



Thin films of polymer blends deposited by matrix-assisted pulsed laser evaporation: Effects of blending ratios

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ABSTRACT

In this work, we show successful use of matrix-assisted pulsed laser evaporation (MAPLE) for obtaining thin films of PEG:PLGA blends, in the view of their use for controlled drug delivery. In particular, we investigate the influence of the blending ratios on the characteristics of the films. We show that the roughness of the polymeric films is affected by the ratio of each polymer within the blend. In addition, we perform Fourier transformed infrared spectroscopy (FTIR) measurements and we find that the intensities ratios of the infrared absorption bands of the two polymers are consistent with the blending ratios. Finally, we assess the optical constants of the polymeric films by spectroscopic ellipsometry (SE). We point out that the blending ratios exert an influence on the optical characteristics of the films and we validate the SE results by atomic force microscopy and UV–vis spectrophotometry. In all, we stress that the ratios in which the two polymers are blended have significant impact on the morphology, chemical structure and optical characteristics of the polymeric films deposited by MAPLE.

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1. Introduction

Within the last years, significant advances have been made in the controlled delivery of therapeutic agents/drugs, especially when traditional delivery methods (e.g. oral tablets or injectable doses) have shown poor therapeutic efficiency [1,2]. At first, reservoir-type implants, consisting of non-biodegradable polymer membranes surrounding a drug core, have shown good performances. However, a major drawback for these systems is that additional surgical procedures are required for removing the implants after the drug delivery is completed. To overcome this limitation, recent progresses have been made in the development of biodegradable implants capable to deliver drugs in a controlled manner [3 and references therein]. As a result, since the biodegradable polymers are easily absorbed within the body by natural metabolic processes, the subsequent removal of the implant is no longer required [4–7].

Furthermore, recent studies have shown that the performances of the polymers used for controlled drug delivery are much improved by blending [8,9]. A major advantage is that the characteristics of the polymeric matrix can be modified without altering the chemical structure of the component polymers. The most attractive feature for controlled drug delivery is that the polymer

blends degrade differently and exhibit different drug release properties than single polymers, offering the possibility of a fine tuning of the drug release rates function of blend composition [9]. Due to this significant advantage, various polymer blends have been successfully used in controlled drug delivery [10,11].

Depending on the site of implantation and on the therapeutic purposes, the drug delivery devices have been developed in a variety of shapes (rods, pellets, nanoparticles). Particularly interesting are the devices in the shape of films. In this case, the drug delivery system usually consists of a drug core covered by a polymeric film that acts like a membrane and controls the drug delivery rates. For fabricating the films, various methods like molding, drop casting, spin coating, have been used [12,13]. For achieving full control over the properties of the films and for preserving the chemical structure of the polymers, novel fabrication procedures had to be developed. Lately, an attractive technique called matrix assisted pulsed laser evaporation (MAPLE) has been intensively used for obtaining thin polymer films [14]. It is generally accepted that MAPLE exhibits significant advantages compared to other fabrication techniques: it is inexpensive, easy-to-operate and, most importantly, preserves the chemical integrity and the functionality of the polymers. [15,16]. Although MAPLE has been extensively used for deposition of films of various polymeric materials, most studies have been dedicated to the case of individual polymers. We have recently shown the first successful use of MAPLE for obtaining films of polymer blends [17], with promising results for controlled drug delivery applications.

Besides obtaining the polymeric films by MAPLE, other prerequisites must be fulfilled for their safe utilization in real applications.

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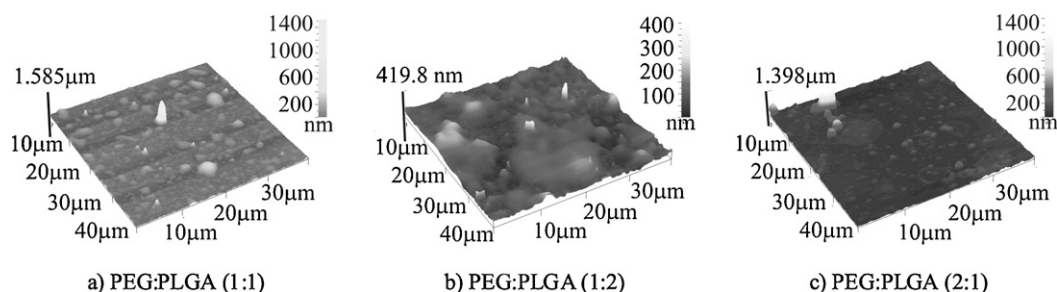


Fig. 1. AFM images ($40 \mu\text{m} \times 40 \mu\text{m}$ areas) of PEG:PLGA films, with the indicated blending ratios.

