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# On the importance of physical and mechanical properties of PLGA films during drug release

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## ABSTRACT

Physical and mechanical properties of the drug-incorporated polymer play a significant role in the release behavior from the drug carriers. Understanding the relative extent of variation in the physical and mechanical properties of the polymer makes it possible to improve the design of polymer carriers to obtain better release profile and increase drug stability. Drug delivery from PLGA loaded with various percentages of diclofenac sodium (DS: 0, 5%, and 10%) at different flow rates of 0 and 7.5 ml/s (flow rate of the healthy internal carotid artery) in phosphate buffered saline (PBS) for different release intervals has been studied. In this research, the change of some physical properties such as free volume fraction, glass transition temperature ( $T_g$ ) and mechanical properties before and during PLGA release have been investigated. In-vitro release tests have been performed in the PBS medium at the temperature of 37 °C. The results showed that during drug release, Young's modulus and ultimate stress were increased while elongation at break was decreased for different drug loaded films and flow rates. In addition, the zero order kinetic model was found to best fit all the release-profiles obtained.

## 1. Introduction

Local drug delivery systems, which have been shown to improve drug efficacy and reduce drug-induced side effects, have been the attention of many researchers [1,2]. In this area, drug-loaded stents, and implants showing the ability to deal with the diseases have been among the challenging topics [3,4]. This issue became so important that the use of drug-eluting stents is one of the main approaches to counteract blood coagulation after stenting [5].

Achieving an ideal and sustained drug release profile to deal with the diseases created after placing implants or stents has been one of the great importance [6]. The inability to control properly drug release from these implants has led to the use of polymers as coatings on devices to achieve better profiles. To increase the drug loading, the use of drug-loaded polymers as a coating of implants has shown the effectiveness and efficiency of using this method [7,8].

Maintaining the proper physical and mechanical properties of the polymer coating used after stenting has been very critical, so that the separation of the coating particles after placement of the stent has led to embolization [9,10].

Considering the important effect of the polymer on drug release profile from the coated drug eluting stents, some studies suggested using the biodegradable polymer for creating the more suitable profile [11]. The correlation between non-biodegradable polymers and late stent thrombosis is another reason for the attempt to search for the alternative drug delivery polymers that are biodegradable [6,12–14]. Among the polymers used as a coating agent, polylactic acid-co-glycolic acid (PLGA) has a prime position for its good biocompatibility, suitable drug release, and good degradability [15]. Also, tunable drug release from PLGA by changing the molecular weight is another reason which this polymer has received acute attention in ongoing drug-eluting stents research [16].

In vitro studies on PLGA-coated stents have identified this polymer as an excellent candidate for more investigation [17]. Analyzing the physical properties, stability, and kinetic of the drug released has always played an important role for investigation of the polymer as a covered for the drug-eluting stent. In this regard for improving the design and properties, studies have analyzed the polymeric films, and the research has tried to improve the degradability and drug release properties [18–21]. The importance of evaluating physical properties is such that

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in the study by Xi et al. [22], the amount of PLGA degradation in vitro and in vivo was investigated. In the study, similar degradation rates were reported for in vitro and in vivo coated stents, while the practical method for measuring the amount of degradation of the coated layer degraded in tissue environments remained a challenge for studies [22]. There are also the studies that have shown the importance of transition temperature and the effect of these properties on the final drug release profile [23,24]. In addition, due to the importance of mechanical properties of coatings on stents after placement in the body and the need to maintain the stability of these properties during the use of drug carriers in place, analysis of mechanical behavior of coatings has been another important parameter. In this area, researchers have always tried to get a more accurate estimate of the results by bringing the experimental environment closer to the real environment [23]. Because of the importance of polymer degradation on the drug release profile and the mechanical properties, studies have tried to investigate and optimize these properties in PLGA polymers [25]. Steele et al. [19] investigated the effect of different ratios of polyethylene glycol to create a favorable release profile from PLGA films. Also, the mechanical properties of PLGA in these cases were evaluated. Moreover, the important effect of  $T_g$  on the degradation and the drug release rate is shown. Moreover, the effect of adsorbed water was investigated by Blasi et al. [26] in their study, the effect of water as a plasticizer or anti-plasticizing was shown. The water absorbed by PLGA acted as a plasticizer and reduced  $T_g$ .

Because of the high cost of the in vivo tests, studies have always tried to bring the in vitro test conditions closer to a more real environment. According to studies, the importance of the flow rate on the stress created on stents [16,27], suggests the presence of the flow rate to make similarity with the real condition. For this purpose, the use of shakers, paddle apparatus (USP 2), the flow-through cell apparatus (USP 4), and the reciprocating holder apparatus (USP 7) methods have been some of the methods that have been used to get a more accurate estimate of drug release from drug-eluting stents [28]. Developing a bio-relevant means of testing DES in vitro models under a speed up regime is an important aim of investigations. This will make it possible to develop the DES's more quickly with the new apparatus and procedures. The data from the various release tests will improve the multi-physical models developed and thus to establish a reliable correlation between speed up and normal tests [29,30].

The study of the physical and mechanical properties of drug delivery systems is a topical subject. In particular, the control of the sustained release profile of the drug from coated stents remains, so far, a major issue of research and development [31–33]. However, to our best knowledge, no special attention has been given to variation of the physical and mechanical properties during the drug release with considering the effect of the flow rate.

In this study, we examined the physical and mechanical properties of PLGA films under static and dynamic flow conditions, for non-loaded and loaded diclofenac sodium samples. The effect of the water absorption, degradation rate, glass transition, free volume fraction on the drug release with considering two parameters of drug percentage and flow rate were analyzed. The mechanical properties of polymer films with considering the same parameters at different times of in-vitro tests were examined.

## 2. Materials and methods

### 2.1. Materials

Poly (lactic-co-glycolic acid) PLGA with the molar ratio of D,L-lactic to glycolic acid, 50–50, MW = 38–54 KDa, ethyl acetate was the solvent used in this regard. A model drug with the water solubility of about  $0.014 \text{ mg ml}^{-1}$  and the molecular weight of 318.13 (named as diclofenac sodium (DS)) was used and phosphate buffered saline (PBS) was the buffer solution for mimicking the human body fluids. All of the ingredients were purchased from sigma Aldrich, France.

