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RESEARCH

Chemical Processing and Physical-Chemical and Mechanical Characterizations of Poly (L-co-D, L lactic acid)/Polyethylene Glycol Mixtures for Application as a Biomedical Device

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ABSTRACT

The chemical processing of polymeric mixtures is a promising alternative for designing materials with new characteristics for biomedical applications. This work proposed to produce and characterize polymeric mixtures obtained using polyethylene glycol (PEG400 or PEG4000) with poly (L-co-D, L lactic acid)/PLDLA for biomedical use. The mixtures were prepared by the casting method. Characterizations were performed by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), mechanical properties (perforation, resilience, elastic modulus, plastic deformation, tensile strength and mucoadhesion) and *in vitro* biodisintegration studies. The results obtained by FTIR and DSC suggest that the chemical interactions that generate the mixtures between the polymers occurred through hydrogen bonds and/or dipole-dipole interactions. Chemical interactions created compounds that were more hydrophilic and had different rearrangements when using PEG400 or PEG4000 in the mixture. The mechanical tests showed changes in the resistance of the materials, highlighting the exponential value of plastic deformation of PLDLA/PEG400, significantly increasing the plasticity of this structure by 111-fold about PLDLA/PEG4000. In the biodisintegration study, after 120 hours, greater mass loss was observed for PLDLA/PEG4000 (68.82 ± 1.46%). Hydrolytic disintegration did not influence pH values, which remained between 7.34 and 7.41 during the study. In conclusion, these mixtures can provide valuable characteristics to produce a biocompatible biomedical device with properties to support tissue regeneration, where the issue of plastic deformation is necessary in collaboration with the formation of pores, after PEG dissolution *in vivo*.

KEYWORDS

Polymers synthetic, Poly (lactic acid) copolymer, Mixture composition, Mechanical properties, FTIR.

INTRODUCTION

The copolymer poly (L-co-D, L lactic acid) (PLDLA) is a constituent of the group of poly (α-hydroxy acids), which correspond to the most prominent materials in the class of bioabsorbable polymers. This class of polymers has other characteristics, such as biodegradability and biocompatibility, and is therefore capable of interacting with biological systems [**1–3**]. The PLDLA copolymer is formed by the combination of monomers of the levorotatory form (L - lactic acid) with the racemic form (D, L - lactic acid) derived from the spatial isomerism of poly (lactic acid) [**1,4,5**].

The characteristic of PLDLA combines the mechanical properties of the levorotatory form (L - lactic acid), reducing the long degradation time required by this

polymer due to the hydrophobicity of the crystalline state. The hydrophilicity of PLDLA increases with the proportion of racemic form monomers (D, L - lactic acid) in the polymeric chain and decreases in tensile and compressive strength [**6,7**].

PLDLA has been widely investigated for several applications, such as prostheses for healing bone fractures [**8**], making fixation devices (pins) [**9**], membranes for use in wound dressings [**10**], processing scaffolds for tissue repair or replacement [**11**], in the development of solid dispersions for optimize drug release and permeation [**12**], and in the manufacture of nanofibers to accelerate the healing of burns [**13**].

Polyethylene glycol (PEG) is a linear synthetic homopolymer from ethyl glycol. PEGs are available in different molecular weights, correlating with melting range and physical appearance. These compounds are readily soluble in water and biocompatible [**14,15**]. The chemical structure has a hydroxyl (–OH) and can be modified by functional groups such as carboxyl (–COOH), thiol (–SH), acrylate (CH_2=CHOO–), and bioactive molecules [**16**].

In tissue engineering, the PEG has been investigated for processing scaffolds due to its bioinert characteristics and ability to be modeled into various structures, forming scaffolds with different architectures [**17**].

Different techniques are used to modify the physicochemical characteristics of PLDLA, such as the union with other polymeric compounds to form mixtures or composites with adequate properties. The most used techniques are solvent evaporation, electrospinning, and rotary jet-rotation [**18**]. Water-soluble polymers with plasticizing properties, such as PEG, have been used as promoters for forming in situ porogenic structures in scaffolds with biomedical applications. [**19**].

Ignatius and Claes (1996) evaluated the biocompatibility of PLDLA, and they found no influence of PLDLA on cell proliferation or morphology. However, inhibitory effects were only observed in the MTT assay at the highest concentration of extracts, while no outstanding effect was seen at lower PLDLA concentrations. Some other studies investigated the proliferation, attachment, and morphology of hepatocytes and osteoblasts on PLGA. All of them found equal or even better results than control materials, suggesting good biocompatibility. The bio-resorption process occurs by hydrolysis and metabolization. The chemical hydrolysis breaks the PLDLA polymer chains with a reduction in the MW followed by a decrease in the mechanical properties of devices and the gradual loss of the mass. The devices broke into tiny fragments before metabolization. The metabolization reduces the PLDLA into glycolic and lactic acid molecules, which are then further metabolized in the liver into water and CO_2 [**20–23**].

