Biocompatible PCL/PLGA/Polypyrrole Composites for Regenerating Nerves

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In the field of regenerative medicine, many studies have focused on regenerating peripheral nerves because clinical problems and functional loss of organs are affecting an increasing number of people. Biocompatible polymers can be potentially used for producing biocompatible tubes in order to aid the regeneration of peripheral nerves. This study aims to prepare polymeric composites based on polycaprolactone (PCL), poly (lactic-*co*-glycolic acid) (PLGA), and polypyrrole fibers (PPy) capable of acting as a conduit for regenerating peripheral nerves. Polypyrrole is synthesized by oxidative chemical polymerization with p-toluenesulfonic acid monohydrate (PTSA) as a doping agent. PCL/PLGA blends (100:0, 90:10, 80:20, and 70:30) (m/m) and PCL/PLGA composites with 10% PPy fibers were prepared by the solvent casting method. PPy with a diameter of 88–974 nm showed electrical conductivity of 2.0×10^{-1} S cm^{-1}. The nontoxic composite films with hydrophilic and porous surfaces presented a thermal stability and degradation period that were suitable for potential use in the regeneration of peripheral nerves.

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1. Introduction

In the field of tissue engineering, studies are actively developing polymeric biomaterials for regenerating peripheral nerves.[1–3] Several biocompatible tubular products approved by the US Food and Drug Administration (FDA) are commercially available for repairing nerve tissues, including NeuroTube® made of polyglycolic acid and Neurolac™ made of poly (D, L-lactic acid-*co*-ε-caprolactone).[4]

Biodegradable polyesters such as poly (lactic-*co*-glycolic acid) (PLGA), polycaprolactone (PCL), and their blends have been widely used for preparing biocompatible tubes.[2,4–7] PLGA is widely used as a substrate for nerve regeneration owing to its biodegradability, nontoxicity, and film-forming ability.[4] PLGA-based materials show micropores on the surface that increase nutrient permeability, thus favoring cell adhesion and proliferation.[8,9] PCL, too, is suitable for manufacturing such tubes because it has low toxicity, good mechanical properties, slow degradation (>1 year), and excellent compatibility for preparing blends with other biocompatible polymers.[3,4,10] Polymers are combined to obtain biocompatible tubes that show properties not attainable by any of the constituents alone.[11] PCL/PLGA blends with different ratios have been considered promising for medical applications owing to their biocompatibility, slow degradability, and surface topography that favors cell adhesion and proliferation.[1,12,13]

Conductive polymers are also considered attractive materials for medical applications because various biological tissues respond to electric fields and stimuli. Studies have shown that conductive polymers have good ability to support and modulate the growth of several types of cells such as nerve cells and bone cells.[6,14]

Polypyrrole (PPy) is the most studied conductive polymer in vitro and in vivo owing to its biocompatibility and easy synthesis route.[4,6] However, polypyrrole has poor mechanical properties and is not biodegradable. On the other hand, biodegradable PCL/PLGA blends have suitable mechanical properties (flexibility) for preparing biocompatible tubes, but they are insulating materials. Thus, the addition of a small amount of the PPy conducting polymer to the PCL/PLGA blends results in a

polymeric material with mechanical and electrical properties appropriate to support and stimulate the growth of nerve cells.

PLGA fibers prepared by electrospinning and coated with PPy showed better electrical activity and cellular interactions compared to fibers without PPy.[13] Similarly, a PCL fiber coated with conducting layers was prepared by adding pyrrole to the polymer solution for electrospinning and then polymerizing in $FeCl_3$ solution containing an anionic surfactant and added pyrrole monomer.[15] Conducting tubes with a PCL-PPy inner layer and PLGA outer layer were prepared, and the results showed that when electrically stimulated, these tubes increased the axon length growth rate by 21% after 3 days.[16]

In addition to biocompatibility, it is desirable that the material should show topographic characteristics such as high porosity.[4,17] The surface must be hydrophilic, because implants with hydrophobic surfaces may be rejected owing to the adhesion of monocytes to these surfaces. Furthermore, the material should show an optimum degradation rate that must be slow enough to provide a support for cell growth but fast enough not to disturb the regeneration process.[4]

In the present study, PPy with fiber morphology was dispersed in PCL/PLGA blends by a solvent casting method for preparing multifunctional tubes for regenerating peripheral nerves. The polymeric biomaterials were then examined using scanning electron microscopy, water contact angle, thermogravimetric analysis (TG), in vitro degradation, cell viability, and electrical conductivity measurements by the two-probe and four-probe methods. The biocompatible films based on PCL and PLGA with PPy fibers show appropriate characteristics for tissue engineering applications.

