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Novel poly (diol sebacate)s as additives to modify Paclitaxel release from poly (lactic-co-glycolic acid) thin films

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ABSTRACT

Paclitaxel (PTX) incorporation in poly (lactic acid-co-glycolic acid) (PLGA) matrices produce films with high tensile rigidity and slow release that fail to deliver the required release rate for most biomedical applications such as in drug eluting stents and cancer treatments. To modify and improve this behavior, a set of poly (diol sebacate)s were synthesized and fully characterized as possible additives. The tensile properties of PLGA blends were evaluated as these materials could be used as coatings in drug eluting stent applications. A significant improvement of mechanical flexibility was observed with 20 % additive content, as it reduced the Young´s Modulus (YM) value and increased the maximum deformation at break. PTX release was studied and correlated with the release of additive from PLGA films. An increase of the initial burst release phase was observed on all blends when compared to the control films of PLGA. Modulation of PTX release was achieved by altering the hydrophilicity degree of the additive or its percentage content on the blend. This supports the possibility that PTX was partitioned into the additive phase. Cytotoxicity analyses of novel additives were performed on mouse embryonic fibroblasts NIH/3T3.

Keywords: PLGA – polymeric biomaterials – drug delivery systems – coating – polymer synthesis

1 Introduction

Controlled drug release is an important field in pharmaceutical and material research. The use of bioresorbable polymers is the main choice for eluting platforms due to the polymer's versatility. In this context, poly (lactic-co-glycolic acid) (PLGA) is commonly used in biomedical applications as a biodegradable polymer due to its biocompatibility and its tunability (i.e. as different properties can be obtained by changing monomer ratio and molecular weight) [1]. PLGA has been extensively used as a drug carrier in order to release a number of bioactive molecules including heparin [2], sirolimus [3,4], paclitaxel [5-8], DNA [9,10] and proteins [11-13] for numerous applications like cancer and cardiovascular diseases treatments, gene delivery therapy, vaccine formulations, among others [14].

Paclitaxel (PTX) is a common hydrophobic drug used as an anti-proliferative agent for drug eluting stent application [15] and chemotherapy for cancer treatment [16]. Modulation of paclitaxel release patterns can be performed by numerous methods including through: the modification of drug content on polymeric matrix, the increase of surface area through the use of porous platforms [17,18] or drug loaded micro- or nanoparticles [19,20], drug conjugation [21], incorporation of additives or use of polymeric blends [22,23], etc. Due to high mechanical rigidity that could limit the PLGA's final application, the use of additives is relevant in order to increase mechanical flexibility and modulate drug release profiles.

Additives can be either synthetic or natural occurring polymers, and can be incorporated to the matrix by simple blending or chemical conjugation to the base polymer. Natural biodegradable additives like chitosan or gelatin have been used extensively for drug release systems with excellent biocompatibility results[24-26]. However, there has been some inconsistencies regarding the purification process that could eventually lead to a variation of degradation rate and profile release depending on the batch used [27]. On the other hand, synthetic additives have proven to exhibit reproducible results and their properties can be easily adjust by chemical modification including co-monomer addition. Amongst others, poly (ethylene glycol) (PEG) is by far the most used synthetic additive due to its excellent biocompatibility and the hydrophilicity that is much needed to accelerate a hydrophobic drug release (e.g. paclitaxel) from a hydrophobic platform, such as PLGA [28].

In the present work, sebacic acid was used along with different long chain diols to produce low molecular weight polymers to be used as additives in order to modify the mechanical properties and paclitaxel release from PLGA films. Additionally, crystalline PEG was used as additive for comparative reasons.

2 Experimental section

2.1 Materials

Sebacic acid (99%), 1,3-propanediol (98%), 1,9-nonanediol (98%), 1,10-decanediol (98%), d6-chloroform (CDCl$_3$), dicholomethane (DCM) and 3-(Trimethoxysilyl)propyl methacrylate (98%) used were purchased from Sigma-Aldrich. PLGA 5010 (50:50 lactic acid:glycolic acid proportion), with intrinsic viscosity of 1.05 dl/g was purchased from PURAC. Paclitaxel (98%) was kindly provided by Bioprofarma (Buenos Aires, Argentina). Poly (ethylene glycol) (PEG) of 8000 Da was purchased from Lanpex SA (Buenos Aires, Argentina).