A critical requirement for efficient therapeutic procedures is a fine tuning of the drug delivery rates. As we mentioned earlier, a decisive factor for the dynamics of drugs release is represented by the blending ratio. Therefore, in this work we extend our initial study [17], reporting MAPLE deposition of polymer blends with various blending ratios.

On the other hand, in controlled drug delivery systems that contain polymers, the drug delivery rates are mainly determined by the dynamics of polymer degradation. Studies have shown that the degradation behavior of polymers is closely related to polymer structure and properties. For example, the pores and channels observed on the surfaces of certain polymeric films are considered to represent transport pathways of the drug through the polymer matrix. Therefore, the morphology of the polymeric films critically impacts their performances for controlled drug delivery applications. In addition, specific functional groups in polymers are known to be directly involved in polymer degradation, playing thus a significant role in the dynamics of drug release. In consequence, the chemical structure of the polymers strongly influences the drug release kinetics. Furthermore, in specific applications (e.g. for intraocular use) the optical constants of the polymeric films (refractive indices, extinction coefficients) directly affect the quality of the eyesight. Hence one can consider that the optical properties of the polymeric films are equally important for the quality of the drug delivery implants. In all, a complete elucidation of the properties of the polymeric films is essential for achieving the desired drug delivery rates, as well as for other specific requirements.

Based on the above considerations, in this work the influence of the blending ratios on the characteristics of MAPLE deposited films of polymer blends will be studied. To meet this objective, we will investigate the morphology of the films, the chemical structure of the polymers within the blends and we will assess the optical properties of the films. Based on these experimental results, we aim to establish a framework for the composition of the polymer blends, which will allow a refined tuning of the drug delivery rates, as well as of other functional implications.

2. Experimental

The polymers (polyethylene glycol PEG (1450 Da), poly (lactide-co-glycolide) PLGA ((40–75) kDa)) (Sigma–Aldrich) were individually dissolved in chloroform, in 1% wt polymer concentration. The two solutions were mixed together at room temperature in PEG:PLGA blending ratios of (1:1), (1:2) and (2:1), then stirred continuously for few hours. For MAPLE deposition, solutions of solvent/polymers were frozen in liquid nitrogen, placed in a vacuum chamber and submitted to laser irradiation. Film deposition was carried out with a Nd:YAG laser working at 266 nm and 10 Hz pulse repetition rate. For irradiating the target, 18000 pulses were used, the size of the laser spot reaching the target being $\sim 1 \text{ mm}^2$. We have previously shown [17] that the quality of the films is much reduced when MAPLE deposition is performed at fluences above 1 J/cm^2 .

Therefore, in the present study, MAPLE deposition of the polymeric films was performed at much lower fluence (200 mJ/cm^2). During laser irradiation, the polymer molecules were collected on a substrate in the form of a thin film, while the volatile solvent was pumped away. The substrates (glass slides, Si wafers and quartz plates) were placed at 4.5 cm, parallel with the target. The so-called “native” samples were prepared by drop casting and used as reference samples.

The morphology of the films was studied with an XE-100 atomic force microscopy (AFM) system. The chemical structure of the polymers within the blends was investigated by Fourier transformed infrared spectroscopy (FTIR). The optical characterization of the films was assessed with a Woollam variable angle spectroscopic ellipsometer system (WVASE).

3. Results and discussions

First, detailed morphological investigations of the MAPLE deposited films were performed. The AFM images of films of polymer blends with different blending ratios are illustrated in Fig. 1. For each film, several different areas of $40 \mu\text{m} \times 40 \mu\text{m}$ were investigated, no dependence of surface roughness on the scanned area being observed. For all blending ratios, the films surfaces are continuous and reasonably smooth. In addition, the surface morphology depends on the blending ratios, smoother films being obtained for blends with higher content of PEG. Indeed, the root mean square roughness (RMS) for (2:1) PEG:PLGA blending ratio was found to be quite low (34.6 nm). In contrast, higher amount of PLGA ((1:2) PEG:PLGA blending ratio) results in increased surface structuring, with RMS up to 87.9 nm. For (1:1) PEG:PLGA blending ratio, RMS roughness was about 51 nm.

