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## Structural properties of biodegradable polyesters and rheological behaviour of their dispersions and films

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**Abstract**—This paper focuses on the dependence of the rheological properties of PLA-PEG and PLGA dispersions and films on the polymer structural properties, in order to obtain useful information to predict and explain the performance of polyesters films as drug-delivery systems. To carry out the work, one PLA-PEG and three PLGA polymers of different molecular mass were synthesized and characterized by NMR, GPC, DSC and TGA-FT-IR. To characterize the viscoelastic behaviour of concentrated solutions in dichloromethane and of the films obtained by a solvent-casting technique, oscillatory shear rheometry was used. The polymer dispersions showed a characteristic Newtonian viscous behaviour, but with different consistency index depending on the nature of the polymer. Freshly prepared, PLGA and PLA-PEG films had elastic modulus ( $G'$ ) greater than viscous modulus ( $G''$ ). The decrease in both moduli caused by an increase in temperature from 25 to 37°C was especially marked for the polymers with  $T_g$  below or around 25°C (PLGA 27 kDa and PLA-PEG 27 kDa). After being immersed in pH 7.4 aqueous solution for one week, PLGA films showed a significant increase in both  $G'$  and  $G''$ , due to the promotion of polymer-polymer interactions in a non-solvent medium. In contrast, the PLA-PEG film became softer and more hydrated, due to the amphiphilic character of the polymer. The water taken up by the film acted as a plasticizer and induced the softening of the system. These results suggest that the presence of PEG chains exerts a strong influence on the mechanical properties of polyesters films and, possibly, the performance as coating or matrices of drug-delivery systems.

*Key words:* PLA-PEG; PLGA; viscoelasticity; biodegradable polymers; polymer films; glass transition temperature.

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## INTRODUCTION

Biodegradable polymers are well established in the pharmaceutical, medical and biomedical fields as useful biomaterials for preparing eroding drug-release devices to be injected, implanted or inserted [1, 2]. These polymers, which are mostly represented by polyesters such as poly(D,L-lactide) (PLA) and poly(D,L-lactide-co-glycolide) (PLGA), are being extensively evaluated for the controlled delivery of many kind of drugs [3]. The incorporation of water-soluble polymers, such as of polyethylene glycol (PEG), by transesterification of PLA and PLGA, notably improves the biocompatibility of blood-contacting biomaterials [4, 5].

The most frequently used drug delivery systems based on biodegradable polymers are microparticles, implants, fibres and films [6]. Structural properties such as monomer composition, mean molecular weight, polydispersity and glass transition temperature of polyesters have been shown to play an important role in the drug release mechanism and rate from the systems made of these polymers [7–10]. Although polyester biodegradation can be modulated by choosing adequate monomer ratios and polymer molecular masses [6, 11], the information regarding the evolution of the mechanical properties of the polymeric devices is much scarce. However few, these studies have shown that to predict membrane rupturing and, therefore, drug release from multiparticulate or single-unit reservoir polyester systems under physiological conditions, is essential to know how the mechanical properties are changed when the device is immersed into aqueous fluids [12–14]. The recording of the elastic ( $G'$ ) and viscous ( $G''$ ) moduli of some hydrogels and polyesters implants clearly indicates that the release of proteins from biodegradable polymer systems is largely controlled by the evolution of the network structure during degradation [15, 16]. In the particular case of drug-loaded films, prepared by solution casting of polymers and drug dissolved in a volatile medium [14], the viscoelastic properties of the initial drug-polymer dispersion also determines to a great extent the homogeneous drug distribution, handling and performance of the films [17].

The aim of this work was to try to correlate the rheological behaviour of the dispersions and films of PLA-PEG and PLGA with the structural properties of the polymers, namely nature, molecular mass and glass transition temperature. Oscillatory shear rheometry, which is a technique commonly used to characterize the rheological behaviour of viscous solutions and, more recently, of solids materials [18, 19], was used to evaluate the viscoelastic character of concentrate solutions in dichloromethane and of the films, as freshly prepared and after being immersed in pH 7.4 aqueous buffer solution for one week. The evolution of the mechanical properties of the films when exposed to this medium may provide useful information about their performance as drug devices.