2. Experimental Section

Poly(L-lactic-*co*-glycolic acid) (PLGA; Purasorb PLG8523 (85/15) L-lactide/glycolide copolymer; inherent viscosity = 2.38 dL g^{-1} in chloroform) was supplied by Corbion Purac (Gorinchem, the Netherlands). PCL (molecular weight [Mn] = 80 000 g mol^{-1}), pyrrole monomer (Py; 98%), ferric chloride ($FeCl_3$; 97%), *p*-toluenesulfonic acid monohydrate (PTSA; 98%), phosphate buffered saline (PBS; pH = 7.4), and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were supplied by Sigma–Aldrich company. Chloroform ($CHCl_3$) was supplied by Synth (Diadema, SP, Brazil). The reagents were used as received, except pyrrole, which was distilled for subsequent polymerization.

2.1. Synthesis of PPy/PTSA Fibers and Preparation of PCL/PLGA and PCL/PLGA/PPy Films

Polypyrrole fibers (PPy) were synthesized by oxidative chemical polymerization, in aqueous medium at 0 °C, with PTSA as a doping agent (PPy/PTSA).[18–20] PCL/PLGA blends films and PCL/PLGA/PPy fibers composites films were prepared by the solvent casting method, in the ratio of PCL/PLGA 100:0, 90:10, 80:20, and 70:30 (m/m). The quantities of PCL and PLGA (total mass = 0.2 g) previously determined were dispersed in 7 mL of chloroform and kept in an ultrasonic bath (40 kHz, Unique, USC-2500A model) during 4 h at room temperature. After, the polymers dispersion were poured into glass Petri-dishes (5.5 cm in diameter). The solvent was evaporated at room temperature for 48 h and then the films were vacuum-dried for 8 h. The films of the PCL/PLGA/PPy composites were prepared by dispersion of PPy fibers to the PCL/PLGA blends according to the methodology described previously. These polymeric systems were maintained for 8 h in ultrasonic bath due to the difficulty of dispersion of the filler. In the preparation of the PCL/PPy film, the methodology used was the same. For all composites films, the amount of PPy added was 10% (m/m) relative to the mass of the biodegradable polymer.

2.2. In Vitro Degradation

The degradation experiments were carried out based on ASTM F1635-11 (2011).[21] The film samples cutted into 5-mm diameter disks was dipped in tubes containing 5 mL of PBS solution, and incubated at 37 °C temperature and 60 rpm-stirring. Each batch contained six specimens for each evaluated incubation time. The specimens were removed from PBS solution after 30, 60, 90, 120, and 150 days. They were carefully washed with deionized water, vacuum-dried to a constant weight, and then weighed to determine mass loss (in mg). The percentages of mass loss were calculated from the following Equation (1):

$$\text{Mass Loss}(\%) = 100 \times (M_0 - M_t)/M_0 \quad (1)$$

where M_0 is the mass before degradation and M_t is the dry mass after each time of degradation. Additionally, the pH of the removed PBS was measured after each time of degradation, in a pH-meter (Digimed, DM-20 model). The presented values represent the average of six specimens ± standard error.

2.3. Characterization Techniques of Polypyrrole and PCL/PLGA and PCL/PLGA/PPy Films

The morphology of PPy powder and the films produced were analyzed using Field-Emission Scanning Electron Microscopy (FESEM; FEI-Inspect F50 instrument). All samples were coated with a thin layer of gold. The fibers diameter was estimated from FESEM and analyzed using NIH ImageJ 1.36b software for treatment and measurement randomly of the fibers. In order to represent the distribuition of PPy fibers diameters 126 measures were collected from three images of FESEM.

The PPy electrical conductivity was determined by the four-point probe method (Keithley Instruments, model 236, and Multimeter HP34401) on pellet prepared by compacting the PPy powder. The electrical conductivity of blends and composites was determined by two-probe method. Silver was painted on the films faces for forming better electrical contacts; then, the electrical conductivity of the films was determined using the two-point probe method (Keithley Instruments Model 247 voltage source and Model 610 electrometer).

TG was carried out in the temperature range from 25 to 1000 °C with a heating rate of 10 °C min^{-1} under a nitrogen atmospheres using a TA Instruments, model Q500.

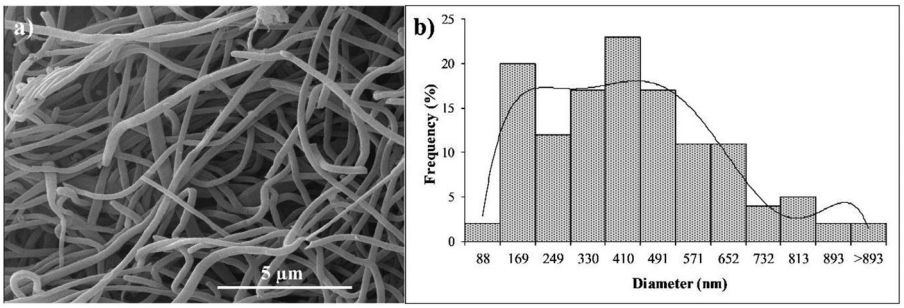

Figure 1. a) FESEM micrographs of PPy fibers; (b) Size distribution histogram of PPy fibers.