### 2.2. Sample preparation

For each set of films 20% w/v polymer to the solvent (ethyl acetate) was prepared with 5 wt% and 10 wt% DS, which means for 1 g of PLGA, 0.05 and 0.1 g drug was added. First the solution of the drug and the solvent was prepared then it was agitated on the magnetic stiller until completely homogenizing the drug in the solvent afterwards the weighted PLGA was added to the solvent and finally the solution was continued to agitate with 700 rpm about 1 h. Then the solution was cast in the mold covered with Teflon, followed by drying at the room temperature for 24 h. Finally, the mold was placed in the vacuum oven at the temperature of  $40^\circ \text{C}$  for 24 h. The rectangular films were cut with the dimensions of  $0.3 \times 5 \times 30 \text{ mm}^3$ . These dimensions are considered as an enlarged dimensions of the strut of a stent.

### 2.3. Characterization methods

#### 2.3.1. Microscopic observations

Scanning Electronic Microscope (HITACHI 4800 SEM), was used to investigate qualitatively the material microstructure and especially the evolution of the polymer morphology during the release test and after the tensile test.

#### 2.3.2. Differential scanning calorimetry (DSC) analysis

DSC Q10 V9.0 was used to find out the temperature evolution near the glassy temperature. The samples were equilibrated at  $0^\circ \text{C}$  and then mounted to the  $70^\circ \text{C}$  with the rate of  $5.00^\circ \text{C}/\text{min}$ , around the range of the glass transition temperature of the PLGA, to see the effect of the in-vitro test on the glass transition temperature.

#### 2.3.3. Dynamic thermo-mechanical analysis (DMTA)

For DMTA tests, the device Dynamic Mechanical Analyzer type Q800 V21.2 was used. The dimensions of the rectangular specimens were approximately  $30 \times 5 \times 0.3 \text{ mm}^3$ . The tests were performed over the entire temperature range of the apparatus at  $0$  to  $70^\circ \text{C}$  with the step of  $2.00^\circ \text{C}/\text{min}$ , at multi-frequency of 1, 2, 5, 10, 25 Hz, and at constant amplitude. The storage and loss modulus are measured fitting to the temperature, and their corresponding values are calculated in this way.

#### 2.3.4. Mechanical testing

Quasi-static tensile tests with the velocity of  $5 \text{ mm}/\text{min}$  were performed with an electromechanical and hydraulic system, Instron 4301 machine at the ambient temperature to see the effects of drug percentage, flow rate and the release on the mechanical behavior of PLGA. The time intervals chosen for the samples of the static state were 0, 1, 12, 24, 48 h and for the continuous state were 0, 1, 3, 6, 12 h because of the release kinetic.

#### 2.3.5. Fourier transform infrared spectroscopy (FTIR)

PLGA-Film degradation was evaluated using Fourier-transform infrared spectroscopy (FTIR) by examining the changes in area or disappearances of certain characteristic peaks. FTIR was performed on a Perkin-Elmer FTIR Spectrometer model on solvent cast pure films after the static in-vitro test of the samples in the PBS at the specified time points: 1, 12, 24, 48 h.

### 2.4. In vitro drug release procedure and associated measurement

The UV–Vis spectrophotometry lambda 35 was used to determine the concentration of DS in the PBS solution. To calculate the accumulative release percentage of the drug, the total amount of DS loaded to the PLGA polymer was also measured after degrading completely the polymer film in the ultrasound at high temperature. To establish the calibration curve of measurements, known concentrations of DS in PBS were measured. The following calibration equation was found with the correlation coefficient of  $R^2 = 0.999$  and used: Absorbance (counts) =

$0.094 + 0.034 \times \text{concentration}$  ( $\mu\text{g/ml}$ ).

#### 2.4.1. Static test

The prepared polymer films with the carriers/drug mass ratio of 5 and 10% of DS to PLGA were immersed in the 10 ml of phosphate buffered saline (PBS) solution with a ratio of  $60.0 \text{ mg ml}^{-1}$  at  $37^\circ\text{C}$  and pH 7.4 at the static state. The results of the release were obtained at the certain time intervals, at each time step 4 ml was sampled for analyzing and 4 ml fresh PBS was added to the solution.

#### 2.4.2. Continuous test

In the continuous state, a test bench was designed to allow the solution to rotate with different flow rates, which was controlled by the LabVIEW. The sample is placed in the chamber, from one side is contacted with the flow medium and the other side with a rigid surface [34].

This test bench has a reservoir which contains 1 L of PBS, at each time step 4 ml of the solution was sampled. The Buffer solution was maintained at the temperature of  $37^\circ\text{C}$  and the pH of 7.4.

### 3. Results and discussion

#### 3.1. Evaluation of drug release

##### 3.1.1. Drug delivery and polymer morphology

Fig. 1 shows the optical microscopic images of the PLGA samples with 5 and 10% of the drug (PLGA-5%DS, PLGA-10%DS) after certain intervals of the release test. These pictures show that by passing the time of the release, the number of the pores created in the samples increases where high quantity of the pores [35] created in the PLGA samples during the release is the main reason for the release.