## MATERIALS AND METHODS

### Materials

The polymers used were synthesized by ring-opening polymerisation of initial cycle dimers D,L-lactide (Aldrich) and glycolide (Boehringer-Ingelheim) following the method described by Gilding and Reed [20] for PLGA and by Gref *et al.* [21] for PLA-PEG. D,L-Lactide was recrystallised in ethyl acetate (Merck) at room temperature until the racemic mixture melting point was attained (124–126°C), while glycolide and polyethyleneglycol were used directly (melting point 88–90°C and 50–58°C, respectively). Stannous octoate and lauryl alcohol (Sigma) were used as catalyst and chain transfer agent, respectively. The polymerization was carried out in glass ampoules immersed in an oil bath maintained at the right temperature and time. The polymer was extracted and precipitate with different solvents. Table 1 summarizes the synthesis conditions employed for each polymer.

### Structural characterization of the polymers

The average molecular mass of each polymer was determined by gel-permeation chromatography (GPC, Waters) using polystyrene standards (Tokyo Soda) with molecular mass 2.8–355 kDa as reference. Filtered tetrahydrofuran (Merck) was used as the mobile phase at a flow rate of 0.9 ml/min [16].

The polymer composition was determined by <sup>1</sup>H-NMR with a Bruker AMX-400 spectrometer using CDCl<sub>3</sub> as solvent. The relative proportions of lactic-glycolic (LA-GA) to glycolic-glycolic (GA-GA) acid bonds were assessed by <sup>13</sup>C-NMR at 100.61 MHz using DMSO-d<sub>6</sub> as solvent.

A computer-interfaced DSC (DSC 821, Mettler Toledo) equipped with a low-temperature environmental chamber was used to determine the glass transition temperature ( $T_g$ ) of the polymers. Approx. 5 mg of each polymer was analysed in a nitrogen atmosphere at a heating and cooling rate of 10°C/min. The  $T_g$  was estimated as the temperature at which the bisector of the angle between the two

**Table 1.**  
Composition and synthesis conditions of the polymers

	Polymer			
	PLGA1	PLGA2	PLGA3	PLA-PEG
Composition (%)	75/25	75/25	75/25	70/30
Stannous octoate (%)	0.1	0.1	0.1	0.4
Lauryl alcohol (%)	0.01	0.01	0.01	—
Temperature (°C)	140	140	140	150
Time (h)	1	2.5	2.25	1
Extraction	Chloroform	Chloroform	Chloroform	1,4-Dioxane
Solvent	Methanol	Methanol	Methanol	Water

tangents intersects the measurement curve. The temperature calibration was done with the melting point of indium. The assays were carried out in triplicate.

Thermogravimetric analysis was carried out by heating 5–10 mg samples at 10°C/min up to 120°C, under nitrogen atmosphere, using a high-resolution TGA 2950 (TA Instruments) equipped with an evolved gas furnace and directly connected to an FTIR Bruker Tensor 27 (Bruker Optik). Loss in weight was analysed with TA Instruments Universal Analysis 2000 software (v. 3.3B), while the decomposition products evaporated from the samples were identified using the FTIR OPUS software and a Bruker Library (Bruker Optik).

#### *Preparation and characterization of polymer dispersions*

Different polymer dispersions were prepared (w/v) in dichloromethane (DCM): (1) 30% PLGA 48 kDa, (2) 25% PLGA 38 kDa, (3) 25% PLGA 27 kDa, (4) 30% PLGA 27 kDa and (5) 25% PLA-PEG 27.5 kDa. These dispersions were subject to rotational viscometry and oscillatory rheometry assays at 25°C in a Rheolyst AR 1000N rheometer (TA Instruments) equipped with an AR2500 data analyser and a cone-plate geometry (4 cm and 1.58°) with a solvent trap cover. Flow curves were fitted to the Ostwald equation [22]:

$$\eta = m \times \gamma^n, \quad (1)$$

by non-linear regression, where  $\eta$  is the viscosity,  $\gamma$  the shear rate,  $m$  the consistency index and  $n$  the fluidity index, which provides information about the Newtonian or non-Newtonian behaviour of the system.