The development of scaffolds with slow-time hydro-disintegration properties is a factor in tissue regeneration, which must be consistent with the cell proliferation time of the tissue of interest [**24**]. The use of PEGs as components in the formulations was used simultaneously to obtain plasticizing and porogenic properties. In this study, we investigated the effect of mixtures containing PEGs with different molecular weights on physicochemical and mechanical properties and biodegradation rates of biomedical devices.

EXPERIMENTAL

Materials

Polyethylene glycol 400 Mw 380-420 g.mol^{-1} and 4000 PA Mw 3500-4500 g.mol^{-1} (Vetec, Rio de Janeiro, Brazil), Dichloromethane (DCM) PA (Synth, São Paulo, Brazil), Poly (L-co-D, L lactic acid 70:30) was gently donated by Biomaterials Laboratory of the Pontifical Catholic University (Sorocaba, Brazil) and the others reagents were of analytical grade.

Preparation of polymeric mixtures

The mixture of polymers was prepared by the solvent casting. PLDLA (Mw 750,000 g.mol^{-1}) was solubilized in dichloromethane (10% w/v). After PLDLA solubilization, 0.5 g of PEG400 or PEG4000 was added. Both dispersions were homogenized (Fisatom - Mod. 753A, São Paulo, Brazil) using a magnetic bar coated with Teflon. The formulations PLDLA/PEG400 and PLDLA/PEG4000 1:2 (w: w) with a molar ratio of ~ 940:1 and ~ 94:1, respectively. A formulation of PLDLA/DCM was used as a control. Each formulation was transferred to an extender with a capacity of 19 cm^3, previously calibrated for a flow rate of 0.25 mL. s^{-1}. The formulations were extended to a glass plate that had been previously degreased. The obtention of the film was performed at 23 ± 2 °C by casting in a ventilated environment, protected from air impurities. The drying was controlled by gravimetry.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra were obtained by LabSolutions software IR s. v.2.10 (Shimadzu, IRAffinity^{-1}, Kyoto, Japan). The stretches of the chemical bonds of the main functional groups of each molecule making up the sample were determined by an attenuated total reflectance (ATR) over the range between 4000 and 600 cm^{-1}, resolutions of 4 cm^{-1}, averaging 128 scans. For each analysis, the mixture samples were manipulated without skin contact and fit on the ATR-8200 HA support.

Differential scanning calorimetry (DSC)

The thermic events were obtained using DSC (Thermal Analyzer TA 60WS, DSC-60, Shimadzu, Kyoto, Japan). Each sample of 2 mg was packed in a hermetically crimped aluminium pan, and heated under dry nitrogen purged at 50 mL. min^{-1}. The samples were from 25 to 125 °C at a rate of 10 °C.min^{-1}.

Mechanical and mucoadhesive properties

Texture profile analysis (TPA) was performed to measure the mechanical properties (elastic modulus, resilience, perforation, tensile strength, plastic deformation, and mucoadhesion) of the samples using a Texture Analyzer (Stable Micro Systems - TA-XT Plus, Surrey, UK), with analytical probe Mini Tensil Grips and support HDP/FS-R. The traveling arm was outfitted with a load cell of 5 Kg, and the resistance of samples to the deformation force imposed on it was recorded. The samples with an area of 4 cm^2 were clamped in a jaw probe constrained to move perpendicular to the axis of traction without rotating, and they were used for the elastic modulus, resilience and perforation tests. The test speed was set to a rate of 2 $mm.s^{-1}$ for perforation and tensile strength and 0.05 $mm.s^{-1}$ for resilience and elastic modulus in compression test mode. All of the tests were made in triplicate.

The mucoadhesion assay was performed using compression-prepared type III mucin discs (Rotary Compressor, Lemaq, Mini Express LM-D8, Brazil). Each disc was previously hydrated and fixed to the lower end of the analytical probe-type SC/P10 (TA-XTplus). The samples were fixed in suitable apparatus Mucoadhesion Rig-A/MUC (Stable Micro Systems Texture Analyzer. Godalming Surrey, UK). Then, The disc was compressed apically → basally on the sample's surface with a force of 0.049 N, and the contact time was determined to be 300s. The probe was removed from the mixture surface with a constant speed of 0.5 $mm.s^{-1}$. The force required to detach the mucin disc from the sample surface was determined by force (N) x time (s) ratio. All of the tests were made in triplicate.