The static water contact angle measurements were performed using a goniometer (Phoenix 300, SEO). All images were captured 5 s after the water droplets touched the sample surface in order to achieve measurements from unchanged sessile water droplets. Six drops of deionized water were applied to each film and the mean of the angles was calculated, considering an experimental error of 2° among the measurements. Reported values are averages ± standard error of at six measurements taken at different points on the surface.

The number of metabolically active cells was determined based on the mitochondrial reduction of a tetrazolium bromide salt (MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay), as an indicative of cell viability. The cell lines were incubated with films, prepared from polymers films, for 24 and 48 h. Composites of PCL/PLGA/PPy were prepared and tested at different proportions: PCL/PPy, PCL/PLGA(90/10)/PPy, PCL/PLGA(80/20)/PPy, and PCL/PLGA(70/30)/PPy. The polymers were incubated by direct contact at $6\,cm^2\,mL^{-1}$, as recommended by ISO 10993 (2009)[22] for the biological evaluation of sterile medical devices that come into direct or indirect contact with the human body. The cell lines studied were HGF (gingival fibroblast-like cells), MRC-5 (human fetal lung), and RAW 264,7 (mouse macrophage-like cells). The cell lines were from American Type Culture Collection (ATCC-Rockville, Maryland, USA). The results are expressed as the percentage of cell viability in relation to the control. The control group consists of cells and culture medium maintained in proper cell culture plates without the presence of samples.

2.4. Statistical Analysis

The results of mass loss and pH were analyzed by two-way ANOVA followed by the Bonferroni test. Contact angle and cell viability were evaluated by one-way ANOVA followed by the Bonferroni test. For all analyzes, a 95% confidence interval was used, with differences considered statistically significant at $p < 0.05$ (San Diego, CA, USA, version 5.0).

3. Results and Discussion

Fiber morphology is a desirable property for biomaterials because it affords similarity to biological tissues, and this can favor the treatment and acceptance of the material by the human body.[23] The prepared PPy showed fiber morphology with diameter of 88–974 nm (**Figure 1**a). FESEM images showed that ≈88% of fibers had sizes distributed in the range of 169–731 nm (Figure 1b), with average fiber diameter of 391 ± 21 nm (mean ± standard deviation, $n = 126$) and minimum and maximum size of 88 and 974 nm, respectively. As obtaining fiber morphology during the polymerization reaction is not an easy procedure, PTSA in this study was used as a dopant and a soft-template that controls the morphology during synthesis.[24–26] The electrical conductivity of the obtained fibers was $2.0 \times 10^{-1}\,S\,cm^{-1}$, which was in the semiconductor range (10^{-7} to $10^{2}\,S\,cm^{-1}$). The synthesis yield was 89%.

The thermal stability of PPy was evaluated by TG (**Figure 2**). The TG and their first derivative, that is, differential thermogravimetry (DTG) curves of PPy show three characteristic stages of weight loss with degradation temperature peaks of 51, 190, and 384 °C. In the first stage from 23 to 120 °C, PPy loses 2.3% mass owing to the volatilization of physically adsorbed water molecules[19,20,24] and oligomers as well as unreacted monomer elimination.[24] In the second stage from 120 to ≈265 °C, PPy loses a further 4.7% mass owing to the removal of unreacted dopant ions (paratoluene sulfonates) from the PPy surface and the possible production and release of gases. In the third stage from 265 to 800 °C, main weight loss of 39.2% corresponding to the maximum degradation temperature of 384 °C occurs owing to the dopant degradation process and breaking of PPy chains. At 989 °C, the residue obtained was 46% relative to PPy that did not degrade.[20,24]

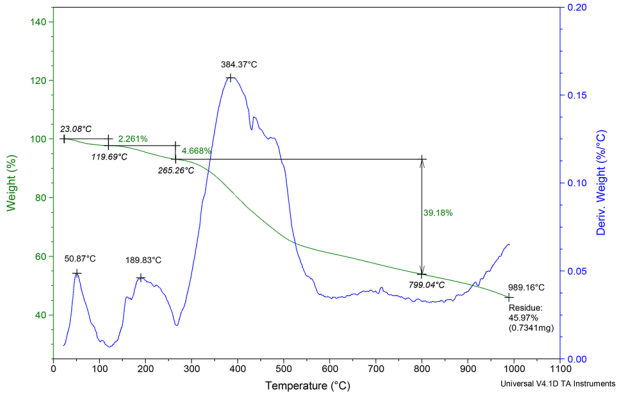

Figure 2. TGA of the PPy: weight loss and DTG curves.