The oscillatory rheometry assay was carried out applying 1% strain and angular frequencies of 0.1–50 rad/s, recording the value of the elastic and viscous modulus ( $G'$  and  $G''$ , respectively) of each co-polymer dispersion.

#### *Preparation and characterization of polymer films*

Each polymer dispersion in DCM (25%, w/v) was poured into polyvinyl chloride (PVC) moulds and the DCM was allowed to evaporate slowly at 5°C for 24 h. Then, the films obtained were taken out of the moulds and cut into 1.0 × 1.5 cm pieces.

The rheological behaviour of the films before and after immersion for 1 week in phosphate buffer (pH 7.4) was evaluated in duplicate at 25°C, applying 1% strain and angular frequencies of 0.05–50 rad/s in a Rheolyst AR 1000 N rheometer (TA Instruments) equipped with an AR 2500 data analyser, an environmental test chamber and a solid torsion kit. The gap was  $9.5 \pm 0.5$  mm. The temperature dependence of the elastic and viscous moduli of dry films ( $G'$  and  $G''$ , respectively) and of  $\tan \delta$  (i.e.  $G''/G'$ ) was recorded for an angular frequency of 0.1 rad/s by measuring these parameters while increasing the temperature from 25 to 37°C at 3°C/min.

Evolution of the molecular mass of the polymer in the films immersed for 7 days at pH 7.4 was recorded by GPC as described above. The degradation index, which

represents the ratio between the number of cleavages and the number of bonds initially presents [23], was calculated as follows:

$$DI = (M_n^0/M_n^t) - 1, \quad (2)$$

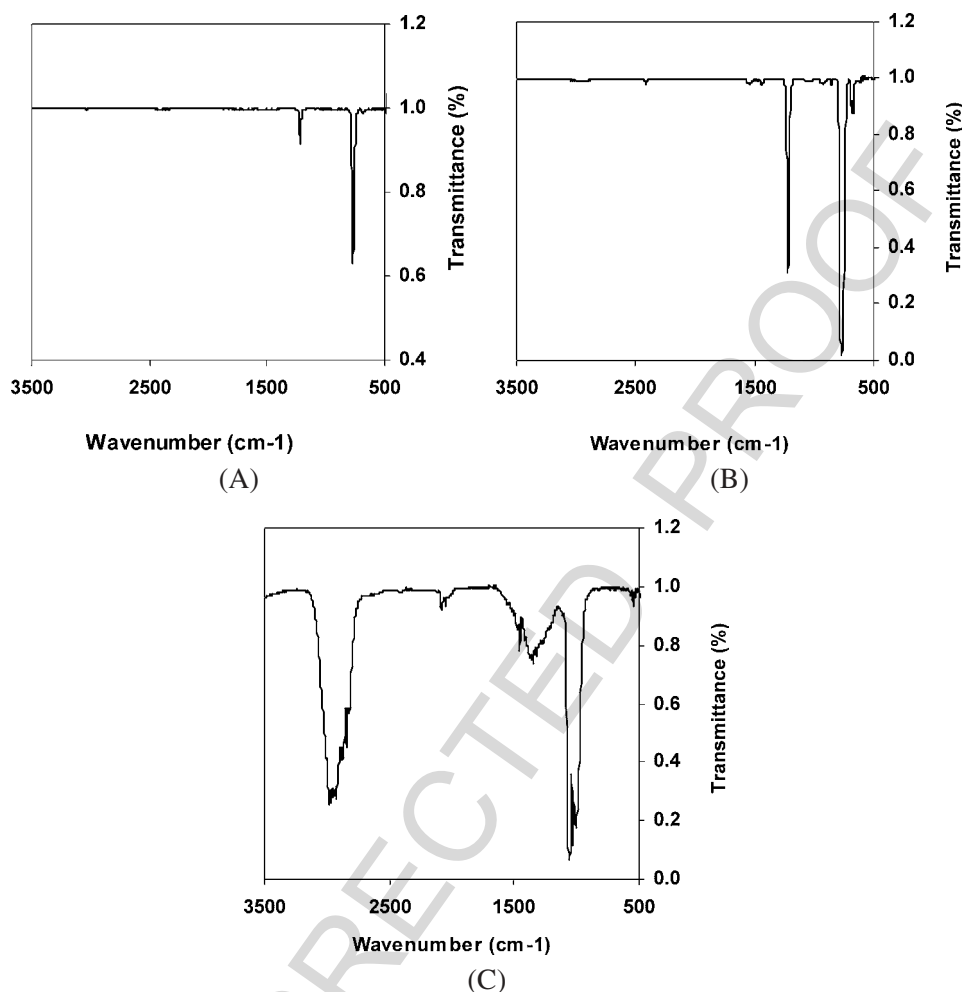
where  $M_n^0$  and  $M_n^t$  are the initial number-average molecular mass and that determined at the time  $t$ , respectively.