In vitro biodisintegration rate

The *in vitro* biodisintegration study follow the method described by Alves *et. al.* (2019) [**25**], with modifications. The samples were hydrated in PBS pH 7.4 (phosphate buffered saline) at 37 ± 1 °C to assess their degree of disintegration. The mixtures were cut into a square shape (1 cm^2) and weighed (Wd) before being immersed in 3 ml PBS at 37 ± 1 °C for 120 hours. They were removed at different times (24, 48, 72, 96, and 120 h), washed in a large volume of deionized water to remove buffer salts, and dried at 37 ± 1 °C until constant weight. Finally, the samples were weighed (Wa), and the weight loss percentage was calculated as follows (equation 1):

$$Weight\ loss\ (\%) = 100 \times \left(\frac{Wd - Wa}{Wd}\right) \qquad (1)$$

where Wd is the dry weight and Wa is the weight after the immersion time.

The pH value of the PBS was measured at each time point using a pH-meter (Tecnal, TE-5, Piracicaba, Brazil). Each sample was made in triplicate.

Statistical analysis

The main results were presented with their standard deviation. The statistical significance of the difference in the parameters was determined using ANOVA followed by the Tukey test when $p < 0.05$; the difference in results was considered statistically significant.

RESULTS AND DISCUSSION

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of components and mixtures are shown in **Fig. 1(A-B)**. In the PEG400 and PEG4000 spectra, the characteristic peaks in the 3454 cm^{-1} and 3471 cm^{-1} relative to the hydroxyl group (OH), at 2868 cm^{-1} and 2883 cm^{-1} attributed the CH_2 due to stretching vibration of diatomic units, while the harmonic stretching of the C−O−C group were observed at 1101 cm^{-1} and 1109 cm^{-1} for PEG400 and PEG4000, respectively [**26–28**]. The differences in the PEG400 and PEG4000 spectra are due to the higher number of ethylene glycol units in the PEG 4000 polymer chain [**29,30**].

The spectral analyze of PLDLA showed characteristic peaks in bands between 2995-2947 cm^{-1} corresponding to the symmetric (CH_2) and asymmetric (CH_3) axial deformation of CH bonds, respectively. The peak at 1753 cm^{-1} corresponds to the carbonyl axial stretch (C=O) of the ester group. The CH_3 folding stretch occurs at 1452 cm^{-1}, while the CH_2 grouping peaks are found at 1361 cm^{-1} and 1382 cm^{-1}, and the corresponding =C–O grouping in the region at 1087 cm^{-1} and 1267 cm^{-1} [**12,31**].

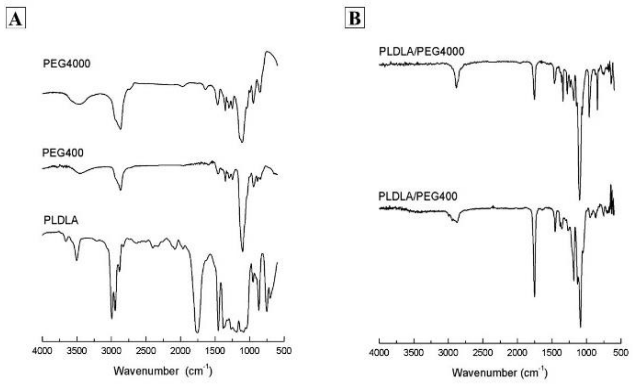

Fig. 1. Fourier transform infrared spectroscopy spectra of components (A) and mixtures (B). PEG (Polyethylene glycol); PLDLA [poly (L-co-D, L lactic acid) 70:30].

The results of the analysis of the FTIR spectra of the PLDLA/PEG400 mixture present changes in the spectrum compared to the pure components, showing slight displacements and a reduction in the characteristic intensity of the peak. However, in the PLDLA/PEG4000 mixture spectrum, in addition to slight displacements and reduced intensity, the absence of the peak in 3471 cm^{-1} was observed in relation to the OH functional group.

These results suggest that the application of the solvent evaporation technique enabled chemical interactions between the OH functional groups of the PEGs with the carboxyl end groups (COOH) present in the PLDLA through hydrogen bonds and through dipole-dipole interactions, since both are polar molecules that contain permanent electric dipoles [**32,33**] (**Fig. 2**).

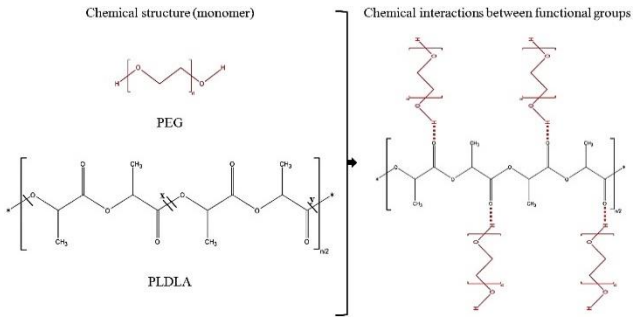

Fig. 2. Chemical interactions between functional groups PLDLA/PEGs. PLDLA (Poly (L-co-D, L lactic acid) 70:30) and PEG (Polyethylene glycol).