2.2 Synthesis and characterization of poly (diol sebacates)s

2.2.1 Poly(diol sebacate)s synthesis

Poly(diol sebacate)s were synthesized by polycondensation reaction. Equimolar quantities (0.04 moles) of each diol and sebacic acid were added to a round bottomed flask equipped with a Dean Stark trap and a reflux condenser. The reaction mixture was heated under stirring condition at 130℃ and N$_2$ atmosphere for 24 hours. Additional vacuum treatment was performed for 2h at the same temperature. Purification was performed by precipitation method. Briefly, 1g of polymer was placed on a 50mL-Falcon tube and dissolved on the lowest volume possible of DCM (1mL) and precipitated with ethanol. The resulting precipitate was centrifuged at 4000 rpm for 10 minutes and the supernatant was discarded, followed by vacuum drying. The purification procedure was performed three times.

2.2.2 Poly(diol sebacate)s characterization

Gel permeation chromatography (GPC) was performed with a Waters instrument equipped with a refractive index detector, a mixed-E column and chloroform as eluent solvent. The number average molecular weight (M$_n$), the weight average molecular weight (M$_w$) and the polydispersity index (PDI) of each polymer was measured. The elution rate was 1mL/min and polystyrene standards were used for the calibration curve.

The chemical structures of the polymers were assessed using proton nuclear magnetic resonance (^{1}H-NMR) and fourier-transform infrared (FT-IR) analyses. The infrared spectra were measured with a Perkin Elmer Spectrum 1000 FT-IR spectrometer. ^{1}H-NMR spectra were recorded in CDCl$_3$ a Bruker Avance II spectrometer.

Thermal Gravimetric Analyses (TGA) (Mettler-Toledo TGA/ SDTA851e/ LF/ 1100, USA) were performed in air, heating at a rate of 10 ºC/min from room temperature to 750ºC. Differential Scanning Calorimetry (DSC) (Mettler-Toledo 821, USA) scans were performed by heating and cooling the samples at rates of 10 ºC/min, in an interval of -50ºC to 150ºC under nitrogen.

Static contact angle (SCA) measurements were performed with a goniometric OCA 20 device (Dataphysics). SCA values were determined using the sessile drop method and distilled water as the dispensed liquid. Young-Laplace procedure was used as processing method. Each polymer were dissolved in DCM and cast into a glass slide. The slides were placed in a petri dish for controlled solvent evaporation. Five static contact angle measurements were performed per polymer film.

2.3   Additives incorporation to PLGA platforms

Film preparation. Poly (1,3-propanediol sebacate) (PPS), poly (1,9-nonanediol sebacate) (PNS) and poly (1,10-octanediol sebacate) (PDS) were used along with commercial PEG as additives in order to modify the properties of PLGA. To achieve this, each additive was incorporated by blending in DCM as solvent with 10% of PTX and PLGA at concentrations of 5, 10 and 20% by weight with respect to PLGA. Films were produced by solvent casting technique for further characterization.

Mechanical testing. For tensile properties, dog bone shape specimens were cut from the polymeric films. Tensile assays were performed at room temperature with a Universal testing machine Instron 3344 equipped with a 100 N load cell. The elongation rates were maintained at 5 mm/min and all samples were elongated to failure.

Water uptake. Swelling index by hydration was performed by immersing the sample films in PBS buffer solution of pH 7.4. The samples were withdrawn at different periods of times and the water excess was carefully removed from the surface. Samples were weighted after each period of time. The swelling index was calculated according to Equation 1.

$$Swelling\ index\ [\%] = \frac{Ws-Wo}{Wo} \times 100 \quad (1)$$

where *Ws* is the wet mass and *Wo* is the dry initial mass.

Degradation. In vitro degradation studies were performed in PBS buffer pH 7.4 at 37ºC. Disk-type polymer samples (8 mm of diameter and 1 mm thickness) were cut and immersed in PBS buffer for predetermined periods of time, after which the samples were withdraw and washed with deionized water. Films were left to dry for 48 hours at 50ºC for final weight measurement.