## RESULTS AND DISCUSSION

Table 2 shows the structural characteristics of each polymer. The three PLGA have the same relative proportions of GA-GA and LA-GA but different molecular mass (48, 38 and 27 kDa). The molecular mass of PLA-PEG was of 27.5 kDa. The PLGA of 27 kDa showed a particularly low  $T_g$  compared to the other polymers studied. When this polymer was stored under vacuum at 21°C during 5 and 10 days, the  $T_g$  value increased until  $8.7 \pm 2.2$  and  $11.6 \pm 3.5^\circ\text{C}$ , respectively. This effect was not observed for the other polymers. These results suggested the remaining in the material of a volatile impurity that acted as plasticizing [24]. To characterize the nature of such an impurity, not detected by GPC, samples of 27 kDa PLGA were heated using a TGA coupled with an FTIR spectrometer. This device allows identification of the nature of the substances that evaporate from the samples [25]. The samples of PLGA of 27 kDa lost 2% of their mass when they were heated from 30 to 90°C; the FT-IR spectra of the volatile compounds are shown in Fig. 1. For comparison, the FT-IR spectra of the solvents used for the synthesis, chloroform and methanol, are also shown. As can be seen, the FT-IR spectra profile of the polymer sample is superimposable with that of chloroform. Since polymer drying by solvent evaporation is finally controlled by internal diffusion [26], in order to obtain a complete removal of residual solvents an additional and controlled vacuum treatment is needed [23–28].

**Table 2.**  
Characteristics of the polymers and their dispersions

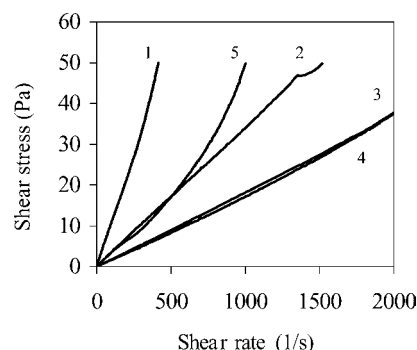
	Polymer				
	PLGA1	PLGA2	PLGA3	PLA-PEG	
Molecular mass (kDa)	48	38	27	27.5	
LA-GA/PEG	67 : 33	68 : 32	67 : 33	73 : 27	
GA-GA/LA-GA	2 : 1	2 : 1	2 : 1	—	
Polydispersity index	1.25	1.75	1.55	1.32	
Yield (%)	100	95	96	76	
$T_g$ (°C)	$30.3 \pm 0.31$	$30.0 \pm 0.4$	$-0.90 \pm 0.44$	$25.8 \pm 1.46$	
Dispersion (% w/v)	30	25	30	25	25
$N$	0.95	1.04	1.07	1.07	0.96
$m$ (Pas)	0.121	0.043	0.009	0.008	0.036