Adding PEGs as an additive to PLDLA results in a novel rearrangement of the molecular structure; it can also act as a water-soluble porogenic agent for in situ pore formation. The formation of pores occurs through the distribution of PEG monomers in new matrices formed by chemical interactions (PLDLA-PEGs) and their removal through dissolution in water [**34**]. In addition, the combination of polymers processed by the solvent evaporation technique and by means of the extension method allows the formation of mixtures with the format of a laminated film after drying.

Differential Scanning Calorimetry (DSC)

The thermal behavior of each component and of the polymer mixtures were analyzed by DSC. The component thermograms are shown in Figure 3-A. PEG4000 showed a sharp endothermic peak up to the melting point of 58.94 °C (onset: 52.43 °C; end set: 62.88 °C and ΔH 193.08 J/g) (35). For PEG400, no thermal event was observed in the temperature range analyzed in this study (25 to 125 °C). A previous study showed an endothermic melting peak for PEG400 at about 5 °C [**36**].

The PLDLA thermogram showed a thermal event corresponding to a T_g with a specific C_P equivalent to 59.48 °C (onset 56.07 °C, end set 62.74 °C), observed from the displacement of the baseline due to a change in the C_P, characterizing the polymer as amorphous [**11**].

The thermograms of the polymer mixtures are shown in **Fig. 3-B**. The PLDLA/PEG4000 showed an accentuated endothermic event up to the melting point of 62.91 °C (onset: 59.16 °C; end set: 65.53 °C and ΔH 78.56 °C). It was not possible to identify T_g referring to pure PLDLA. Regarding the melting point of pure PEG4000, there was a shift towards higher temperatures (about 4 °C), and changes in the melting enthalpy (ΔH) were also observed, which indicates the occurrence of chemical interactions between polymers, favoring the molecular structural rearrangement. In the PLDLA/PEG400 thermogram, it was possible to observe a thermal event between 48.86 °C (onset) – 52.12 °C (end set), indicating a T_g with C_P corresponding to 50.52 °C. This thermogram confirms the formation of a miscible mixture between the two polymers; however, it has different characteristics than the PLDLA/PEG4000 mixture, showing an amorphous state. The results presented in the FTIR spectra **Fig. 1 (A-B)** associated with the DSC thermograms, made it possible to confirm the occurrence of chemical interactions between the components, forming miscible polymer mixtures.

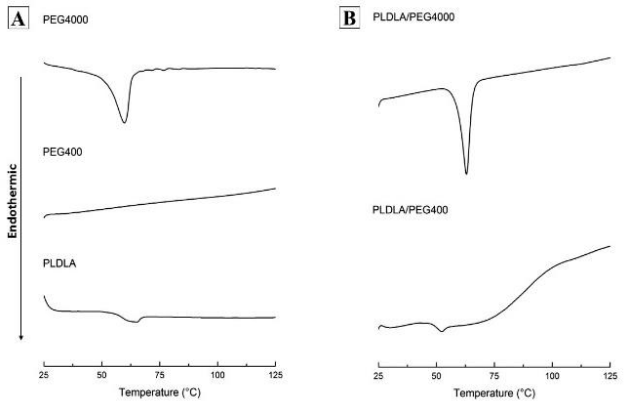

Fig. 3. Differential scanning calorimetry (DSC) thermograms of components (A) and mixtures (B). PEG (Polyethylene glycol); and PLDLA (poly (L-co-D, L lactic acid) 70:30).

Mechanical and mucoadhesive properties

The results obtained in the study of the mechanical and mucoadhesion properties of the PLDLA/PEG400, PLDLA/PEG4000 mixtures, and PLDLA samples are shown in **Table 1** and **Table 2**.

Analysis of the results showed that the mixture with both PEGs altered the mechanical properties of PLDLA. For the resistance to perforation of polymeric mixtures, a decrease in this property was observed when compared to PLDLA pure; this occurred in both (PLDLA/PEG400 > PLDLA/PEG4000). This test corresponds to the force required at the maximum distance of a compression cycle to break the interlacing of the polymeric chains formed by the conjugation of the mixture's components [**37**].

The resilience property is related to the material's ability to undergo deformation without altering its initial shape with the conjugation of the polymers, and it was possible to observe the formation of mixtures with close resilience values with no significant statistical difference ($p > 0.05$).

The mucoadhesion is defined as the bond established by the contact between the surface of two materials, one of which is the mucous membrane (mucin). These bonds occur through intimate contact between the materials, with the consequent interpenetration of polymeric chains in the

mucous layer and the formation of interfacial bonds [**38**]. *In vitro*, mucoadhesion assay mimics the mucous membranes lining the cartilage tissues such as the trachea, esophagus, auditory (middle and inner ear), and other tissues such as ocular, nasal, buccal, pulmonary, gastrointestinal, vaginal, and rectum perineal [**39**].