The mass losses were calculated from the dry mass at point p (*Mp*) and the initial dry mass (*Mo*) of the sample, according to Equation 2.

$$mass\ loss\ [\%] = \frac{(Mo - MP)}{Mo} \times 100 \qquad (2)$$

Paclitaxel (PTX) release. Having in mind the potential application in drug eluting stents, each polymeric blend was used to generate a film over a stainless steel plate of 2,0 x 1,0 cm by solvent casting. As a pre-treatment, metallic plates were silanized with 3-(trimethoxysilyl)propyl methacrylate in order to ensure polymer adhesion. Briefly, plates were dried overnight at 80℃ and immerse in 5% of 3-(Trimethoxysilyl)propyl methacrylate using hexanes as solvent. After 2 hours of orbital shaking the samples were withdraw and rinsed with hexanes to eliminate the unattached reagent, and left it to dry under air flow.

10% of PTX was used and three different samples were prepared for each PLGA blend for statistical analysis. The samples were dissolved in DCM and the solutions were poured into the pre-treated metallic plates and left for 24 hs at room temperature for solvent evaporation, followed by vacuum oven at 50℃ for 3 days. PBS pH 7,4 with 0,3% sodium dodecyl sulfate (SDS) was used as a release medium to ensure PTX dissolution (solubility: 61.9 ± 1.7 µg/ml). Polymeric blend-coated plates were immersed in 5 ml of release buffer under orbital shaking at 37ºC. Samples were taken after determined periods of time and replaced with fresh buffer. Sink conditions were maintained though all experiment.

PTX content was determined by HPLC using a HICROM Ultrasphere C18, 5 m, 250 mm x 4.6 mm and water/MeOH/ACN (25:11:64) as eluting solvent mixture at 1.0 mL/min rate. Samples were previously filtered using a nylon filter of 0.45 µm. A 20 µl injection volume was used and PTX detection was detected at 227 nm. Calibration curve was produced using standard solutions of the following concentration: 0.5, 12.5, 25, 50 y 75 mg/L.

Cytotoxicity assay. NIH/3T3 embryonic mouse fibroblasts (ATCC® CRL-1658™) were used as cell model for in vitro adhesion and cytotoxicity evaluation. Dulbecco's Modified of Eagle's Medium (DMEM) (Gibco, USA) was used as cell-gown culture, supplemented with 10% fetal calf serum (FSC, Gibco) and 2 mM L-glutamine (Gibco), at 37 ºC in humidified atmosphere, 95% air and 5% CO_2. Polymeric blend films were prepared as mentioned above, using 20 % of each additive. Films were cut into 5 mm discs and sterilized by 70% ethanol treatment for 24 hs. Polymer discs were placed in 96-well plates, air-dried for 24 h under sterile conditions and exposed to UV light for 15 min. NIH/3T3 cells were trypsinized and seeded in 96-well plates at a density of 2500 and 5000 cells per well in presence and absence of polymer discs to be used as positive control (TC plastic). Cell attachment and proliferation were assessed by the MTS assay using a chromogenic kit (CellTiter 96™ AQueous Non-Radioactive Cell Proliferation Assay,

Promega) after 48 h of seeding. The plates were revealed at 492 nm and 690 nm with a microplate reader and the signal intensity was reported as the mean of the absorbance measured in four wells. Results were statistically analyzed with one-way ANOVA test followed by Tukey´s multiple comparison test.

3 Results and Discussion

3.1 Synthesis and characterization of poly(diol-sebacates)

In this work, novel poly (diol-sebacate)s were synthesized for the purpose of using them as additives to modify the final properties and profile release of paclitaxel from PLGA platforms for future implant coating applications. Three sets of low molecular weight polyesters were synthesized via a catalyst-free polycondensation reaction, as shown schematically in Figure 1. Sebacic acid was used in combination with diols of different chain lengths: 1,3-propanediol, 1,9-nonanediol and 1,10-decanediol resulting in PPS (poly (1,3-propanediol sebacate)), PNS (poly (1,9-nonanediol sebacate)) and PDS (poly (1,10-decanediol sebacate)) polymers, respectively.

(Insert Figure 1)

Table 1 summarizes the properties of PPS, PNS and PDS. Polycondensation reaction rendered molecular weight values of 6300, 6500 and 6900 Da for PPS, PNS and PDS, respectively.

(Insert Table 1)

The ^{1}H-NMR spectra for PPS, PNS and PDS polymers are presented in Figure 2 and corroborate the expected polyesters. Methylene peaks from sebacic acid units are visible in a range from 1.2 to 2.5 ppm, while methylene peak from diol units with major proximity to ester bond appear at 4.1 ppm. Marked peak areas were used to assess monomer ratio which are exhibited in Table 1.