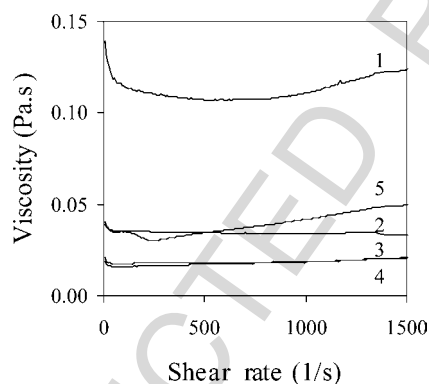
**Figure 1.** FT-IR curves for (A) PLGA 27 kDa, (B) chloroform and (C) methanol.

#### *Characterization of the dispersions*

The flow profiles of the copolymer solutions showed an almost linear relationship between the shear rate and the shear stress values (Fig. 2), which is characteristic of Newtonian behaviour. The viscosity of the polymer solutions remained practically constant along the strain interval analysed (Fig. 3). The increase in viscosity observed, in some cases, at the highest shear rate, can be attributed to the evaporation of a certain amount of DCM, a highly volatile solvent, from the solvent trap cover. This may cause a small increase in the concentration of the polymer as the experiment goes at higher shear rates, although in all cases this effect was practically irrelevant. The flow profiles were well fitted ( $r^2 > 0.99$ ) by the Ostwald equation; for all dispersions the  $n$  values are about 1. In contrast, the  $m$  values depended not only on molecular mass but also on the monomeric composition of



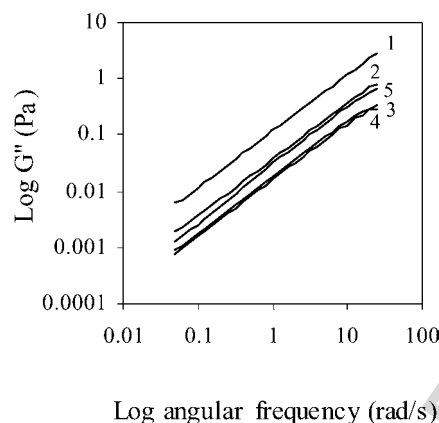
**Figure 2.** Flow curves of the polyesters dispersions in DCM. (1) 30% PLGA 48 kDa, (2) 25% PLGA 38 kDa, (3) 25% PLGA 27 kDa, (4) 30% PLGA 27 kDa and (5) 25% PLA-PEG 27.5 kDa.



**Figure 3.** Dependence of viscosity of PLGA and PLA dispersions on the shear rate applied. (1) 30% PLGA 48 kDa, (2) 25% PLGA 38 kDa, (3) 25% PLGA 27 kDa, (4) 30% PLGA 27 kDa and (5) 25% PLA-PEG 27.5 kDa.

the polymers (Table 2). At 25%, the significantly greater viscosity of PLA-PEG solution, compared to that of PLGA 27 kDa, is related to their different affinity for the solvent. PLA-PEG has an amphiphilic character owing to the hydrophilic PEG chains. In aqueous medium, the polymer chains self-assemble as core (PLA)–shell (PEG) structures [29]. In a better solvent for PLA (organic medium), it is foreseeable that the polymer chains adopt a more uncoiled conformation, although the interactions among the hydrophilic groups of PEG segments could be promoted. This conformational disposition may justify the greater resistance to flow of PLA-PEG chains compared to those of PLGA.

When the stress is applied as a sinusoidal time function, in the oscillatory rheometry assays, the resulting time-dependent strain provides information about the role that the viscous ( $G''$ ) and elastic ( $G'$ ) components play in the mechanical behaviour of each system analysed. Figure 4 shows the dependence of  $G''$  on the angular frequency of each polymeric dispersion. For all systems analysed the value of  $G'$  was invaluable. Additionally, the log–log plot of  $G''$  versus angular frequency



**Figure 4.** Influence of the angular frequency on the viscous modulus ( $G''$ ) of PLGA and PLA dispersions. (1) 30% PLGA 48 kDa, (2) 25% PLGA 38 kDa, (3) 25% PLGA 27 kDa, (4) 30% PLGA 27 kDa and (5) 25% PLA-PEG 27.5 kDa.

had a slope close to 1. This behaviour indicates that the dispersions behave as a Maxwell fluid in which the polymer concentration is below its entanglement value [30, 31].