In this analysis, a lower mucoadhesion value was registered for PLDLA/PEG4000 due to the degree of ordering of the polymer chains in the mixture (crystallinity), a characteristic confirmed in the DSC analysis. This arrangement makes it challenging to intertwine the polymeric chains of the material with the mucin. For the PLDLA/PEG400 mixture and PLDLA sample, nominally different mucus adhesion values were recorded, however, there was no statistically significant difference ($p > 0.05$). The amorphous characteristic of this mixture and PLDLA was confirmed in the DSC assay. The polymers' structural disarrangement favored the chains' interlacing with the mucin.

Table 1. Mechanical properties (perforation, resilience and mucoadhesion).

Samples	Perforation (MPa)	Resilience (MPa)	Mucoadhesion (MPa)
PLDLA	$25.8x10^{-3} \pm 2.3x10^{-3a}$	$33.5x10^{-3} \pm 3.3x10^{-3a}$	$7.7x10^{-4} \pm 1.0x10^{-4a}$
PLDLA/ PEG400	$21.9x10^{-3} \pm 0{,}5x10^{-3b}$	$5{,}12x10^{-3} \pm 0.2x10^{-3b}$	$8.9x10^{-4} \pm 1.4x10^{-4a}$
PLDLA/ PEG4000	$6.1x10^{-3} \pm 1.9x10^{-3c}$	$4{,}83x10^{-3} \pm 0.5x10^{-3b}$	$4.8x10^{-4} \pm 0{,}4x10^{-4b}$

Equal letters in each column indicate no statistically significant difference between the mean values ($p > 0.05$). ($n = 3$). Note: PEG400 (Polyethylene glycol 400); PEG4000 (polyethylene glycol 4000) and PLDLA (poly (L-co-D, L lactic acid) 70:30).

Tensile strength is a measure of the force or tension required to stretch the material (longitudinal tension) to the point of rupture of the polymeric chains or before the permanent result of deformation [**37**]. In the tensile strength test, a greater breaking force was recorded for PLDLA/PEG4000 but a lower plastic deformation capacity. In contrast, for the PLDLA/PEG400, values of inverse quantities were recorded, with greater plastic deformation capacity and less breaking force.

These results are directly correlated with the chemical interactions established between the PEGs and the PLDLA to obtain the mixture, interactions confirmed through the FTIR and DSC spectra. Given the molecular weight presented by each polyethylene glycol [Mw 380-420 $g.mol^{-1}$ (PEG400) and Mw 3500-4500 $g.mol^{-1}$ (PEG4000)], polymer chains of different sizes were provided to form the mixture, directly influencing the mechanical properties.

The combination of the larger chains of PEG4000 with PLDLA obtained a mixture with a degree of ordering; this organized structure reflects greater resistance to rupture, however, with less elasticity, whereas the combination of smaller chains of PEG400 with PLDLA results in a mixture with no defined degree of organization (amorphous) which resulted in less breaking force. During the stress exerted in the test, the chemical interactions of the PEG400 chains were broken, causing the alignment of the PLDLA polymer chains, reflecting high plasticity, about 111-fold greater than the PLDLA/PEG4000 mixture.

Table 2. Mechanical properties (tensile strength, plastic deformation and elastic modulus).

Samples	Tensile strength (MPa)	Deformation plastic (MPa)	Elastic modulus (KPa)
PLDLA	$66.6x10^{-3} \pm 3.6x10^{-3a}$	$26.1x10^{-3} \pm 6.3x10^{-3a}$	1.835 ± 0.063^{a}
PLDLA/ PEG400	$16.7x10^{-3} \pm 0.6x10^{-3b}$	$316.3x10^{-3} \pm 13.8x10^{-3b}$	1.708 ± 0.063^{ab}
PLDLA/ PEG4000	$22.6x10^{-3} \pm 1.1x10^{-3c}$	$2.8x10^{-3} \pm 0.1x10^{-3c}$	1.645 ± 0.063^{b}

Equal letters in each column indicate no statistically significant difference between the mean values ($p > 0.05$). ($n = 3$). Note: PEG400 (Polyethylene glycol 400); PEG4000 (polyethylene glycol 4000) and PLDLA (poly (L-co-D, L lactic acid) 70:30).