(Insert Figure 2)

FTIR spectra confirmed the structure of the obtained polymers (Figure 3). All spectra showed a sharp and strong peak at 1729 cm^{-1} corresponding to the carboxylic C=O stretching of polyesters, confirming the ester bond formation. Characteristic peak signals corresponding to the stretching of C-H bond of methylene groups are visible at 2851 and 2918 cm^{-1}. These peak signals are more intense in PDS and PNS when compared to shorter diol-chain PPS. It can be

notice the lack of signal corresponding to OH stretching at 3300 cm^{-1}, mainly because most of OH from diols were consumed during synthesis reacting with COOH in order to form new ester bond with subsequent water release.

(Insert Figure 3)

Thermal analyses showed a similar degradation temperature (Td) of 440ºC for all polyesters. DSC scans displayed a clear tendency (Table 2): the melting temperature (Tm) and the crystallization temperature (Tc) shift to higher temperature values with an increase of diols chain length. Furthermore, the obtained polymers presented no glass transition temperature (Tg), fact that underlines their crystalline nature.

The delivery of highly hydrophobic drugs such as PTX from slow degrading hydrophobic polymeric platform is commonly improved by the incorporation of hydrophilic additives such as PEG[29-31]. In order to evaluate the potential use of the currently investigated polymers as additives, its SCA values were measured using distilled water as the dispensed liquid. While PLGA exhibited a SCA value of 71.2 ±1.2º; PPS, PNS and PDS presented much lower values of 53.4 ± 2.6º, 60.5 ± 1.4º and 62.4 ± 0.9º, respectively. The higher hydrophilicity of the herein obtained polymers, in comparison with that of PLGA, is therefore an indication that they might be suitable for the purpose of the present work.

3.2 Polymeric blends

The herein studied poly (diol sebacate)s were used to modify PLGA films properties, and were additionally compared with crystalline PEG/PLGA blends which has been extensively studied and reported in literature [5,32]. Figure 4 shows the ATR-FTIR spectra of the polymer blends with 10% PTX. The spectra of the PLGA/additive blends were similar and there were no chemical bond formation between PLGA, additives and PTX, as no new additional peaks were registered.

(Insert Figure 4)

Mechanical properties were measured with and without PTX in order to evaluate the tensile effect of drug incorporation into the blend. Young's modulus (YM) was calculated from the slope of the initial and elastic part of the stress-strain curves and it was used as a measurement of the film elasticity. Figure 5 shows the effect of PPS concentration on mechanical performance. As can be seen, PLGA films are very brittle and rigid with a maximum elongation of 4.0 ±0.2% and

high YM value of 1457 ±41 MPa. Additionally, PLGA tensile curves exhibit a localized Yield point followed by specimen fracture. The incorporation of 5 % of PPS was enough to modify the tensile curve shape, as presented in Figure 5A. It was noticed that YM values vary with PPS incorporation (Figure 5B). With an increase of PPS content, a decrease on YM value was registered denoting a higher film flexibility (i.e. changing from brittle to a more ductile material). No significant change in YM values was observed when concentration exceeded 20% of PPS incorporation; therefore, this value was selected for further characterization of the rest of the additives.

(Insert Figure 5)

Figures 6A and 6B show the tensile curves of polymeric blends without and with PTX incorporation. A summary of the mechanical properties are depicted in Table 2. The addition of 20% of synthesized linear polyester increses maximum deformation porcentages of films and decreases YM values.

PNS and PDS/PLGA blends exhibited YM values of 866 ± 111 and 857 ± 149 MPa respectively. The similarity of their mechanical behavior can be attributed to their chemical structure, which differs only by one CH_2 unit of the diol monomer. On the other hand, PPS showed a YM value similar to PEG, and much lower than the ones registered for PNS and PDS blends.

Analizing the effect of PTX incorporation to the blend (Figure 6B), it can be seen that it had a negative impact on tensile behaviour ensuring the need of using additives in order to modify this property. Although the addition of PTX to PLGA film lowers the YM value, no increase on elongation was observed. Moreover, there was no visible clean fracture of specimens; a progressive loss of film integrity and strength was measured instead. The same behavior was seen for PNS and PDS blends, although incorporation of these additive increase the elongation up to 21.1 ± 5.7% and 25.2 ± 2.8%, respectively. Once again, the addition of PPS showed similar behavior than the addition of PEG; the incorporation of PTX did not have an influence on ultimate elongation, although it did increase the YM value when compared to the blends without the drug.