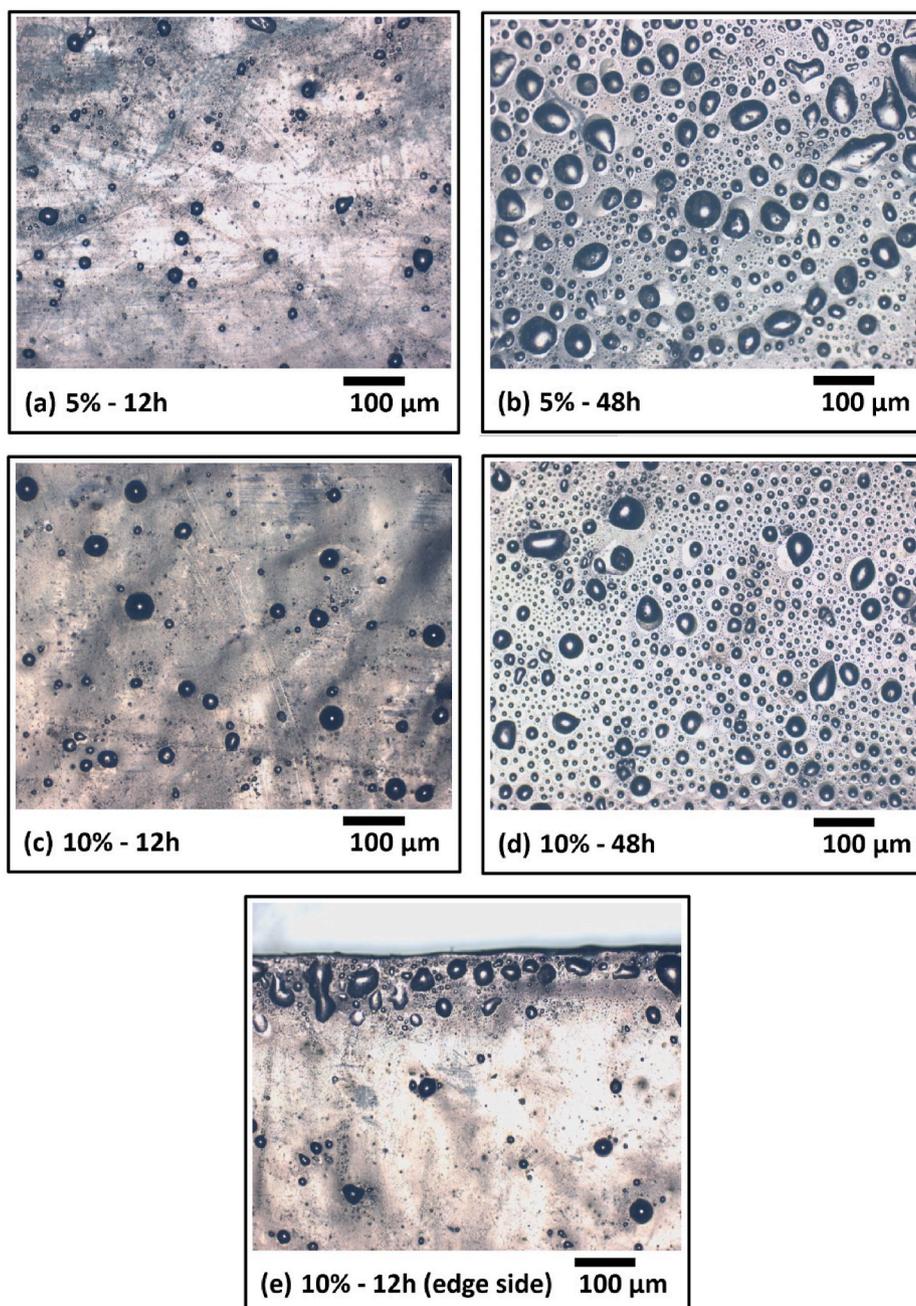


Fig. 1. Optical microscopic observations of the samples (a) PLGA-5%DS after 12 h, (b) PLGA-5%DS after 48 h, (c) PLGA-10%DS after 12 h, (d) PLGA-10%DS after 48 h, (e) PLGA-10%DS after 12 h from the edge of the sample, of drug release test under the static state.

Fig. 1(e) is taken from the edge of the surface of the same sample of Fig. 1(c) by comparing these two figures it is evident that the high quantity of the pores are formed near to the edge of the samples. Therefore, the water absorption of the samples is not homogenous in the entire surface of the samples. Moreover, the effect of the drug percentage is noteworthy. The calculation of the number of pores by the ImageJ for the samples of PLGA-10%DS and PLGA-5%DS after 48 h of release showed that the number of pores in the 10% sample is two times more than the samples with 5% of DS, this is where the surface area of the PLGA-5%DS sample is occupied by 22% of the pores whereas it is 28% for the PLGA-10%DS. One can note that higher percentages of the pores in PLGA-10%DS can be the reason for the high release kinetic of these samples compared to PLGA-5%DS.

According to the calculation by ImageJ from the high magnification micrographs, the PLGA-5%DS polymer film contains pores of 3–140  $\mu\text{m}$  in size, with a mean size of 12.42  $\mu\text{m}$  after 48 h of release and pores of 3–120  $\mu\text{m}$  in size with a mean size of 9.92  $\mu\text{m}$  for the PLGA-10%DS after 48 h of release. One can note that by increasing the initial drug load for the samples, the number of the pores created during the release increases however mean size of the pores is smaller compared to the low initial drug loaded samples. As a reason one may note that because each particle of the drug is absorbing the water, therefore as there are more drug particles more pores are formed.

This is the necessity of the drug release where the water penetrates around particles and helps them to release. Once the particles absorbed the water and form the bubbles some small bubbles grow after the drug particles have absorbed the water and some other isolated bubbles blast and results in the pores.

Fig. 2 shows the SEM micrographs of the PLGA-10%DS after 48 h of release test at two different flow rates of (a) 0 and (b) 7.5 ml/s. The effect of the flow rate on the structure of the PLGA films is evident from these figures. It is observed that without flow the bubbles are created by water absorption, however in the case with flow the bubbles seem to be exploded and the porous structure is seen which results in more release of the drug and of course decreasing the mechanical properties of the samples. Moreover Fig. 2(b) clearly shows the effect of the swelling of the polymer under the continuous state. The results show that the flow rate significantly changes the morphology of the polymer, where it

increases the roughness of the samples in the mesoscale.

It is notable from Fig. 2(c) and (d) which are the magnitude forms of Fig. 2(b) that the flow rate increases the detachment of the polymer chains and increases the molecular spacing which causes a fragile structure of the polymer. It is interesting to investigate the glass transition temperature during drug release. The latter could help to analyze the ductile-fragile transition [26,36–38].

### 3.1.2. Glass transition temperature evaluation during drug release

Amorphous polymers are identified by a glass transition temperature ( $T_g$ ), which is the point of the transformation between a highly viscous brittle material called glass and a less viscous, more elastic rubbery state. The rubbery state (above the  $T_g$ ) is a structure with high molecular mobility and is thus more susceptible than the glassy state to physical, chemical, and mechanical changes. Fig. 3 shows the variation of the glass transition temperature versus the time of the incubation in the PBS solution. The results show that increasing the drug percentages in the polymer films increase the  $T_g$  value, where the drug particles are acting as the anti-plasticizer. In this regard by increasing the drug percentages,

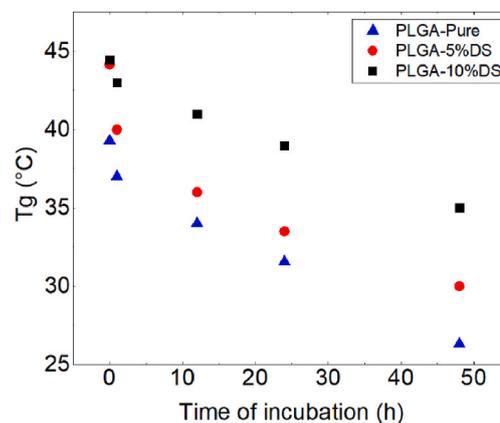


Fig. 3. Evolution of the glass transition temperature ( $T_g$ ) of PLGA-Pure, PLGA-5%DS and PLGA-10%DS according to the test time at the static state.