Furthermore, the changes at the level of chemical bonds were investigated by FTIR. For all blending ratios, all the spectral features are equally present in the MAPLE deposited films and in the native samples, with similar intensity ratios (Fig. 2a–c). This indicates that MAPLE did not damage the structural composition of the polymer blends. Assignments of the infrared absorption bands of PEG:PLGA blends specified in Table 1 are accordingly to [18–20]. We also found that, for all blending ratios, all absorption bands of the component polymers are well reproduced in the FTIR spectra of the blends, demonstrating that both polymers within the blends keep their chemical structure. Another interesting finding is that MAPLE does not seem to induce chemical interactions between the two polymers, since all infrared absorption bands of the polymer blends belong to one of the component polymers, no additional features being observed.

Next, the influence of the blending ratios on the infrared absorption bands of the polymer blends was investigated by FTIR measurements. To this end, we calculated the intensities ratios of two infrared absorption bands: the band at 1100 cm^{-1} (assigned to C–O–C stretching vibration in PEG [18] and the band at 1762 cm^{-1} (attributed to the C=O stretch in PLGA [19,20]). Fig. 2d shows

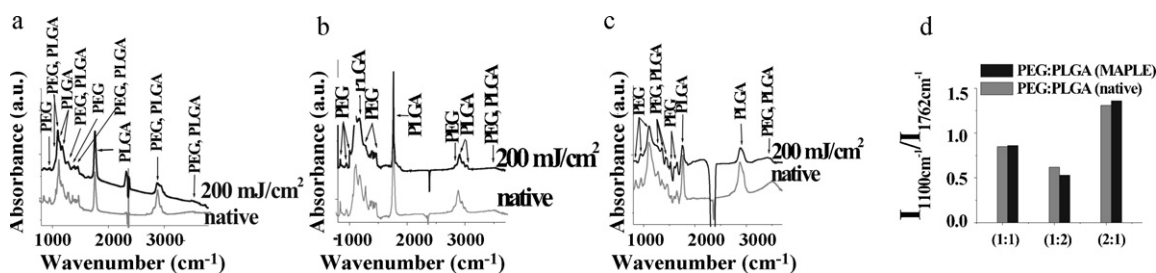


Fig. 2. FTIR spectra of PEG:PLGA films, with blending ratios: (a) 1:1; (b) 1:2; (c) 2:1. For comparison, FTIR spectra of native polymers are shown. (d) $I_{1100\text{cm}^{-1}}/I_{1762\text{cm}^{-1}}$ intensities ratios, as determined from the FTIR spectra of MAPLE deposited films and of native samples.

a good match between the FTIR spectra of the polymer blends and the blending ratios. More specifically, the intensities ratios $I_{1100\text{cm}^{-1}}/I_{1762\text{cm}^{-1}}$ follow the same trends as the blending ratios. In addition, the intensities ratios $I_{1100\text{cm}^{-1}}/I_{1762\text{cm}^{-1}}$ are similar for MAPLE deposited films and for the native samples, confirming the perfect resemblance between the chemical structures of the MAPLE deposited films and of the native samples.

Studies have stressed that particular attention must be addressed to the use of chloroform as solvent in MAPLE, since it often results in reactive species following UV irradiation. Formation of reactive species is accompanied by modifications of the FTIR spectra of MAPLE deposited films in respect to the native samples [21]. In our initial report [17], we have carefully checked if, in our experimental conditions, both polymers are safely transferred by MAPLE. We have shown that the spectra of MAPLE deposited films were identical with the native, for PEG as well as for PLGA, as long as the fluence was kept below 1 J/cm^2 . Consequently, in the present work, very low fluences were used (200 mJ/cm^2), ensuring that both polymers preserve their chemical structure. In the FTIR spectra of MAPLE deposited films (Fig. 2), all bands belong to the component polymers of the blend; no other infrared absorption bands, that could be associated with alteration of the chemical structure of the polymers by reactive species deriving from chloroform, were observed. Therefore, even if reactive species might be produced, these do not seem to affect the chemical structure/functionality of our polymers.

Finally, we completed our study by investigating the optical characteristics of MAPLE deposited films. It is already established that spectroscopic ellipsometry (SE) is a suited technique for measuring the optical constants of the materials [22]. However, until present, very few data are reported on the optical characterization of polymer thin films using SE. In this work, we show successful use of SE for determining the optical constants of our MAPLE deposited

films. Measurements were performed in the (300–800) nm spectral range, at angles of incidence 60° and 70° . The optical model consisted of 4 layers: a Si substrate, a SiO_2 layer, a polymer layer and a rough top layer. The latter takes into account the roughness of the surfaces, being composed by polymeric material and air [23]. The values for the bulk dielectric functions of Si and SiO_2 substrates were obtained from literature [22].

