania, X. Liu, R. Gokhale, S.Y. Chan, Effect of type and ratio of solubilising polymer on characteristics of hot-melt extruded orodispersible films, Int. J. Pharm. 455 (2013) 138–147, https://doi.org/10.1016/j.ijpharm.2013.07.046.
[28] H.S. Liu, W.C. Chang, C.Y. Chou, B.C. Pan, Y.S. Chou, G.S. Liou, C.L. Liu, Controllable electrochromic polyamide film and device produced by facile ultrasonic spray-coating, Sci. Rep. 7 (2017) 11982, https://doi.org/10.1038/s41598-017-11862-1.
[29] S.S. Keller, L. Gammelgaard, M.P. Jensen, S. Schmid, Z.J. Davis, A. Boisen, Deposition of biopolymer films on micromechanical sensors, Microelectron. Eng. 88 (2011) 2297–2299, https://doi.org/10.1016/j.mee.2011.02.093.
[30] M.G. McGrath, A. Vrdoljak, C. O'Mahony, J.C. Oliveira, A.C. Moore, A.M. Crean, Determination of parameters for successful spray coating of silicon microneedle arrays, Int. J. Pharm. 415 (2011) 140–149, https://doi.org/10.1016/j.ijpharm.2011.05.064.
[31] S. Bose, S.S. Keller, T.S. Alstrom, A. Boisen, K. Almdal, Process optimization of ultrasonic spray coating of polymer films, Langmuir 29 (2013) 6911–6919, https://doi.org/10.1021/la4010246.
[32] R.W. Sirianni, E.H. Jang, K.M. Miller, W.M. Saltzman, Parameter estimation methodology in a model of hydrophobic drug release from a polymer coating, J. Control. Release 142 (2010) 474–482, https://doi.org/10.1016/j.jconrel.2009.11.021.
[33] N. Ojah, D. Saikia, D. Gogoi, P. Baishya, G.A. Ahmed, A. Ramteke, A.J. Choudhury, Surface modification of core-shell silk/PVA nanofibers by oxygen dielectric barrier discharge plasma: studies of physico-chemical properties and drug release behavior, Appl. Surf. Sci. 475 (2019) 219–229, https://doi.org/10.1016/j.apsusc.2018.12.270.
[34] T.M. Bedair, Y. Cho, T.J. Kim, Y.D. Kim, B.J. Park, Y.K. Joung, D.K. Han, Reinforcement of interfacial adhesion of a coated polymer layer on a cobalt-chromium surface for drug-eluting stents, Langmuir 30 (2014) 8020–8028, https://doi.org/10.1021/la501990p.
[35] B. Song, S. Xu, S. Shi, P. Jia, Q. Xu, G. Hu, H. Zhang, C. Wang, Superhydrophobic coating to delay drug release from drug-loaded electrospun fibrous materials, Appl. Surf. Sci. 359 (2015) 245–251, https://doi.org/10.1016/j.apsusc.2015.10.085.
[36] R.W. Korsmeyer, R. Gurny, E.M. Doelker, P. Buri, N.A. Peppas, Mechanism of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1983) 25–35, https://doi.org/10.1016/0378-5173(83)90064-9.
[37] T. Higuchi, Rate of release of medicaments from ointment bases containing drugs in suspension, J. Pharm. Sci. 50 (1961) 874–875, https://doi.org/10.1002/jps.2600501018.
[38] M.L. Ho, Y.C. Fu, G.J. Wang, H.T. Chen, J.K. Chang, T.H. Tsai, C.K. Wang, Controlled release carrier of BSA made by W/O/W emulsion method containing PLGA and hydroxyapatite, J. Control. Release 128 (2008) 142–148, https://doi.org/10.1016/j.jconrel.2008.02.012.
[39] Q. Xu, J.T. Czernuszka, Controlled release of amoxicillin from hydroxyapatite-coated poly(lactic-co-glycolic acid) microspheres, J. Control. Release 127 (2008) 146–153, https://doi.org/10.1016/j.jconrel.2008.01.017.