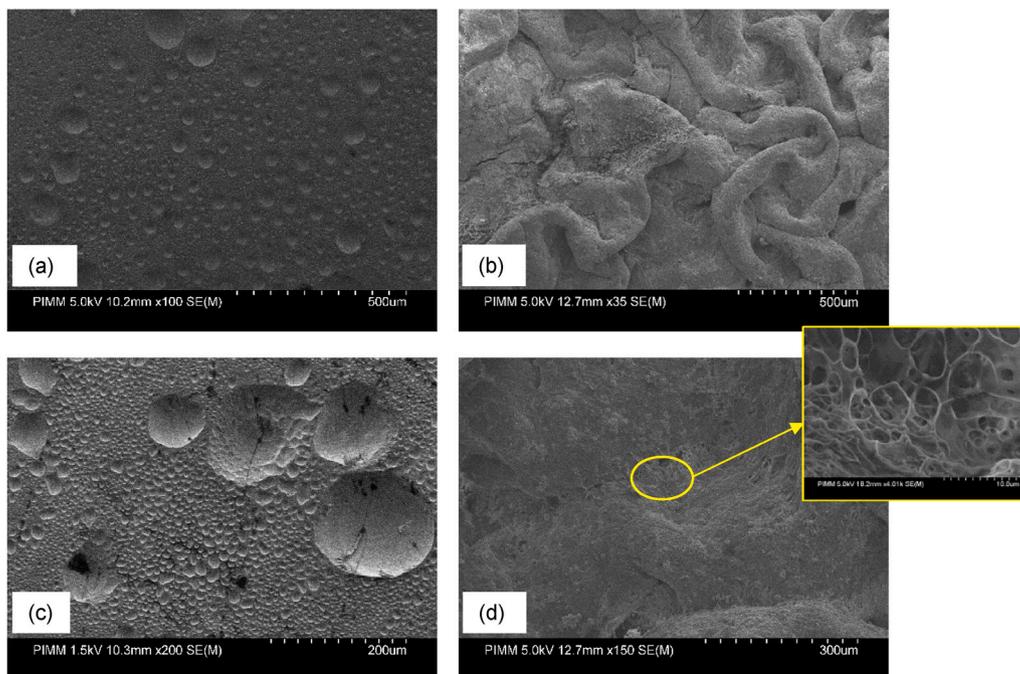


Fig. 2. SEM micrographs of PLGA-10%DS after 48 h of drug release at (a), and (c) the flow rate of 0, (b), and (d) flow rate of 7.5 ml/s, but at different magnifications.

PLGA films become more brittle. However, by increasing the time of the test, water molecules are acting as the plasticizers and decrease the glass transition temperature. The decrease in the  $T_g$  during the time of the test is normally related to the hydrolysis of the PLGA films due to the increasing of the water absorption [38]. One can notice that the release rate in PLGA can be related to glass transition temperature due to the higher macromolecular chain mobility of the polymer above its  $T_g$ . In this respects the  $T_g$  of the samples during the release decreases, however initially the test temperature (37 °C) is below the  $T_g$  of the samples but during the test  $T_g$  of the samples decrease therefore they are exposed at the temperature above their  $T_g$  it is the reason when the material reaches the glass transition temperature for some time, then is cooled slowly to room temperature that makes the material stronger and more ductile [39]. On the other hand there is the effect of the aging of the material during the time of the test. This is another reason where affects the toughness of the polymer, demonstrated in the mechanical analysis part. One can notice that the release rate from the PLGA samples which are exposed to the temperature above their  $T_g$  can be related to the higher macromolecular chain mobility and the drug diffusion through it.

### 3.1.3. Free volume fraction calculation of PLGA

The porous structure and free volume fraction change the release properties of the loaded PLGA films [35]. In the amorphous phase small holes as the free volume are created. Effect of this parameter is investigated for the PLGA films without drug and with 5%, and 10% of drug and its influence on the release behavior.

One can note that when increasing frequency, the  $\alpha$ -transition temperature,  $T_\alpha$  (related to  $T_g$ ) has an increasing trend to high temperatures. The increase of glass transition temperature during multi frequency DMTA tests is shown in Fig. 4.

The visco-elastic behavior of the polymer is related to the frequency of applied loading. This dependence between temperature and viscosity is proportional to frequency and also correlating relation which describes the temperature dependence of the molecular relaxation times in glass forming substances at the glass transition temperature  $T_g$  [40], will be explained by Williams-Landel-Ferry (WLF) equation:

$$\ln \frac{F}{F_r} = -\frac{C_2}{C_1} \frac{1}{(T_g - T_{gr})} + \frac{1}{C_1} \quad \text{Equation 1}$$

where  $F$  = frequency,  $T$  = temperature,  $F_r$  = reference frequency (1 Hz),  $T_{gr}$  = reference temperature and  $C_1$ ,  $C_2$  the characteristic constants of the material are associated to the free volume fraction,  $f_g$  in the glass transition state which is expressed by:

$$C_1 = \frac{B}{f_g} \quad \text{and} \quad C_2 = \frac{f_g}{\Delta\alpha} \quad \text{Equation 2}$$

$B$  is constant near to 1,  $\Delta\alpha$  = thermal expansion coefficient and  $f_g$  =

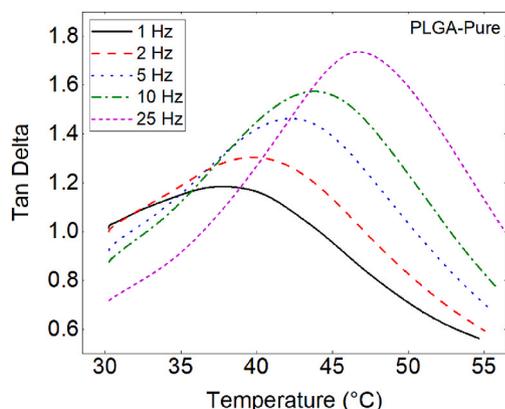


Fig. 4. Increase of glass transition temperature during multi frequency DMTA tests.

free volume fraction.

The ratio of  $C_1$  to  $C_2$  represents the slop of the straight-line plot of  $\frac{1}{\log \frac{F}{F_r}}$  against  $\frac{1}{T_g - T_{gr}}$  as it is shown in Fig. 5, where the linear regression coefficient is almost 1. This means that PLGA with and without drug under this study obeys the time-temperature equivalence principle.