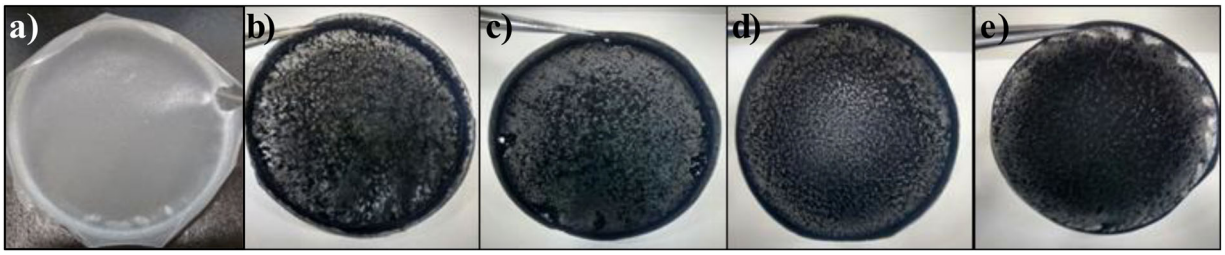

Figure 3. Film images: (a) Pure PCL; (b) PCL/PPy; (c) PCL/PLGA(90:10)/PPy; (d)PCL/PLGA(80:20)/PPy; (e) PCL/PLGA(70:30)/PPy.

The obtained PPy fibers were used to prepare PCL/PLGA/PPy fiber composite films. The film surface morphology is an important aspect that must be evaluated because it influences the processes of degradation and tissue regeneration.[2,17] **Figure 3** shows the macroscopic aspect of the prepared films.

It is observed that PPy dispersion in pure PCL is not homogeneous (Figure 3b), and it tends to improve with an increase in the amount of added PLGA in the blends (Figure 3c–e). This is because PPy disperses better in the amorphous phase, in this case, PLGA.[27] **Figure 4** shows a better visualization of the PLGA influence on the dispersion of PPy in the PCL matrix.

The in vitro hydrolytic degradation assay is a cheap and easy methodology for understanding the behavior profile of biodegradable polymers in living tissue without the use of animal experiments.[28] In this study, the results revealed that the prepared films showed mass loss of 1–5% during the evaluated incubation time (**Figure 5**).

These results indicate that the addition of PLGA or PPy did not significantly influence the loss mass of PCL matrix and blends during the evaluated time. Significant changes due to addition of PPy start to appear only with longer degradation times for blend with higher PLGA contents, such as PCL/PLGA (70:30). According to what is observed in Figures 3 and 4, PPy tends to disperse better in the blends with 30% PLGA reducing the surface roughness. This may retard the beginning of the degradation process of component matrix by means of ester bonds hydrolysis.

The films were degraded in phosphate-buffered saline (PBS) solution, and the pH of the medium was monitored as a function of incubation time. The PBS solution allows for a degradation simulation to the in vivo process to occur. The pH values were in the range of 7.28–7.34 for all films during the evaluated incubation days. This behavior confirms that the degradation process of the studied polymer systems is slow, because the

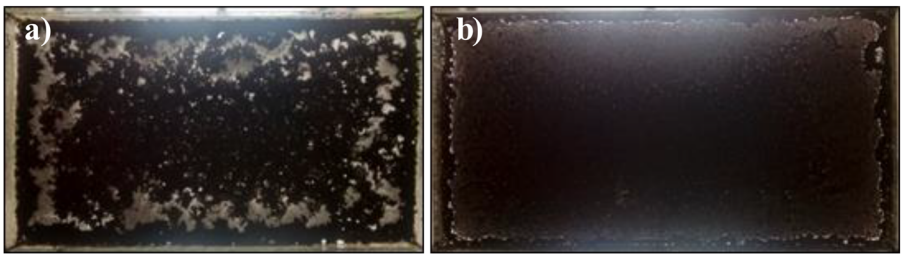

Figure 4. Film images: (a) PCL/PPy; (b) PCL/PLGA(70:30)/PPy.

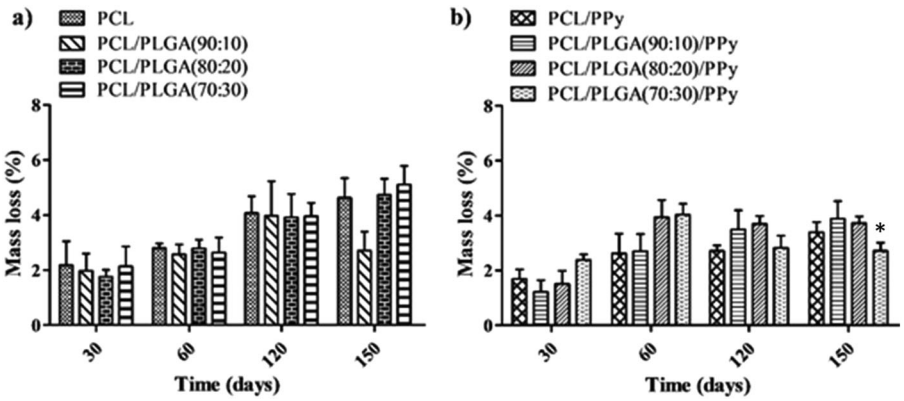

Figure 5. Percent of mass loss as a function of degradation time for (a) pure PCL and blends; (b) PCL/PLGA/PPy composites. $^{*}p < 0.05$ versus PCL/PLGA (70:30) in 150 days, two-way ANOVA followed by the Bonferroni test ($n = 6$).