As expected from the flow data, the greater molecular mass of the polymer, the higher  $G''$  values of the dispersions. In the case of PLGA 27 kDa, the values of  $G''$  were similar for both concentrations studied, and lower than those observed for the PLA-PEG dispersions. This observation suggests that the replacement of glycolic acid with PEG has a strong repercussion on the rheological behaviour of the polyesters dispersions, which may affect to the preparation of the films. In fact, the flow properties determined the spreadability of the solution when poured into the moulds; i.e. it was easier to extend the lowest consistency solutions than the solutions elaborated with the highest molecular mass polymers. Therefore, one should aim to obtain layers of similar depth to produce films of similar thickness.

#### *Characterization of the films*

All freshly prepared films, prior to immersion in pH 7.4 phosphate buffer, showed values of  $G'$  higher than of  $G''$ , practically independent of angular frequency (Figs 5A and 6A). The  $G'$ - and  $G''$ -curves no longer cross-over. This pattern is characteristic of a well-structured polymer network, with the  $G'$ -curve level being an index of the number of cross-links along the original polymer chains [16, 30]. In the case of our polyesters, the films are formed by physical entanglement as the solvent evaporates, although macromolecular interactions, mainly hydrophobic and, if PEG is present, hydrogen-bonding and helix-type associations are also expected [32].

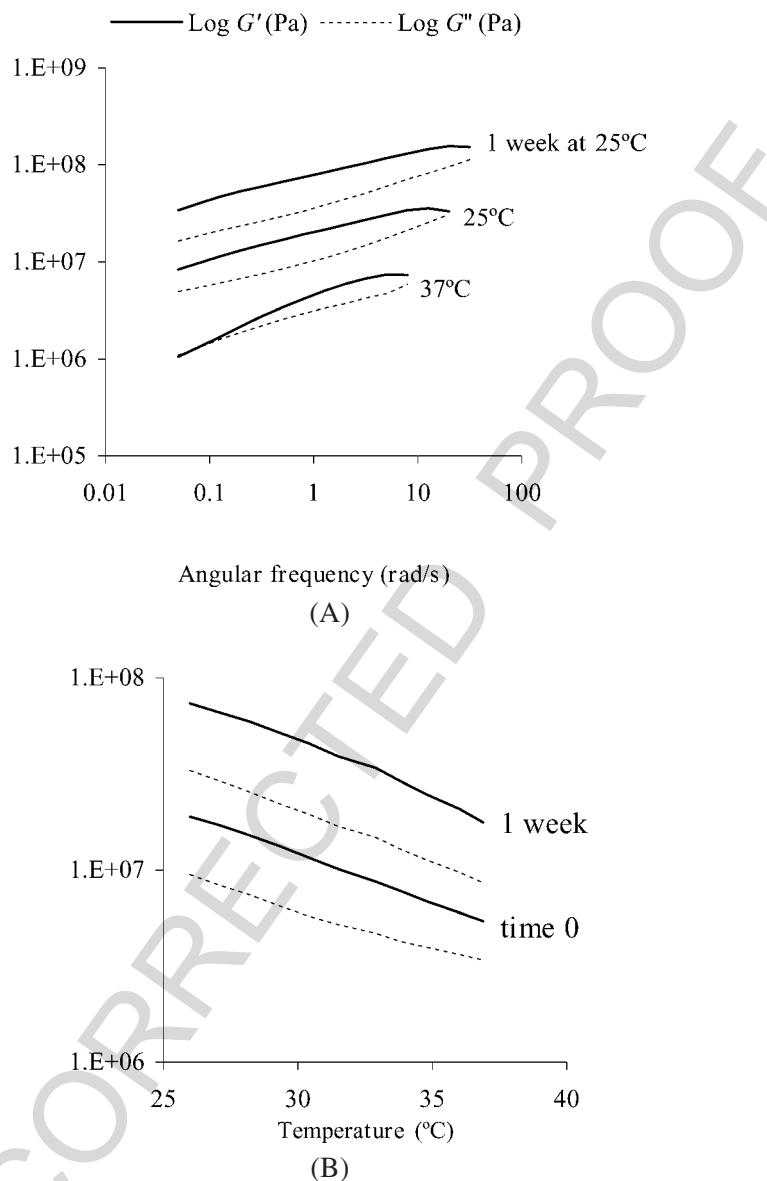
In all cases, when the temperature was raised from 25 to 37°C, which is beyond the glass transition temperature, the values of both moduli decreased due to the softening effect of the heating. The magnitude of the fall depended on the nature of