Therefore, the value of free volume fraction coefficient by using  $\left( f_g = \sqrt{\frac{B \Delta\alpha A}{2.303}} \right)$ ,  $C_1$ ,  $C_2$  and  $\Delta\alpha$  for PLGA-Pure, PLGA-5%DS and PLGA-10%DS samples are calculated and presented in Table 1.

One can conclude that the effect of the drug concentration on the change of polymer molecules on mixing should be considered, or it needs to be combined with the effect of the free volumes of the constituent solvent, polymer and drug in a polymer carrier film, in the determination of its thermodynamic properties. It is notable from the results, that the free volume fraction of the polymer increases slightly with the percentage of drug loading.

### 3.1.4. Mechanical properties of PLGA

Using PLGA films as an example, the stress-strain curve can be divided into an elastic, yielding and strain-hardening region.

Fig. 6 shows that in all the samples the plasticity of the polymer after 1-h immersion in the PBS increases where they have high strain compared to the virgin ones. This is for the plasticizing effect of the water on the PLGA. However, after 1 h the effect of the test temperature, 37 °C which is near to the transition temperature of the polymer used and also the effect of the anti-plasticizer created by the addition of the drug substance [26], the effect of the swelling and erosion, moreover the creation of the pores decrease the elongation of the samples. It is obtained from Fig. 6 that by increasing the immersion time of the samples, the polymer becomes fragile, where it increases the Young's modulus and the maximum stress of the samples. These results are coherent with the analysis of the evaluation of the glass transition temperature.

This difference is more remarkable when certain percentages of the drug were added to the polymer films. However, by increasing the percentage of the drug from 5% to 10%, an increase in the elongation, decrease in the Young's modulus and maximum stress is observed. It seems plasticization of the polymer increases after a certain limit percentage of the drug. However, one can note that the more elongation for the samples of PLGA-10%DS compared to the PLGA-5%DS can be due to the small-sized pores which were observed in the optical microscopic observations.

In the case of the continuous state with the flow rate of the 7.5 ml/s, the effect of the drug percentages was not highly detectable on the maximum stress of the polymer. However, the elongation at the beak has decreased to about half (shown in Fig. 7).

Figs. 8–10 show the comparison of the Young's modulus, ultimate

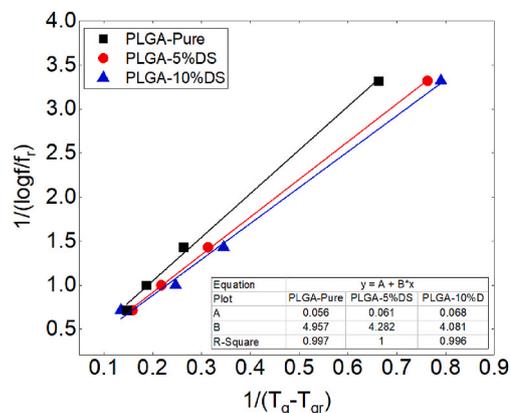


Fig. 5. Linear regression of WLF equation on the results obtained from DMA tests for the PLGA samples.

**Table 1**

The values related to the free volume fraction parameters for the samples of PLGA-Pure, PLGA-5%DS and PLGA-10%DS.

| Parameters | $C_1$    | $C_2$    | $f_g$ | $\Delta\alpha$        |
|------------|----------|----------|-------|-----------------------|
| PLGA-Pure  | 17.85714 | 88.51786 | 0.024 | $2.74 \times 10^{-4}$ |
| PLGA-5%DS  | 16.39344 | 70.19672 | 0.026 | $3.7 \times 10^{-4}$  |
| PLGA-10%DS | 14.70588 | 60.01471 | 0.029 | $4.9 \times 10^{-4}$  |

stress and strain at break values for the different percentages of the drug (0, 5%, and 10%) at different time intervals of the static and continuous in-vitro tests. The results from Fig. 8(a) and (b) show that by increasing the flow rate from 0 to 7.5 ml/s the Young's modulus of the samples have decreased to unless half. This decrease was much higher significant

for the samples with 10% of the drug. Another remark is that by comparing these two graphs one can note that variation of the drug percentage makes more variance in the mechanical properties than the variation of the flow rate. Presence of the drug has increased the Young's modulus of the polymeric samples, in contrast increasing the flow rate has decreased them.

Fig. 9(a) and (b) show the maximum stress of the PLGA with different percentages of drug at the flow rate of 0 and 7.5 ml/s, respectively. From Fig. 9(a), it is evident that increasing the drug percentage to the 5% of diclofenac sodium increase the maximum stress however in the case of 10% this value is decreased. The later can be explained by the higher swelling of the samples of PLGA-10%DS compared to PLGA-5%DS. By comparing Fig. 9(a) and (b), the effect of the flow rate on the maximum stress is evident. Where by changing the flow rate from 0 to 7.5 ml/s, the