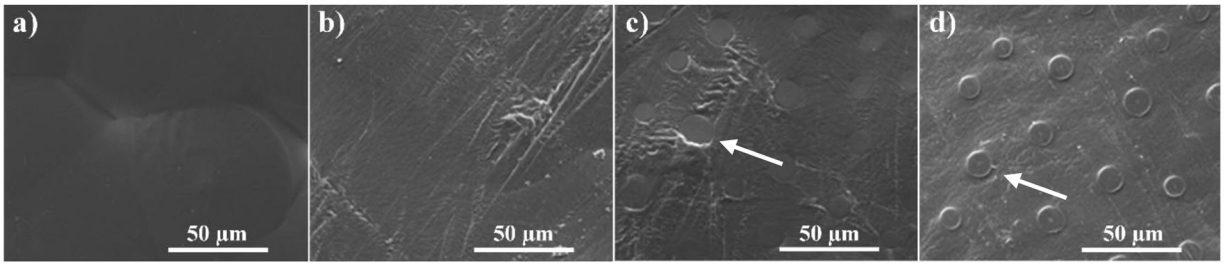

Figure 6. FESEM micrographs of (a) pure PCL; (b) PCL after 90 days of incubation; (c) PCL/PLGA(70:30); (d) PCL/PLGA(70:30) after 90 days of incubation.

acidic degradation products of PLGA are not present in sufficient quantity to cause a change in the pH value of the PBS solution.[29] These results are promising as they indicate that these systems are potentially suitable for treating peripheral nerve injuries, because these are slow-healing lesions that require the material to remain for at least six months without deterioration.

Figure 6 shows FESEM micrographs of pure PCL and PCL/PLGA (70:30) films before and after 90 days of incubation in the PBS solution.

FESEM micrographs show that the surface of the PCL film is not significantly affected by the degradation time (Figure 6a and b). However, the addition of PLGA in the PCL matrix modifies the film surface because the immiscible PLGA phase is dispersed in the matrix as spherical domains (indicated by arrows in Figure 5c). After 90 days of exposure to the PBS solution, spherical domains are swollen owing to the first phase of the degradation process involving the incorporation of water molecules (indicated by arrows in Figure 4d).[30]

Figure 7 shows SEM micrographs of the PCL/PLGA/PPy composites films before and after 150 days of incubation. A comparison of the FESEM micrographs of PCL films and PCL/PLGA (70:30) blends before degradation (Figure 6a and c) with those of their respective composites (Figure 7a and d) shows the fibrous and irregular surface morphology resulting from PPy addition. Figure 7 shows that the surfaces of the films of the composites are not significantly affected by the degradation time; this agrees with the mass loss results obtained using the in vitro degradation test. The existence of interconnected pores with different sizes favors cell growth and proliferation guided by PPy fibers and thus facilitates the formation of new biological tissues in tissue engineering.[31]

Electrical conductivity is a desirable property for materials used for regenerating nerves.[32] **Table 1** shows the electrical conductivity values of the prepared films. These values show that the addition of 10% PPy to the PCL insulation matrix (10^{-10} S cm^{-1}) resulted in a semiconductor material with electrical conductivity of the order of 10^{-5} (S cm^{-1}). The electrical conductivity depends on the conductive filler dispersion in the polymer matrix to construct conducting networks controlled by the PPy load and matrix microstructures.[27] Although not showing a tendency, higher percentages of PLGA increased the electrical conductivity of the PCL/PPy matrix. This result may be related to better dispersion of PPy with an increase of PLGA amount in the matrix (Figure 4).

The thermal stability of the biocompatible scaffold is an important factor that must be evaluated because thermal degradation can generate smaller molecules as well as