A study using the PLDLA polymer in mixtures to obtain fixation devices (pins) by fusion method, with different proportions of poly (caprolactone triol) – PCL-T, revealed changes in the mechanical and morphological properties of the material. These changes demonstrated potential for material applications, where flexibility is required [**9**]. Another study characterized PLDLA-co-TMC (trimethylene carbonate) membranes mixed with silk fibroin by the casting method using chloroform as a dissolution medium. This chemical processing with the addition of fibroin altered mechanical properties, revealing a decrease in Young's modulus (elastic modulus) and increasing elongation at break (plastic deformation) [**10**]. However, some materials can cause a reduction in the mechanical properties of PLDLA. This fact was observed when mixing PLDLA with bioglass through selective laser sintering to manufacture scaffolds. The processing resulted in scaffolds that showed a reduction in flexural modulus and strength values, due to the increase in bioglass concentration. The high concentration reduced the chemical affinity between the polymeric and ceramic phase [**40**]. It has been shown through various processes that it is possible to simulate the mechanical properties of PLDLA by incorporating other materials and employing different chemical processing methods. This emphasizes the significance of investigating the versatility offered by PLDLA for manufacturing biomedical devices for a variety of applications. Furthermore, examining the compatibility of materials and their physical-chemical interactions is essential.

In vitro biodisintegration study

The *in vivo* and *in vitro* biodisintegration process of bioresorbable polymers begins by diffusing water molecules into the material's polymer chains, resulting in

the hydrolysis of the ester bonds in the amorphous phase and converting the long polymer chains into smaller fragments (oligomers to monomers) with more hydrophilic terminations. Monomers produced by the biodisintegration process are metabolized to carbon dioxide and water and eliminated by the lungs and kidneys through the tricarboxylic acid cycle [**41,42**].

According to literature data, the fragments formed by the PLDLA disintegration process (70/30) did not show biological toxicity *in vitro* and *in vivo* studies. In a study carried out by Más *et. al.* (2016) PLDLA demonstrated promising cell viability for applications in bone tissue engineering. *In vitro* analysis revealed cytocompatibility with osteoblastic cells, promoting significant growth for 14 days. *In vivo*, implants in rats exhibited support for the growth of new bone tissue, with degradation close to native bone formation and reduced inflammatory response [**8**].

Also focused on bone tissue engineering, Asami *et. al.*, 2022 demonstrated the cell viability of PLDLA-TCM. *In vitro* experiments, 3D-printed scaffolds using filament extrusion promoted cell adhesion and growth, with osteoinductive activity. *In vivo*, implants with PLDLA-TMC, containing or not mesenchymal stem cells, showed bone regeneration, reduced inflammation and facilitated angiogenesis after 12 weeks [**43**].

Fig. 4 (A-B) shows the mass loss (%) of mixtures immersed in PBS at 37 ± 1 °C on the 120 hours (5 days). The results obtained were, on average, 61.85 ± 1.57% for the PLDLA/PEG400 and 68.82 ± 1.46% for PLDLA/PEG4000 mixture at the end of this test ($p < 0.05$).

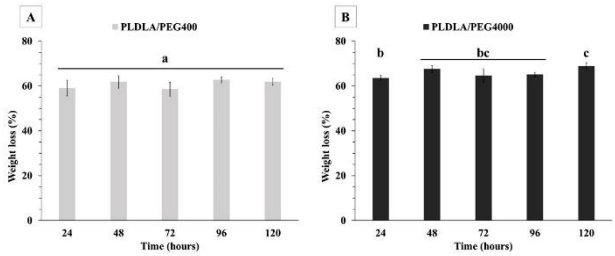

Fig. 4. Weight loss (%) of mixtures PLDLA/PEG400 (A) and PLDLA/PEG4000 (B) in PBS at 37 °C function time up to 120 hours (5 days). Equal letters over time mean no statistical differences were found ($p > 0.05$). (n = 3). PEG (Polyethylene glycol), PLDLA (poly (L-co-D, L lactic acid) 70:30).

The disintegration rate must match the new tissue's formation; then, the biodisintegration rate is a crucial factor for applying biomedical devices intended for tissue engineering [**44,45**].

According to the *in vitro* biodisintegration test results in fully hydrated conditions after 120 h, the PLDLA/PEG4000 mixture had a more significant mass loss ($p < 0.05$) than the PLDLA/PEG400 mixture (**Fig. 4 A-B**). However, this significant difference occurred in the first and the last 24 hours. These results are justified by the properties of each polymer.

The linear aliphatic polyesters, such as PLA, PGA, and their copolymers, show a limited rate of biodisintegration. Conversely, PEG is unsuitable for most tissue engineering because it has a fast biodisintegration and lacks desirable mechanical properties, which, in turn, is linked with an increase in MW [**44**]. When PEG and PLDLA copolymers were produced together, the individual advantages, like biodesintegration rate, were added, and the individual limitations were overcome.