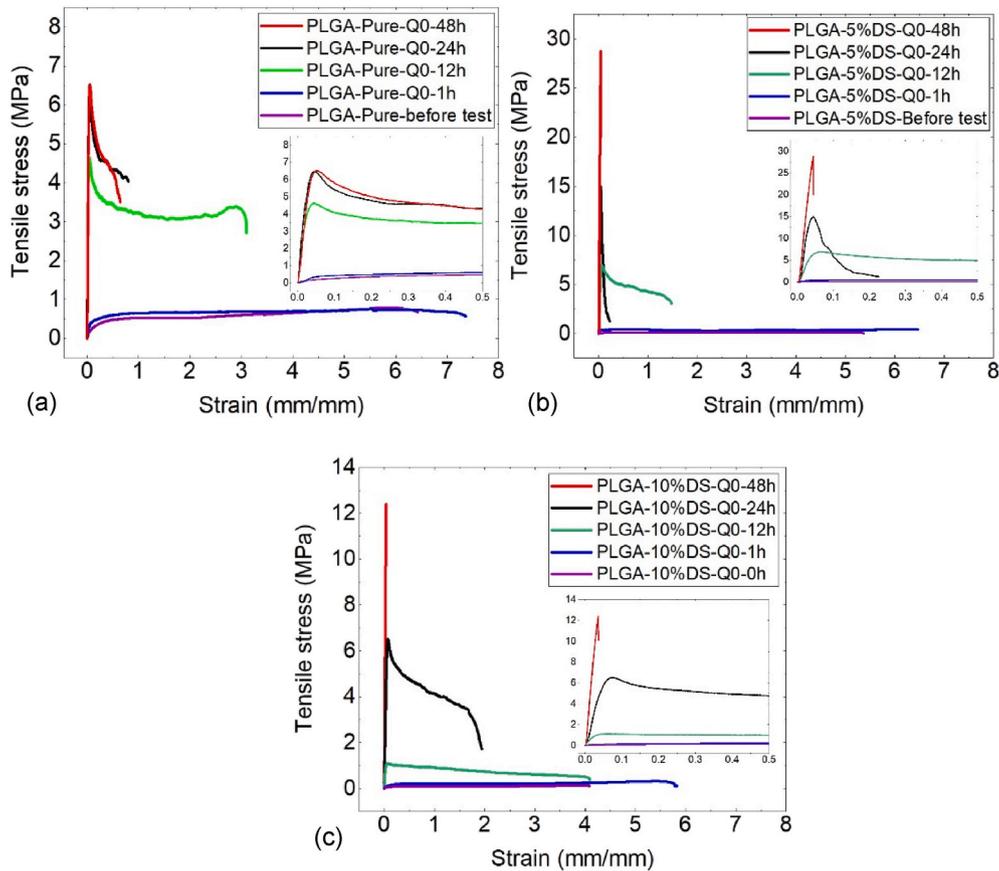


Fig. 6. Stress-strain curves of the PLGA-pure, PLGA-5%DS, and PLGA-10%DS after static test.

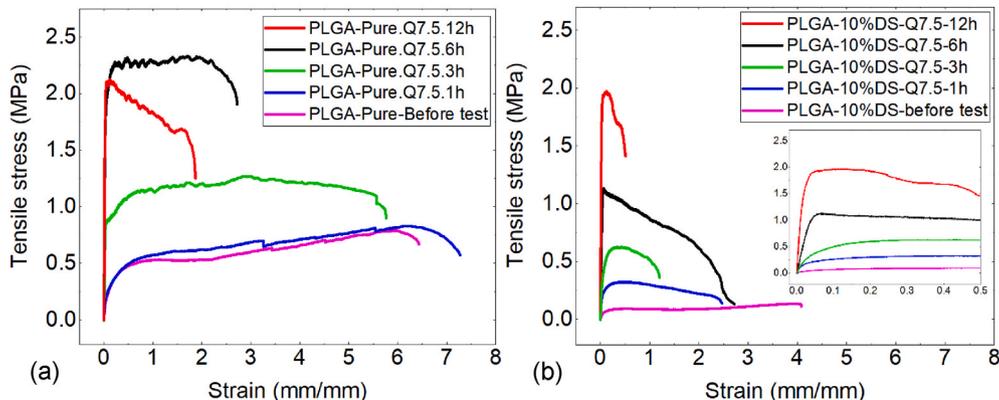


Fig. 7. Stress-strain curves of (a) PLGA-Pure and (b) PLGA-10%DS after in-vitro test under the flow rate of 7.5 ml/s.

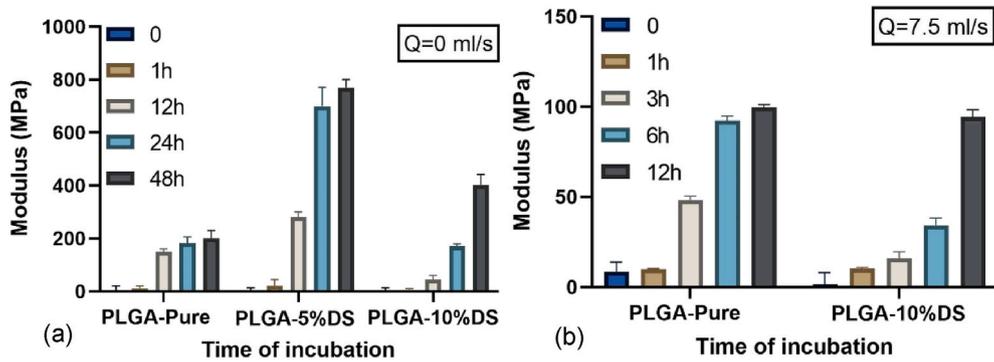


Fig. 8. Young's modulus of the PLGA samples with different percentages of DS at different times of in-vitro tests under the (a) static and (b) continuous state.

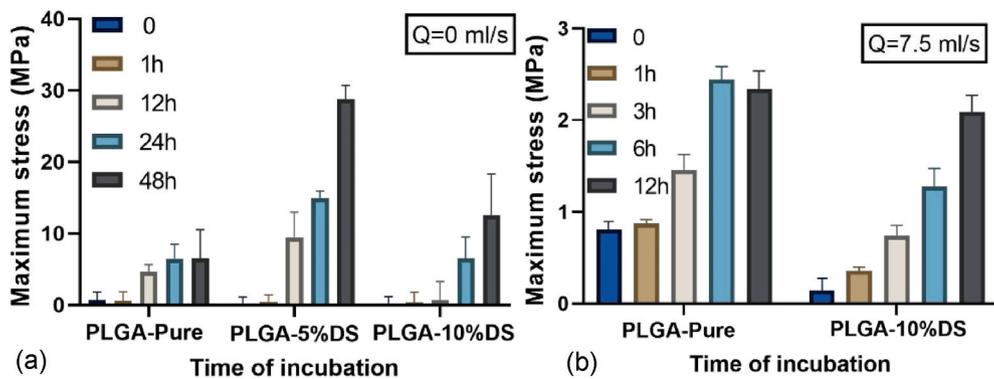


Fig. 9. Maximum stress of the PLGA samples with different percentages of DS at different times of in-vitro tests under the (a) static and (b) continuous state.

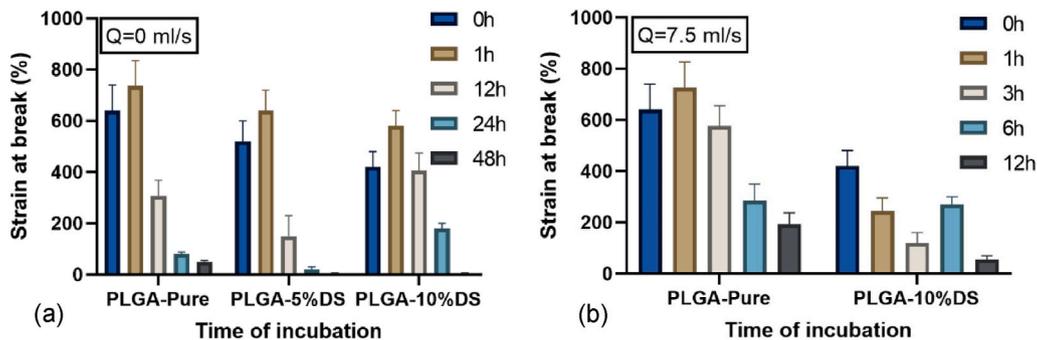


Fig. 10. Strain at break of the PLGA samples with different percentages of DS at different times of in-vitro tests under the (a) static and (b) continuous state.

maximum stress has decreased from about 5 MPa to 2.5 MPa for the samples of PLGA-Pure after 12 h of in-vitro tests. Whereas this difference is more notable for the samples of PLGA-10%DS.