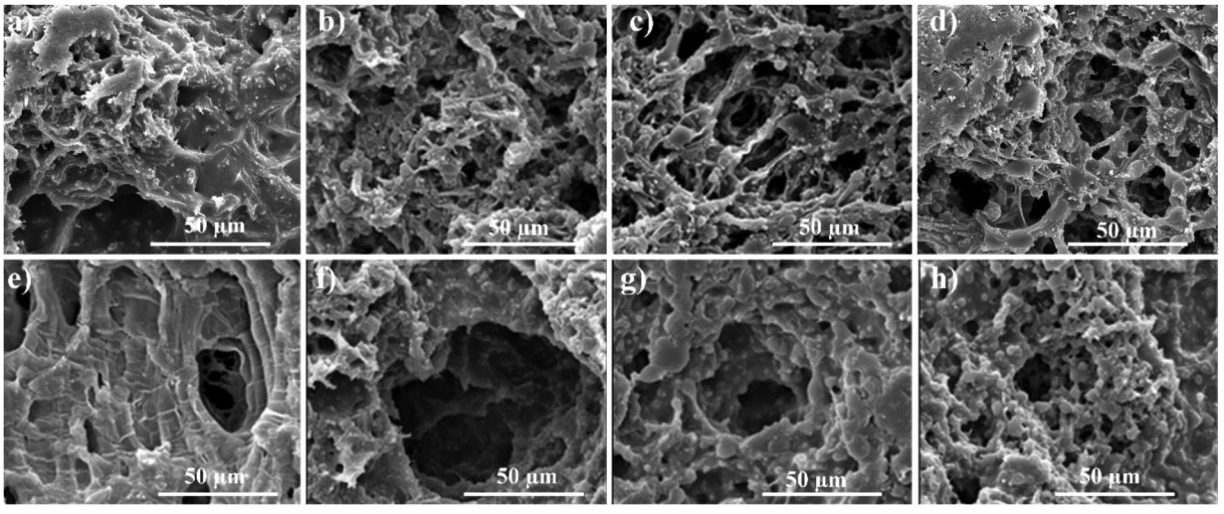

Figure 7. FESEM micrograph of sample before incubation: (a) PCL/PPy; (b) PCL/PLGA(90:10)/PPy; (c) PCL/PLGA(80:20)/PPy; (d) PCL/PLGA(70:30)/PPy. Samples after 150 days of incubation: (e) PCL/PPy; (f) PCL/PLGA(90:10)/PPy; (g) PCL/PLGA(80:20)/PPy; (h) PCL/PLGA(70:30)/PPy.

Table 1. Electrical conductivity measurements ($S\,cm^{-1}$) and thermal properties of pure PCl, blends, and composites.

Sample	Electrical conductivity [$S\,cm^{-1}$]	T_{onset} [°C]	$T_{máx.}$ [°C]	T_{endset} [°C]
PCL	1×10^{-10}	310	397	466
PCL/PLGA(90:10)	*	278	399	445
PCL/PLGA(80:20)	*	275	398	455
PCL/PLGA(70:30)	1×10^{-11}	268	401	434
PCL/PPy	2×10^{-5}	343	406	462
PCL/PLGA(90:10)/PPy	1×10^{-6}	348	407	462
PCL/PLGA(80:20)/PPy	5×10^{-3}	346	409	458
PCL/PLGA(70:30)/PPy	5×10^{-3}	346	408	465

*Not evaluated.

degradation byproducts that can interfere with the chemical composition of the material and alter its cytotoxicity and biocompatibility.[33] TA was performed to evaluate the thermal stability of the samples. Table 1 summarizes the T_{onset}, T_{endset}, and T_{max} values.

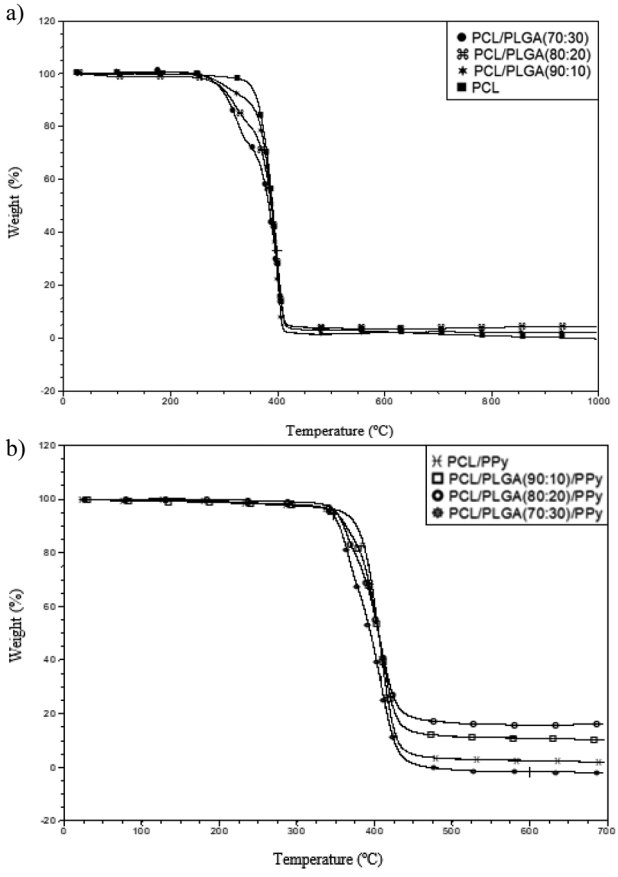

Figure 8. Thermogravimetric analysis of the films: (a) blends; (b) composites.