For determining the optical properties and the thickness of the films, a standard fitting procedure, consisting of two steps, was performed. In the first step, the experimental data were fitted in the (600–800) nm spectral range. In this range the films are non-absorbing, as indicated by ultraviolet-visible (UV-vis) spectrophotometry; in consequence, the Cauchy model was used for the fit [24]. From the fitting, the films thicknesses (h_{SE}) were obtained (Table 2).

Subsequently, the thicknesses were fixed to the h_{SE} values from Table 2 and the fitting was extended to the whole measured spectral range. As a result, the preliminary optical constants were obtained. Next, for obtaining the final values of the optical constants of the films (refractive indices and extinction coefficients), a second step was performed. The whole measured spectral range was fitted with oscillators, using the thicknesses and the preliminary optical constants determined in the first step. We tried different fitting procedures, the best fit being obtained with two Gaussian oscillators. This is probably due to the fact that our films consist of two different materials/polymers.

For a Gaussian oscillator, the real part (ε_1) and the imaginary part (ε_2) of the dielectric function ($\varepsilon = \varepsilon_1 + i\varepsilon_2$) are given by [25]:

$$\varepsilon_1 = \frac{2}{\pi} P \int_0^\infty \frac{\xi \varepsilon_2(\xi)}{\xi^2 - E^2} d\xi \quad (1)$$

$$\varepsilon_2 = A_n e^{-(E-E_n/\sigma)^2} - A_n e^{-(E+E_n/\sigma)^2} \text{ with } \sigma = \frac{B_{rn}}{2\sqrt{\ln(2)}} \quad (2)$$

where A_n is the amplitude, E_n is the position of the oscillation, B_{rn} is the broadening, ξ is the photon energy and P is the Cauchy principal value [23]. This type of oscillator produces a Gaussian line shape in ε_2 with a Kramers–Kronig consistent line shape for ε_1 . The total real part of dielectric functions is the complete analytical solution to the Kramers–Kronig integral.

$$\varepsilon_1 = \varepsilon_\infty + \frac{2}{\pi} P \int_0^\infty \frac{\xi \varepsilon_2(\xi)}{\xi^2 - E^2} d\xi \quad (3)$$

where ε_∞ is the pure real part of the dielectric constant.

Table 2

Films thicknesses and mean-squared error (MSE) for films of PEG:PLGA blends with the indicated blending ratios, as determined by SE and AFM. The errors in thickness evaluation are indicated by \pm .

PEG:PLGA blend ratio	h_{SE} (nm)	MSE	h_{AFM} (nm)
1:1	186.2	40.53	204 ± 15
1:2	158.3	19.09	145 ± 18
2:1	143.3	30.98	159 ± 8

Table 1

Assignments of the infrared absorption bands from the FTIR spectra of PEG:PLGA blends.

Band (cm^{-1})	Assignment	Polymer
900–800	C–O stretching vibration	PEG
1150/1060	C–O–C antisymmetric stretching vibration	PEG
1043	C–CH ₃ stretching vibrations	PLGA
1450–850	C–H bends	PLGA
1090	C–O–C asymmetric stretching	PLGA
1134	CH ₃ rocking vibrations	PLGA
1184	C–O–C asymmetric stretching	PLGA
1200/1400	CH ₂ wag and twist modes	PEG
1400/1300	C–OH deformation vibration	PEG
1475/1445	CH ₂ antisymmetric scissoring vibrations	PEG
1762.6	C=O stretch	PLGA
2940/2855	CH ₂ antisymmetric stretching vibrations	PEG
2885	C–H stretch of CH ₂	PLGA
3010, 2955	C–H stretch of CH ₃	PLGA
3500	OH band	PEG
3509.9	OH end groups	PLGA
2350	CO ₂	Atmosphere

Table 3

Gaussian parameters corresponding to the oscillators used for fitting the experimental data, as determined by SE. The indices (1, 2) correspond to the two Gaussian oscillators.