Fig. 10(a) and (b) show the strain at break for the PLGA with different percentages of drug at the flow rates of 0 and 7.5, respectively. Comparing the results of the strain at break show that, increasing the initial drug load and flow rate have decreased the elongation at break. Where the effect of the flow rate is much significant when the samples are loaded with drug. Moreover, the effect of the flow rate and drug percentage is more significant by increasing the time of the release test.

Moreover, one can see from Fig. 11, the difference between two samples in contact with PBS after 1 and 24 h. The elongation is notable after 1 h of immersion; however, the bulking phenomenon is observed for the samples of PLGA-10%DS after 24 h of immersion due to the swelling. Indeed, the deformation of PLGA samples are decreased with the time of release.

From the mechanical results one can observe that the higher modulus

and maximum stress is for the samples of PLGA-5%DS. This can be explained by more homogeneity of samples in this case. This means the drug can play a role of reinforcement for PLGA, but not for all percentages. However, when the percentage of the drug is increased, the loss of properties can be due to less homogeneity. Fig. 12 shows the presence of the drug particles in the polymer film. This figure reveals how the presence of the drug in the polymer film can change the structure of the samples and in consequence their behavior during the tensile test. Drug particles change the softness of the samples in the echelles of the micron. It is observed from Fig. 12 that the drug particles in the polymer cause the small cracks which can affect the mechanical and physical properties and, in the consequence, change the release properties. This is a bidirectional phenomenon where changing the physical and mechanical properties will change the mechanism of the release and the release rate.

Fig. 13(a) shows the crack propagated after the tensile test for the samples of PLGA+10%DS after 48 h of drug release. As it is highlighted

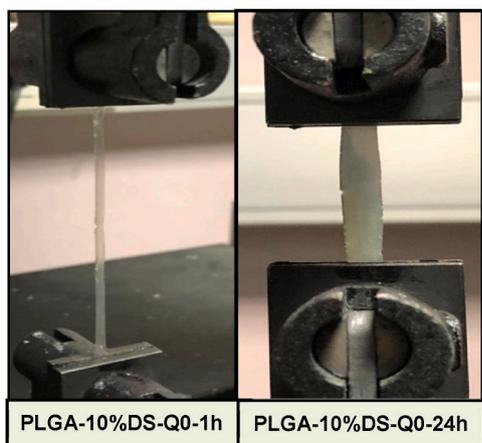


Fig. 11. Tensile test of the PLGA-10%DS after 1 h and 24 h of drug release test at static state.

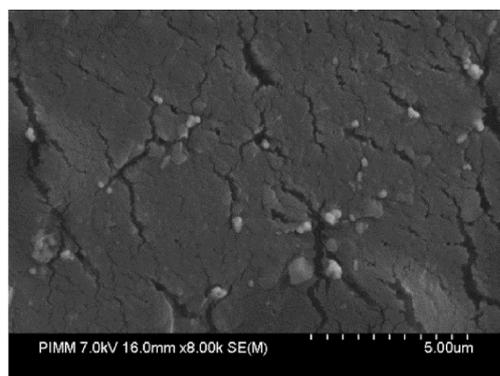


Fig. 12. SEM micrograph of the PLGA-10%DS before release test.

with the circles in Fig. 13(b) it was found that the large-sized pores can be the origin of the crack initiation and the fracture of the samples. By analyzing the fractography of the samples, it can be noted that these micro-cracks, which are the origin of the phenomenon of local damage, further, their coalescence can result in the final rupture of the sample. Hence according to the tensile results, the samples of the PLGA-5%DS had lower strain at break compared to the PLGA-10%DS.

### 3.2. Polymer degradation

In order to analyze the chemical and physical degradation of the polymer carriers FTIR spectra and SEM observations were respectively

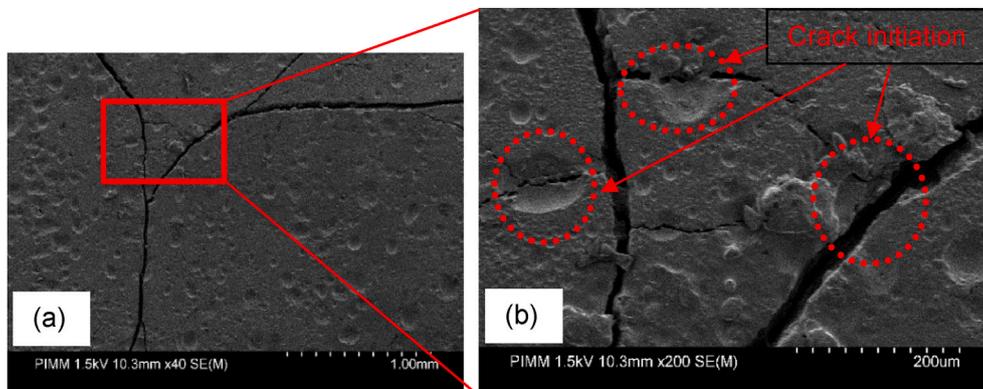


Fig. 13. SEM micrographs of the PLGA-10%DS after drug release of 48 h under the static state after tensile test with the magnification of (a) 1 mm and (b) 200 μm.

utilized. For the PLGA-Pure samples at the flow rate of 0 at different time intervals FTIR results are presented in Fig. 14. The peaks between the range of the 1000–1500 and the peak between the 1500–2000  $\text{cm}^{-1}$  are the characteristic peaks for the PLGA [41]. The bands of the  $\text{CH}_2$  and  $\text{CH}_3$  are observed in the region of the 1500–1300  $\text{cm}^{-1}$ . The band 1452  $\text{cm}^{-1}$  corresponds to the anti-symmetric vibration of  $\text{CH}_3$  from the lactic unit and the 1422  $\text{cm}^{-1}$  represents the bending of the  $\text{CH}_2$  from the glycolic unit [42].