Table 1 and **Figure 8** shows that the addition of PLGA to the PCL matrix reduces the T_{onset} values of blends.

This result indicates that the polymer degrades faster with an increase in the amount of added PLGA, although T_{max} values showed no significant variation. PPy addition increased the thermal stability of blends, and the composites showed higher T_{onset} values. The thermal stability of the composites did not show changes with the addition of different amounts of PLGA.

Hydrophilicity is an important property for biomaterials as it increases cell adhesion, proliferation, and growth.[34,35] Contact angle values were measured to evaluate the hydrophilicity of the film surfaces, as shown in **Table 2**.

The results shown in Table 2 and **Figure 9**a and b indicate that the contact angles of the blends are lower than that of PCL. These results agree with those reported by Tang et al.,[36] indicating that PLGA addition reduces the contact angle of the PCL/PLGA blends via increased hydrophilicity. Contact angles change with surface morphology, roughness, level of interaction between the liquid and the solid, etc. Recent studies have been carried out on hydrophilic polymers showing that introducing roughness will increase the hydrophilicity.[37,38] In our case the contact angle of PLGA and PCL are almost the same. Therefore, we believe that the contact angle which decreases for the blend is related to their greater roughness in comparison to the pure polymers. For the composites, the addition of 10% PPy reduced the contact angle for PCL film by ≈8° (Figures 9c). Melo et al.[39] reported that polypyrrole doped with PTSA showed a contact angle close to 65° that is smaller than the PCL found here. We believe that the higher hydrophilicity of PPy and the composite roughness are responsible for the contact angle decrease of PCL film. The addition of PLGA to the PCL/PPy matrix improved the PPy dispersion reducing the roughness and consequently increasing the contact angle in comparison to the PCL/PPy sample.

3.1. Cell Viability Assay

The cell behavior on the polymer surface has been found to depend on different factors such as the chemical structure, macromolecular weight, and morphology.[36,40] Tang et al.[36]

Table 2. Measurements of the contact angle between the film-water interface.

Sample	Contact-angle (°)
PLGA	78,8 ± 1,7
PCL	77,8 ± 0,6
PCL/PLGA(90:10)	75,4 ± 0,1
PCL/PLGA(80:20)	74,8 ± 0,3
PCL/PLGA(70:30)	73,7 ± 0,3
PCL/PPy	69,6 ± 0,3
PCL/PLGA(90:10)/PPy	73,6 ± 0,3
PCL/PLGA (80:20)/PPy	73,1 ± 0,4
PCL/PLGA(70:30)/PPy	72,6 ± 0,7

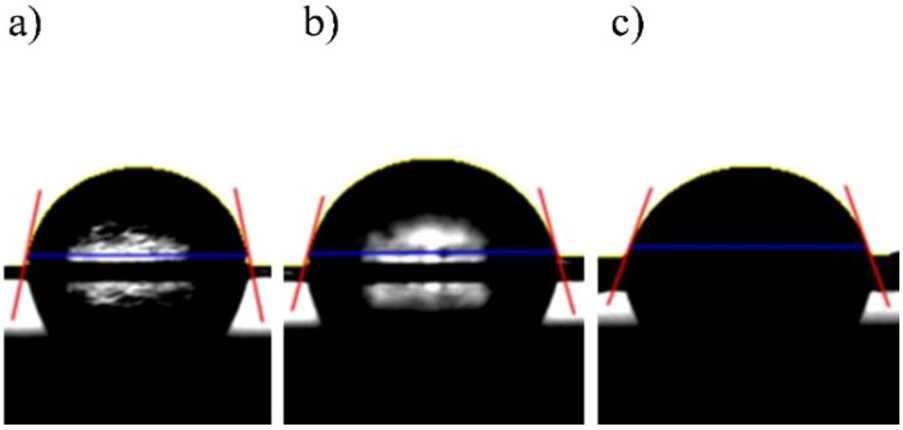

Figure 9. Contact angle for: (a) PCL, 78°; (b) PCL/PLGA(70:30), 74°; (c) PCL/PPy, 70°.

studied the biological response of films made from different PCL/PLGA blends (70/30, 80/20, and 90/10) and found that regular patterns of hydrophilic PLGA microdots on the surface improved the biological response. In our study, the cytotoxicity analysis using MTT showed similar results (not presented here) for PCL/PLGA blends with the same ratios as those evaluated by Tang et al.[36] To evaluate the effects of PPy fibers, composite films were evaluated using an MTT assay of three distinct cell lines, as shown in **Figure 10**.