PEG:PLGA blend ratios	A_n	E_n (eV)	B_m (eV)
1:1	$A_1 = 0.221$	$E_1 = 3.754$	$B_{r1} = 0.952$
	$A_2 = 0.076$	$E_2 = 2.221$	$B_{r2} = 0.425$
1:2	$A_1 = 0.232$	$E_1 = 2.264$	$B_{r1} = 0.735$
	$A_2 = 0.318$	$E_2 = 3.710$	$B_{r2} = 0.824$
2:1	$A_1 = 0.145$	$E_1 = 2.296$	$B_{r1} = 0.678$
	$A_2 = 0.323$	$E_2 = 3.863$	$B_{r2} = 0.954$

The refractive index (n) and the extinction coefficient (k) are related to the dielectric functions by [25]:

$$\varepsilon_1 = n^2 - k^2 \quad \text{and} \quad \varepsilon_2 = 2nk \quad (4)$$

The Gaussian parameters corresponding to the fit of our experimental data are specified in Table 3.

From the fitting, the refractive indices (n) of the MAPLE deposited films were determined (Fig. 3a). These are found to depend on the blending ratios, the films with higher amount of PEG exhibiting lower refractive indices than those with higher content of PLGA. This observation is supported by the SE results from our initial report [17]. There, we have obtained preliminary values of the optical constants using the Cauchy model and we have shown that the films of PEG have lower refractive index than the films of PLGA.

Reports on the refractive indices for PEG and PLGA are quite limited. Refractive indices of around 1.47–1.48 have been reported for PEG microparticles [26], while refractive index of 1.59 has been considered for PLGA microparticles used for drug delivery [27]. One must, however, take into account that the refractive indices can vary, function of the preparation conditions and of the environment of the polymeric chains.

For PEG:PLGA films with (1:1) and (2:1) blending ratios, the values of the refractive indices are close to those reported in the literature for the component polymers. On the other hand, for (1:2) PEG:PLGA blending ratio, quite high values of the refractive indices were obtained. PLGA was shown to have higher refractive index than PEG, thus one can expect higher refractive indices in films where the amount of PLGA dominates. Still, the refractive indices for films with (1:2) blending ratio are significantly higher than the values generally known for polymeric systems.

The mechanism responsible for refractive index changes in polymers is not yet elucidated. One possible cause is considered to be chemical decomposition of polymers [28 and references therein]. Still, in our experiment, MAPLE deposition was performed at very low fluences, where no chemical decomposition occurs (as shown by FTIR). In consequence, the high values for the refractive index for films with (1:2) PEG:PLGA blending ratio cannot be ascribed to chemical modifications of the polymers. Several other causes

for refractive index changes in polymers are currently discussed, being often related to structural relaxation influenced by polymer segmental mobility [29 and references therein]. Such structural changes might also occur in PEG:PLGA films deposited by MAPLE. Local structural restrictions might be enhanced in films with higher content of PLGA (e.g. due to its longer chains) and might account for the higher values of the refractive index observed for these films.

For accurate analysis of the factors involved in refractive index changes, these assumptions have to be further investigated. In the present work, a first important step was accomplished, by establishing *if and to what extent* the optical constants of the films depend on PEG:PLGA blending ratios. At this point, one can clearly state that the blending ratios affect the optical constants of the films. The results offer reference criteria for appropriate selection of the blending ratios, so that the refractive indices to be matched with the requirements of each application. This is important for applications such as implants to be used at intraocular level, where the refractive indices of the polymeric films have to ensure proper functionality of the visual system.

Furthermore, the extinction coefficients (k) of MAPLE deposited films were determined from the fitting (Fig. 3b). For all blending ratios, two maxima were found: one at around 330 nm and the other at 540 nm. As indicated by UV–vis measurements of films of PEG, respectively of PLGA (data not shown here), the absorption maximum at 330 nm is associated to PEG, while the one at 540 nm belongs to PLGA. It should be noted that, for all blending ratios, the absorption of the polymeric films are extremely low over the whole investigated spectral range.

The intensities of UV–vis absorption peaks are not fully consistent with the blending ratios. For example, for (1:2) PEG:PLGA blending ratio, the film contains less PEG than PLGA; therefore the peak at 330 nm (associated to PEG) should have lower intensity than for the other blending ratios ((1:1) and (2:1)).

For explaining the changes of intensity of UV–vis absorption peaks in polymers, tentative explanations have been advanced in the literature. Studies have indicated that the intensity of peaks in the UV–vis absorption spectra can be influenced by polymer stereochemistry (e.g. to tri-dimensional spatial arrangement of the polymeric chains). Also, confinement of certain groups in the polymeric chains due to their local environment was shown to play a role [30]. These effects might also occur in PEG:PLGA films deposited by MAPLE, thus the UV–vis absorption within the films does not have to be necessarily consistent with the blending ratio.