the co-polymer: one order in the case of PLGA 38 kDa and two orders for PLGA 27 kDa and PLA-PEG 27.5 kDa, probably due to the lower  $T_g$  of the latter ones. At 37°C, the films combined a high flexibility and capacity to recover the initial shape after being deformed, and the required physical strength to resist physiological stress [33].

Finally, the films were immersed in pH 7.4 buffer for one week at 25°C. This temperature was chosen to evaluate the possible incidence of the structural properties on the evolution of the mechanical behaviour of the films, since the  $T_g$  of the two high-molecular-mass PLGA and PLA-PEG is above 25°C, while the  $T_g$  of PLGA 27 kDa is well below 25°C. It has been observed previously that some polyester systems with  $T_g$  below the release medium temperature degrade and release the drug faster, because of the softening of the polymer matrix [12, 13]. After incubation of any PLGA film in the buffer, an increase in the values of both moduli was observed (Fig. 5A); the magnitude of the change being similar for all PLGA films, regardless of their molecular mass and  $T_g$ . The contact with the aqueous medium caused an increase in the rigidity of the films, which also passed from transparent to white coloured. The mass of PLGA films decreased slightly during the immersion (final weight  $98.7 \pm 0.75\%$ ) due to the erosion process caused by some polymer degradation. The decrease in molecular mass of the polymer in the films after 1 week in buffer (pH 7.4) was significant (DI about 2). An opposite rheological behaviour was observed for the PLA-PEG 27.5 kDa film. After 1 week incubation in buffer (pH 7.4), both moduli decreased with respect to the values obtained at 25°C before immersion (Fig. 6B). The softening of the film, which remained totally transparent, was especially evident when temperature was raised to 37°C. This film also showed a significant increase in mass,  $107 \pm 1.9\%$  after immersion in the buffer, and a slight diminution in polymer molecular mass (DI about 0.3).