A major improvement was noticed for the herein developed PLGA/PPS blend that was able to support higher stress before plastic deformation occur with a yield strength of 25.2 ± 0.9 MPa when compared to PLGA/PEG which exhibited a value of 9.2 ± 1.4 MPa. This makes the former system a stronger blend.

(Insert Figure 6)

(Insert Table 2)

The water uptake curves of films with drug incorporation are depicted in Figure 7A. The amount of water taken up by the films with additives is much higher than that of the PLGA/PTX. Within the first 24 hours of immersion, the highest water uptake was registered for PLGA/PEG/PTX and PLGA/PPS/PTX with 5.0±1.1% and 7.0±2.1, respectively; the lowest value was registered for PLGA/PTX with a value of 0.25±0.05%. This tendency continued during the entire incubation period. These results were expected, since the PPS has the lowest contact angle value and therefore a higher hydrophilicity compared to PNS and PDS.

Figure 7B presents the mass loss over time curves. The control PLGA/PTX films had a slow degradation rate, during the first week of incubation, with a 1±0.6% mass loss. Incorporation of additives accelerates the degradation rate though dissolution of hydrophilic domains generated on the surface by phase segregation (PLGA-additive). In this matter, the most hydrophilic additives will be released in a faster manner with consequent pore formation and water penetration through PLGA matrix, as can be seen for PLGA/PPS/PTX and PLGA/PEG/PTX which registered within the first week of incubation a mass loss of 9.0±1.1% and 8.1± 1.6%, respectively.

(Insert Figure 7)

Most drug release applications need the drug to be active in a specific concentration, especially during the first days of treatment. In drug eluting stent applications, a release rate of 15 µg/cm^2 per day is required [19]. PTX release from hydrophobic PLGA matrix, as expected due to its slow degradation, failed to deliver the drug at the required rate, as shown in Figure 8. PTX release from PLGA followed a triphasic profile which is consistent with the literature [5,33,34]. A reduced initial burst release occurred during the first 5 days of incubation at a rate of 6 µg/cm^2 per day, which is a result of the dissolution of PTX that is present at the surface of the film. After this, PTX diffusion through PLGA matrix occurred at a slower rate of 3 µg/cm^2 per day and lasted approximately 30 days. In a later stage, PTX fast release (11 µg/cm^2 per day) corresponded to critical oligomer formation though PLGA hydrolytic degradation and consequent release to the medium, accelerating PTX release and culminating in coating break down.

(Insert Figure 8)

Figures 8A and 8B show the PTX release of PLGA films with 20% of additive. Incorporation of additives increase the initial release of the drug, as can be seen in Figure 8B. PLGA/PEG platforms have an initial release of 28 µg/cm^2 per day during the first week of incubation, which

later stabilized at a rate of 15 µg/cm^2 per day for the following two weeks and then lowered to 7 µg/cm^2 per day followed by coating breakdown. On the other hand, PLGA/PPS showed that the initial accelerated PTX release (i.e. 25 µg/cm^2 per day) lasted a longer period of time (i.e. 3 weeks), which later slowed down to 15 µg/cm^2 per day. PNS and PDS addition to PLGA matrix showed similar results, exhibiting release rates in between those of PLGA control and blends with PPS and PEG. Additionally, we proved that the release rate can be modified by altering the additive content, as can be seen in Figures 8C and 8D. With higher PPS content, a higher release rate was observed.

These results support the hypothesis of PTX being partitioned on the additive phase. This hypothesis was confirmed for PLGA/PEG platforms [32]. Kang et al. proved by Raman scattering microscopy a preferential distribution of PTX in the PEG phase, probably through hydrogen bond formation [32,35,36]. This will translate in a rapid dissolution of the more hydrophilic PEG domain on the surface that will induce PTX release to the medium, with subsequent pore formation and water penetration, accelerating the release process. This is the most probable reason why PPS addition exhibited higher PTX release rate than PNS or PDS addition, as PPS has a more hydrophilic character and is faster released to the aqueous medium. This theory also supports the fact that PTX release rate is additive-content dependent: the higher the additive content is, the stronger the interaction between the drug and the additive will be, which in turn will accelerate its release. Therefore, via this way, the hydrophobic drug release from hydrophobic PLGA platform can be modulated to specific release rate either by altering hydrophilicity of the additive or by modifying additive content.