The cell viability of the HGF, MRC-5, and RAW 264,7 cell lines after 24 h in contact with PPy-containing samples that did not show statistically significant differences. However after 48 h the PCL/PPy film showed a statistically significant ($p < 0.05$) decrease in cell viability only for the HGF line. The cell viability for the other tested cell lines was similar to that of cells cultured in a culture plate (control). Thus, PPy when present in PCL/PLGA blends does not induce toxicity in the studied cell lines.

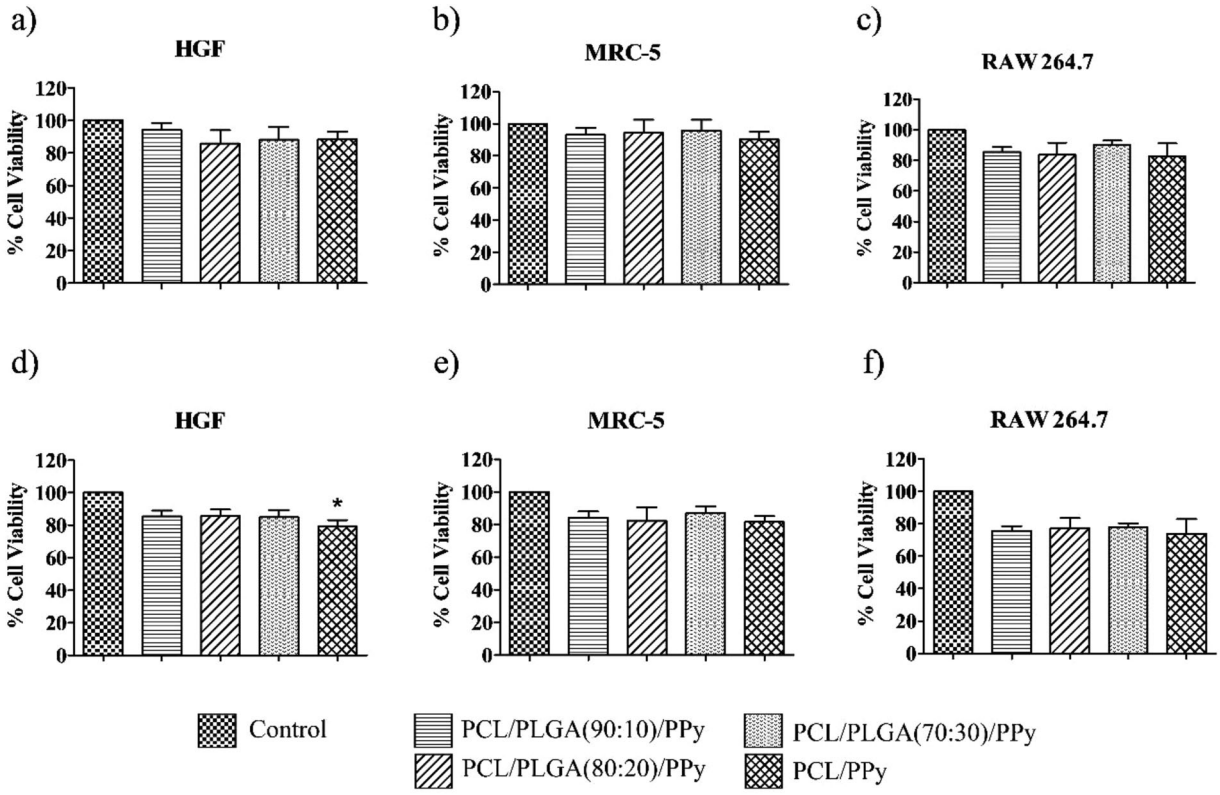

Figure 10. The metabolic activity was measured by MTT assay for: (a,d) HFG; (b,e) MRC-5; and (c,f) RAW 264.7 after (a–c) 24 h or (d–f) 48 h of culture with PCL/PPy and PCL/PLGA/PPy (90:10), (80:20) e (70:30).*$p < 0{,}05$ versus Control. One-way ANOVA followed by the Bonferroni test.

4. Conclusion

PTSA-doped PPy fibers having diameter of 88–974 nm showed electrical conductivity of the order of 10^{-1} S cm^{-1}. The dispersion of PPy fibers in the biodegradable PCL/PLGA polymeric matrix resulted in a material with rough and fibrous morphology containing interconnected pores and with a hydrophilic surface. This result is important because this morphology favors nutrient permeation and facilitates cell adhesion and proliferation. The addition of PPy fibers to the PCL/PLGA blends resulted in thermally stable and electrically conductive materials. The addition of PLGA or PPy fibers did not change the degradation process of PCL matrix and blends during the evaluated time. Cytotoxicity results showed that PPy when present in PCL/PLGA blends does not induce toxicity in the studied cell lineages. Therefore, biocompatible supports based on PCL and PLGA with PPy fibers show appropriate characteristics for tissue engineering applications.

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Keywords

composites, conducting polymers, poly (lactic-*co*-glycolic acid), polycaprolactone, polypyrrole

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