Factors such as the high molar weight of PLDLA do not make this mixture more hydrophilic in the presence of PEGs. The absolute values of the mixtures in the biodisintegration test and their mass loss in the first 24 hours indicate the solubility of PEGs in the PBS medium. That, in turn, supports the PLDLA structure and increases the porosity of the mixtures.

Each mixture presents a percentage of 66.67% (w) of PEGs in its composition and we can observe a loss of mass in the period of 24 hours of 59.08 ± 3.54% and 63.56 ± 1.09% for PLDLA/PEG400 and PLDLA/PEG4000, respectively. During the study, an increase in these percentages is observed until the end of the study, with values of 61.85 ± 1.57% for PLDLA/PEG400 and 68.82 ± 1.46% for PLDLA/PEG4000. The percentage shown indicates that the total release of PEG400 has not occurred. However, it was evidenced that the mixture composed with larger chains of ethylene glycol in its structure favors better biodisintegration, with the total release of PEG in 120 hours. This fact reinforces the application of PEGs as a promoter for the formation of porogenic structures *in situ*, due to the removal of PEG chains in the spatial structure of PLDLA, in addition, it confirms that the changes observed in pH are associated with fragmentation of PEG during the study.

In a study on the hydrolytic degradation of poly (lactic acid), De Jong *et al.* (2001) concluded that cleavage at the end of the chemical structure of bioabsorbable polymers depends on the pH of the medium in which it is inserted. In the acidic environment, hydrolytic degradation occurs through a splitting mechanism of the end chain of lactyl monomer units, resulting in lactic acid, a chiral compound such that (R)-lactic acid and (S)-lactic acid exist simultaneously. However, in alkaline medium, the process of hydrolytic degradation can occur through rectification, forming a lactide unit, which is subsequently hydrolyzed, resulting in lactoyl lactic acid [**46**]. The pH of the disintegration medium monitored for 120h had no significant variation, only 0.06 on the pH scale (**Fig. 5**). This result suggests the chemical stability and biocompatibility of both formulations.

In a study by Tsai *et al.* (2015) was investigated *in vitro* (PBS buffer – pH 7.4) the behavior of PLA scaffolds in relation to the rate of biodisintegration and pH monitoring. The PLA scaffolds showed no apparent mass loss in 28 days of study. The pH value remained similar to 14 days and dropped to pH 7.1 in 21 days [**47**].

Monitoring the pH during the study of biodisintegration of scaffolds is a very important parameter, since tissue engineering seeks to mimic the possible

reactions presented *in vitro*, and the acid-base balance is essential for the tissue remodeling process [**48**], and both scaffolds did not show sudden pH changes during the studies.

This versatility of poly (lactic acid) derivatives in undergoing hydrolytic degradation in acidic or basic environments makes these materials a promising alternative for applications where pH is a fundamental characteristic. Because most of the biochemical processes presented by the human body are related to its pH value. For example, the ideal value for healthy skin is slightly acidic and is between 4.7 and 5.75. This acid balance is essential for the skin's barrier function, regulating bacterial flora and preventing infections. However, when an injury occurs, the pH of the skin is altered, exposing the more neutral pH of the surrounding tissue [**49**].

With this type of application in mind, a study developed a bioactive dressing based on electrospun poly (L-lactide-co-D, L-lactide) nanofibers containing Lawsonia inermis for the treatment of burns. The results demonstrated that the nanofibers loaded with Lawsonia inermis had a larger diameter and a more efficient release rate. The *in vivo* study, the dressing significantly accelerated the closure of the lesion, promoting epithelialization and the formation of collagen fibers [**13**].

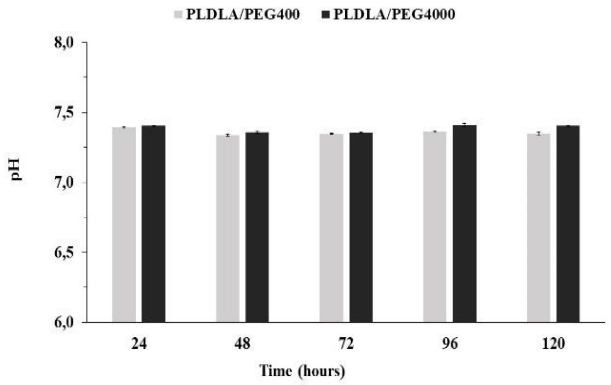

Fig. 5. pH of polymer mixture in PBS at 37 °C function time up to 120 hours (5 days). (n = 3). PEG (Polyethylene glycol); PLDLA (poly (L-co-D, L lactic acid) 70:30).

Fig. 6 (A-B) shows the results of a DSC analysis that was conducted on the polymer mixture to confirm the solubility of the PEGs after 24 and 120 hours of the study.