In order to evaluate possible toxic effects of novel synthesized additives on cell tissue, cytotoxicity tests were performed using the direct contact method. Embryonic mouse fibroblasts NIH/3T3 were used as cell model in two different cell concentration: 2500 and 5000 cells per well. Tissue culture plastic was used as positive control for cell adherence and proliferation. As polymer films with additives weren't completely transparent, their absorbance were used as background signal and subtracted from the measurements of the samples with cells. Figure 9 shows the absorbance of each polymer blend film. Cells were able to attach and proliferate on all films with comparable values of TC plastic control. Incorporation of PPS, PNS and PDS had better results on cell adherence and proliferation than PEG addition. Similar tendency were observed when different cell concentration was seeded, except for PLGA/PPS which exhibited higher cells content than the rest, when 5000 cells per well were used. It is worth to be mentioned that after 72 hours of incubation, complete confluence was observed on all film, this is the reason why 48 hours was selected as an optimal period of time.

 (Insert Figure 9)

4   Conclusions

In the present work, three poly (diol-sebacate)s were synthesized using different chain length diols by polycondensation reaction. The herein developed compounds were physico-chemically and thermally characterized. The use of this novel polyesters as additives was proven to be successful in modifying final properties of PLGA matrix and modulating paclitaxel release profiles into a more accelerated release rates. PTX release rate could be controlled and adjusted to specific needs by using the different synthesized additives or by altering its content in the PLGA platform. A major improvement in the mechanical properties, to the already available in literature PLGA/PEG systems, was noticed for the herein developed PLGA/PPS blend that was able to support higher stress at break. Additionally, PLGA/PPS blends showed an improved PTX release profile than PLGA/PEG systems, being able to sustain a higher PTX concentration release over a longer period of time in the initial phase (i.e. 3 weeks for PLGA/PPS vs. 1 week for PLGA/PEG). Moreover, embryonic mouse fibroblasts NIH/3T3 were used for cytotoxicity analysis and proved to exhibit a similar behavior to that of the TC plastic (+) control.

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Legends to Figures:

Figure 1. Scheme of poly (diol sebacate)s synthesis. Where n= 1, 7 or 8 and m= polymer units.

Figure 2. ^{1}H-NMR of PPS, PNS and PDS.

Figure 3. FTIR spectra of PPS, PNS and PDS.

Figure 4. ATR- FT-IR of PLGA blends containing 20% of PPS, PNS, PDS and PEG, with 10% of PTX.

Figure 5. A) Tensile curves of PLGA blends with different PPS content. B) Young Modulus variation with PPS content.

Figure 6. A) Tensile curves of PLGA blends. B) Tensile curves of PLGA blends with 10% of PTX.

Figure 7. A) Water uptake of PLGA blends. B) Mass loss over degradation process of PLGA blends.

Figure 8. A) PTX cumulative release from PLGA blends with 20% of each additive: PPS, PNS, PDS and PEG. B) PTX initial release phase from PLGA blends with 20% of each additive: PPS, PNS, PDS and PEG. C) PTX cumulative release from PLGA blends with 5, 10 and 20 % of PPS. D) PTX initial release phase from PLGA blends with 5, 10 and 20 % of PPS.

Figure 9. In vitro cell viability/proliferation of NIH/3T3 fibroblast on PLGA blends with 20% PPS, PNS, PDS and PEG.
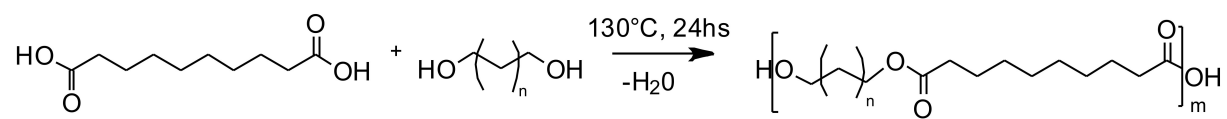
Table 1. General properties of synthesized polymer.

Material	Mn (Da)	Mw (Da)	PDI	Monomer Molar Proportion (SA/diol)	^{1}H-NMR Monomer Molar Proportion (SA/diol)	SCA (º)	Td (ºC)	Tc Tm (ºC)
PPS	5800	6300	1.08	1:1	1.04:1	53.4 ± 2.6º	435	Tc: 19 Tm: 48
PNS	6100	6500	1.06	1:1	1:1	60.5 ± 1.4º	440	Tc: 48 Tm: 64
PDS	6500	6900	1.05	1:1	1.01:1	62.4 ± 0.9º	445	Tc: 58 Tm: 71

Table 2.