Additionally, for (1:2) blending ratio, a right shift of the peak at 330 nm is observed. The shifting towards longer wavelengths has been assigned to aggregation of polymer chains, leading to delocalization of electrons across the chains resulting in electronic species with lower band gaps [31], or to increased chain length resulting in stronger delocalization of the excited-state wavefunction [32,33]. These considerations could tentatively explain the shifting of the peak at 330 nm for (1:2) PEG:PLGA films, due to their higher content

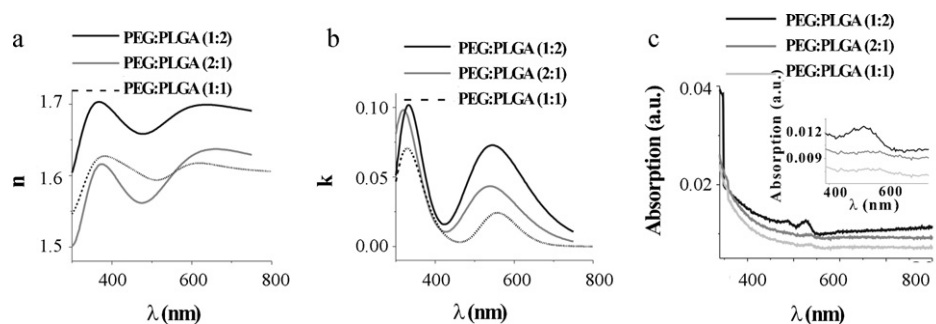


Fig. 3. (a) Refractive indices vs wavelength and (b) extinction coefficients vs wavelength for the indicated polymeric films, as determined by SE. (c) UV–vis absorption spectra of the same samples.

of PLGA (i.e. longer chains). For complete elucidation of the factors responsible for changes in intensity and shifting of the absorption peaks, detailed spectroscopic studies will be performed.

The most important point for these results is that, for all blending ratios, the absorption of the films in the visible spectral range is extremely low. This indicates high potential of PEG:PLGA blends for specific controlled drug delivery applications (e.g. at intraocular level, where undesirable effects might occur if the polymeric implants would absorb strongly in the visible spectral range).

The SE fitting procedure also provides a numerical value called MSE (mean-squared error), which shows the discrepancy between experimental and generated data [25]. In our case, the MSE values are reasonably low (Table 2), proving the goodness of the fit. Furthermore, the accuracy of the fit was checked by means of two independent measurements. First, the film thicknesses were determined by AFM (h_{AFM}) (Table 2). To this end, a mask covering an area of the substrate was used. By removing the mask after film deposition, a step-profile was produced. Its height (i.e. film thickness), was subsequently determined by AFM, similar values with those determined by SE being obtained. Secondly, the absorption spectra of the films were measured by UV–vis spectrophotometry (Fig. 3c). Similar absorption maxima were found for both SE and UV–vis spectrophotometric measurements. The slight differences between the absorption values determined by SE and UV–vis spectrophotometry are most likely due to different instrumental sensitivities of the two techniques.

4. Conclusions

We have demonstrated that MAPLE is an effective technique for obtaining thin films of PEG:PLGA blends with different blending ratios. In addition, we have shown that the blending ratios exert significant influence on the characteristics of the MAPLE deposited films. We have found that the films are smoother for blends with higher content of PEG. FTIR measurements have indicated that MAPLE deposition did not damage the structural composition of the polymer blends and that both polymers within the blend preserve their chemical structure. In addition, we have shown that the intensities ratios of the infrared absorption bands of the polymer follow the same trends as the blending ratios. Furthermore, we have assessed the optical constants of the films by SE measurements and we have validated the results by AFM and UV–vis spectrophotometry. We have found that the blending ratios influence the optical characteristics of the films, higher content of PEG within the blends resulting in films with lower refractive indices.

In consequence, we stress that the ratios in which polymers are blended play a significant role for the morphology, chemical structure and optical characteristics of the MAPLE deposited films. Based on these findings, we point out that the blending ratios are expected to exert major influence for the dynamics of the drug release and should be carefully selected, for meeting the requirements of each therapeutic application. In all, the results indicate that PEG:PLGA MAPLE deposited films are suitable candidates for controlled drug delivery. Before their use in real applications, investigations of the drug release rates through the polymeric films function of the blending ratios will be performed in subsequent studies.

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