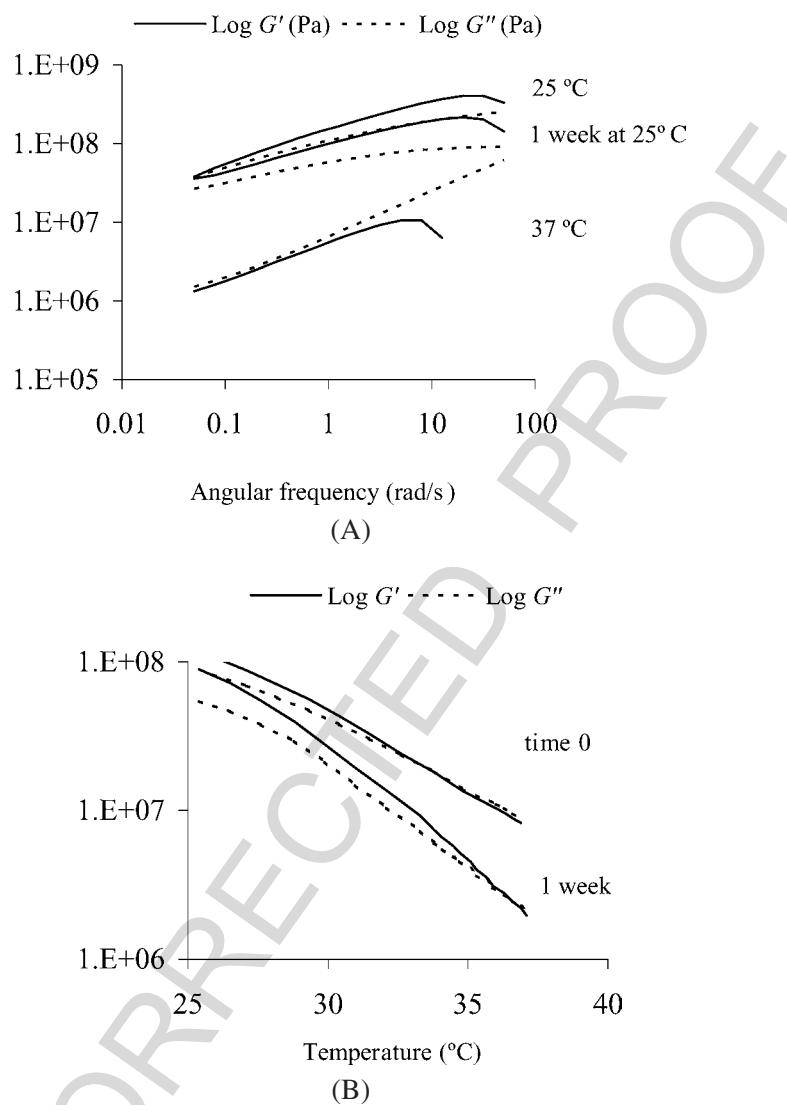
The rheological differences between the PLGA films and the PLA-PEG film may be explained, taking into account their structural properties, which condition the affinity for the medium, as follows. PLGA films are quite hydrophobic and, in consequence, their low affinity for the buffer medium causes a change in the polymer conformation to minimize the contact with water molecules. As observed for other polymers that suffer solvent-induced phase transitions, under bad solvent conditions, the polymer-polymer interactions are promoted, which results in an increase in the stiffness of the film [34]. The time of incubation was enough to significantly alter the molecular mass of PLGA. In contrast, PLA-PEG film has a more hydrophilic character due to the presence of PEG [4, 28, 35]. The water taken up by the film acts as a plasticizer and induces the softening of the system, although the molecular mass of the film remains practically constant. This different evolution of the mechanical properties during exposure to an aqueous environment can have considerable repercussions on the behaviour of these polyesters films when used as drug-delivery systems [4, 35].



**Figure 5.** Dependence of the elastic ( $G'$ , continuous line) and viscous ( $G''$ , dotted line) moduli of PLGA 38 kDa films on (A) angular frequency at 25°C and 37°C before immersion and at 25°C after immersion for 1 week in buffer (pH 7.4) and (B) temperature before and after 1 week in buffer (pH 7.4).

## CONCLUSIONS

PLGA and PLA-PEG dispersions show Newtonian behaviour in a wide shear-stress range, with consistency indices that depend on the nature and molecular mass of the polymer and on its concentration in the dispersion. All dispersions flow good



**Figure 6.** Dependence of the elastic ( $G'$ , continuous line) and viscous ( $G''$ , dotted line) moduli of PLA-PEG 27.5 kDa film on (A) angular frequency at 25°C and 37°C before immersion and at 25°C after immersion for 1 week in buffer (pH 7.4) and (B) temperature before and after 1 week in buffer (pH 7.4).

enough to prepare films by the solvent-cast technique. After one week of incubation in pH 7.4 buffer, the viscous and elastic moduli of PLGA films increase despite they lose mass by erosion and the polymer significantly degrades. The opposite behaviour is observed for the more hydrophilic PLA-PEG film. These results indicate that the affinity of the polymer for the medium exerts a stronger effect on the evolution of the rheological properties of the films, than other structural characteristics such as molecular mass or glass transition temperature.

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