[40] J. Choi, B.N. Jang, B.J. Park, Y.K. Joung, D.K. Han, Effect of solvent on drug release and a spray-coated matrix of a sirolimus-eluting stent coated with poly(lactic-co-glycolic acid), Langmuir 30 (2014) 10098–10106, https://doi.org/10.1021/la500452h.
[41] Y. Zhang, T. Shams, A.H. Harker, M. Parhizkar, M. Edirisinghe, Effect of copolymer composition on particle morphology and release behavior in vitro using progesterone, Mater. Des. 159 (2018) 57–67, https://doi.org/10.1016/j.matdes.2018.08.024.
[42] W. Xu, K. Yagoshi, Y. Koga, M. Sasaki, T. Niidome, Optimized polymer coating for magnesium alloy-based bioresorbable scaffolds for long-lasting drug release and corrosion resistance, Colloids Surf. B Biointerfaces 163 (2018) 100–106, https://doi.org/10.1016/j.colsurfb.2017.12.032.
[43] B.K.D. Ngo, M.A. Grunlan, Protein resistant polymeric biomaterials, ACS Macro Lett. 6 (2017) 992–1000, https://doi.org/10.1021/acsmacrolett.7b00448.
[44] P.F. McDonald, J.G. Lyons, L.M. Geever, C.L. Higginbotham, In vitro degradation and drug release from polymer blends based on poly(dl-lactide), poly(l-lactide-glycolide) and poly(ε-caprolactone), JMatS 45 (2009) 1284–1292, https://doi.org/10.1007/s10853-009-4080-9.
[45] M. Zilberman, O. Grinberg, HRP-loaded bioresorbable microspheres: effect of co-polymer composition and molecular weight on microstructure and release profile, J. Biomater. Appl. 22 (2008) 391–407, https://doi.org/10.1177/0885328207077591.
[46] C. Wischke, S.P. Schwendeman, Principles of encapsulating hydrophobic drugs in PLA/PLGA microparticles, Int. J. Pharm. 364 (2008) 298–327, https://doi.org/10.1016/j.ijpharm.2008.04.042.
[47] A. Mochizuki, T. Niikawa, I. Omura, S. Yamashita, Controlled release of argatroban from PLA film—effect of hydroxylesters as additives on enhancement of drug release, J. Appl. Polym. Sci. 108 (2008) 3353–3360, https://doi.org/10.1002/app.27970.
[48] Z. Chu, Q. Zheng, M. Guo, J. Yao, P. Xu, W. Feng, Y. Hou, G. Zhou, L. Wang, X. Li, Y. Fan, The effect of fluid shear stress on the in vitro degradation of poly(lactide-co-glycolide) acid membranes, J. Biomed. Mater. Res. A. 104 (2016) 2315–2324, https://doi.org/10.1002/jbm.a.35766.
[49] Q. Zheng, Z. Chu, X. Li, H. Kang, X. Yang, Y. Fan, The effect of fluid shear stress on the in vitro release kinetics of sirolimus from PLGA films, Polymers 9 (2017), https://doi.org/10.3390/polym9110618.
[50] A. Raval, J. Parikh, C. Engineer, Mechanism and in vitro release kinetic study of sirolimus from a biodegradable polymeric matrix coated cardiovascular stent, Ind. Eng. Chem. Res. 50 (2011) 9539–9549, https://doi.org/10.1021/ie102163z.
[51] T. Hu, J. Yang, K. Cui, Q. Rao, T. Yin, L. Tan, Y. Zhang, Z. Li, G. Wang, Controlled slow-release drug-eluting stents for the prevention of coronary restenosis: recent progress and future prospects, ACS Appl. Mater. Interfaces 7 (2015) 11695–11712, https://doi.org/10.1021/acsami.5b01993.