The results of the DSC analyzes carried out after the biodisintegration study periods were compared with the thermograms presented in Fig. 3 (A-B). The analyzes confirmed that the PEGs were being released from the mixtures into the PBS over time, evidenced by the changes in the thermograms of each mixture observed after 24 and 120 hours. In Figure 6-A referring to the PLDLA/PEG400 thermograms, changes were observed in the curve profile, showing a thermal event with an increase in C_P compared to the mixture before the beginning of the study, resulting in a C_P of 54.98 °C and 55.51 °C in the period 24 and 120 hours, respectively. These values demonstrate the controlled release of PEG400 to PBS as a function of incubation time, increasing C_P due to the prevalence of PLDLA.

In **Fig. 6-B**, changes related to the PLDLA/PEG4000 mixture were observed after the 24 and 120 hours. A reduction in the crystallinity was confirmed with a thermal event at 61.45 °C (onset 57.59 °C, end set 65.16 °C). After 120 hours of biodisintegration, a thermal event similar to the isolated PLDLA (**Fig. 3-A**) was confirmed, with C_P at 58.37 °C, indicating the absence of crystallinity and total release of PEG4000 to PBS medium.

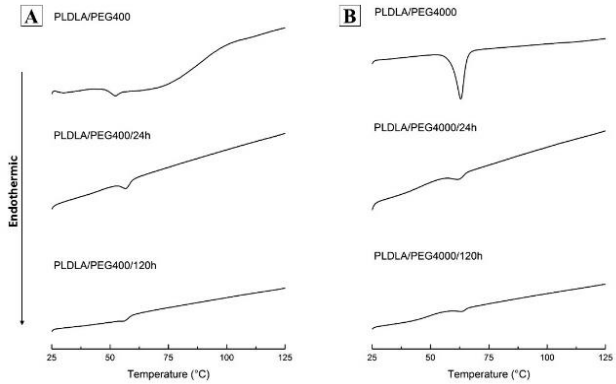

Fig. 6. Differential scanning calorimetry (DSC) thermograms of mixtures after *in vitro* biodisintegration study in PBS (pH 7.4 at 37 ± 1 °C) for 120 hours. (A) PLDLA/PEG400 (24h and 120h) and (B) PLDLA/PEG4000 (24h and 120h). PEG (Polyethylene glycol); PLDLA (poly (L-co-D, L lactic acid) 70:30).

CONCLUSION

Mixtures with varying physicochemical and mechanical properties were produced by mixing PLDLA and PEG polymers with different molar masses (400 or 4000). When smaller PEG chains (400) interacted chemically, it caused an amorphous structural rearrangement. That resulted in a significant increase in the plastic deformation's mechanical property ($p < 0.05$). When the PEG chains (4000) interacted chemically, the structure became crystalline, and the mechanical properties decreased, except for the elastic modulus, which remained rigid. Chemical interactions between the components were confirmed by FTIR and DSC analysis, which resulted in the rearrangement of the polymeric structure and the formation of miscible mixture between PLDLA and PEG. The *in vitro* biodisintegration study showed a more significant mass loss for the PLDLA/PEG4000 mixture ($p < 0.05$). Both samples exhibited a consistent biodisintegration pattern that created a porous structure due to the dissolution of PEG chains in PBS (pH 7.4). The results suggest that chemical interactions in the polymer mixture occur due to the formation of hydrogen bonds and/or dipole-dipole interactions between the compounds. Mixture with hydrophilic and plasticizing attributes and porogenic properties were obtained through these interactions. Developing a biocompatible biomedical device with *in situ* scaffold characteristics was essential to consider the

mechanical properties and other results of the PLDLA/PEG400 mixture and the controlled drying time.

In this way, the study provides insights into the properties of PLDLA and PEG mixtures and their interactions, structures, and degradation. These data are essential for advancing the chemical processing of these polymers, especially for the development of biomedical devices. Understanding physicochemical and mechanical properties can guide the design of biocompatible materials, improving clinical safety and efficacy. *In vitro* biodisintegration offers perspectives for controlling the degradation of these materials. Thus, this study encourages future research to explore new mixtures and propose variations in production processes to improve physicochemical and mechanical properties. Furthermore, it makes it possible to investigate functionalizations to confer specific properties, such as the capacity for controlled release of drugs or bioactives.

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CONFLICTS OF INTEREST

There are no conflicts to declare.

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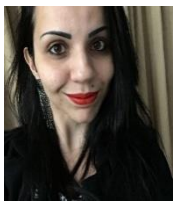

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GRAPHICAL ABSTRACT

Poly(L-co-D, L lactic acid) (PLDLA) and polyethylene glycol (PEG) polymers are processed by solvent evaporation technique. During processing, as a result of polymeric mixing, chemical interactions occur through hydrogen bonds and/or dipole-dipole interactions. The combination of the solvent evaporation technique with the extension method allows the formation of mixtures in the form of a laminated film after drying.