Mechanical properties of PLGA plus additives.

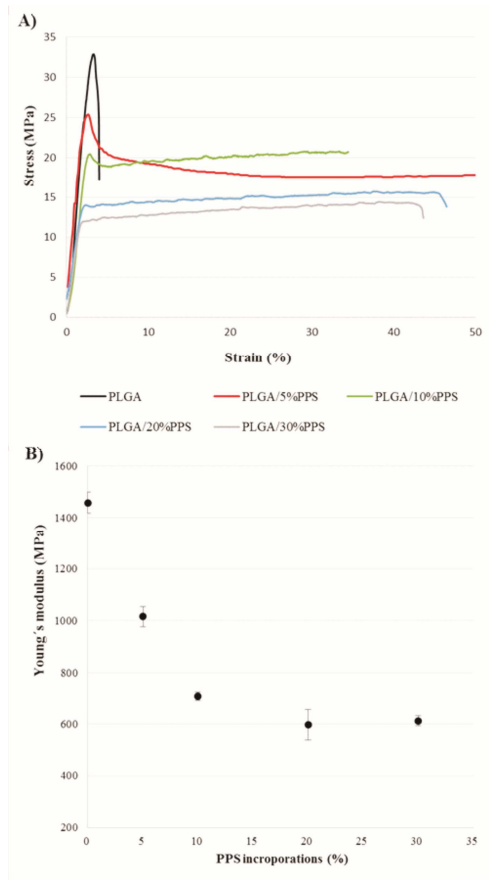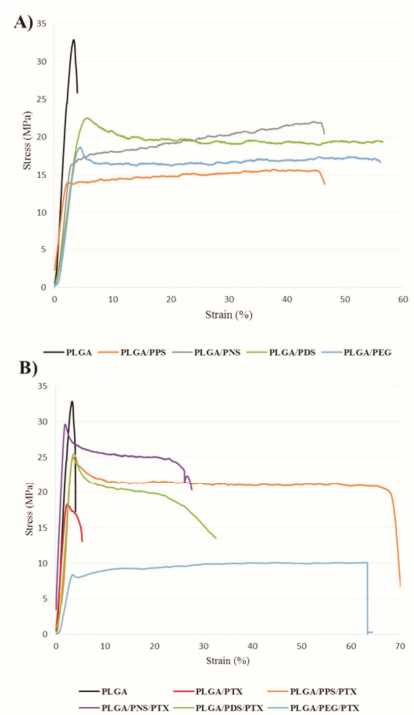| Material	YM (MPa)	Yield strength (MPa)	Ultimate strain (%)	Ultimate stress (MPa)
PLGA	1457 ± 41	32,8 ± 2,6	4.0 ± 0.2	32,8 ± 2.6
PLGA/PTX	829 ± 92	18.3 ± 3.1	5.7 ± 1.4	18.3 ± 3.1
PLGA/PPS	596 ± 60	13,1 ± 1,6	48.0 ± 4.0	15.8 ± 2.1
PLGA/PPS/PTX	958 ± 72	σ2 :25.2 ± 0.9 σ1: 23.6 ± 1.3	60.1 ± 7.3	23.1 ± 4.3
PLGA/PNS	866 ± 111	19.6 ± 1.0	48.0 ± 8.0	21.4 ± 1.1
PLGA/PNS/PTX	986 ± 197	σ2 26.1 ± 1.6 σ1: 24.2 ± 1.4	21.1 ± 5.7	25.4 ± 0.2
PLGA/PDS	857 ± 149	σ2 :22.1 ± 5.1 σ1: 21.8 ± 1.3	50.0 ± 12.0	22.1 ± 5.1
PLGA/PDS/PTX	986 ± 197	σ2 26.1 ± 1.6 σ1: 24.2 ± 1.4	25.2 ± 2.8	18.8 ± 2.1
PLGA/PEG	572 ± 116	σ2 19.8 ± 2.3 σ1: 17.5 ± 1.2	55 ± 1	19.8 ± 2.3
PLGA/PEG/PTX	750 ± 96	σ2: 9.2 ± 1.4 σ1: 8.3 ± 0.5	50.8 ± 4.2	9.7 ± 0.3