In the 1300–1000  $\text{cm}^{-1}$  region of the infrared spectra, the initial peak observed at 1163 is assigned to the anti-symmetric stretching of COC for glycolic and lactic units. The symmetric stretching of COC is observed at 1082  $\text{cm}^{-1}$  for both glycolic and lactic units. The two other peaks observed in this region at 1129 and 1047  $\text{cm}^{-1}$  are assigned to the vibration of  $\text{CH}_3$  from the lactic units. In PLGA, the band at 890  $\text{cm}^{-1}$  is assigned to C–COO of the glycolic units.

Relatively same decrease in the size of the peaks during the test are shown in Fig. 14, it is related to the decrease in the thickness of the samples because of the dilatation observed in the width and length of the samples during the immersion time. The results showed that there is no chemical degradation after 48 h of immersion, under the static state. However, it is necessary to perform the test after several immersion time to confirm if there is the chemical degradation phenomenon.

Microscopic of the surface morphology of the PLGA-Pure films before and after 1, 12, 24, 48 h of incubation in PBS at the flow rate of zero are presented in Fig. 15. The surface of the samples before incubation is smooth. By getting in the time of immersion, the creation of the small bubbles is apparent, where they are resulting in opaque white and rough surface of the samples consisting of the microscopic bubbles because of the water absorption and starting the phenomenon of physical degradation which is evident in Fig. 15(c). As shown in this figure by getting in the time the bubbles will be changed to the pores. Finally, the pores are connected to each other and results in the weakness of the

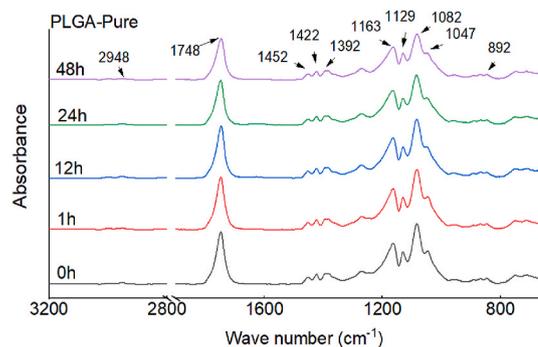


Fig. 14. FTIR spectroscopy of PLGA-Pure after certain times of incubation at the static state.

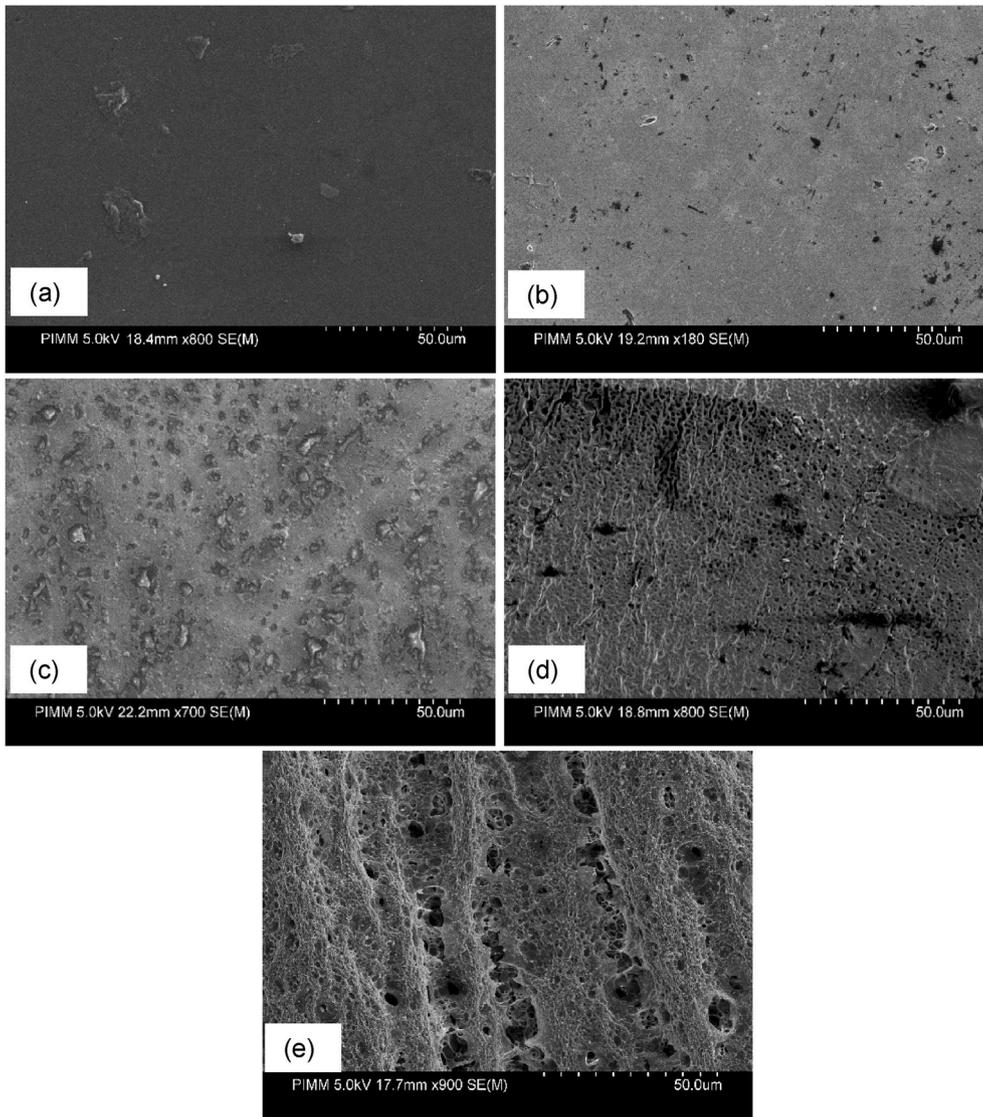


Fig. 15. SEM micrographs of the PLGA-Pure samples in PBS at zero flow rate after (a) 0, (b) 1, (c) 12, (d) 24, (e) 48 h.

mechanical properties of the samples and fracture of them.

### 3.3. Drug release results and mechanisms

Fig. 16(a) shows the drug release profiles from the PLGA-5%DS and

PLGA-10%DS films at the static condition and Fig. 16(b) shows the drug release profile of PLGA-10%DS films at dynamic condition with the flow rate of 7.5 ml/s.

Fig. 16(a) indicates that increasing the drug load from 5 to 10% in the first 12 h doesn't indicate significant variations in the drug release.

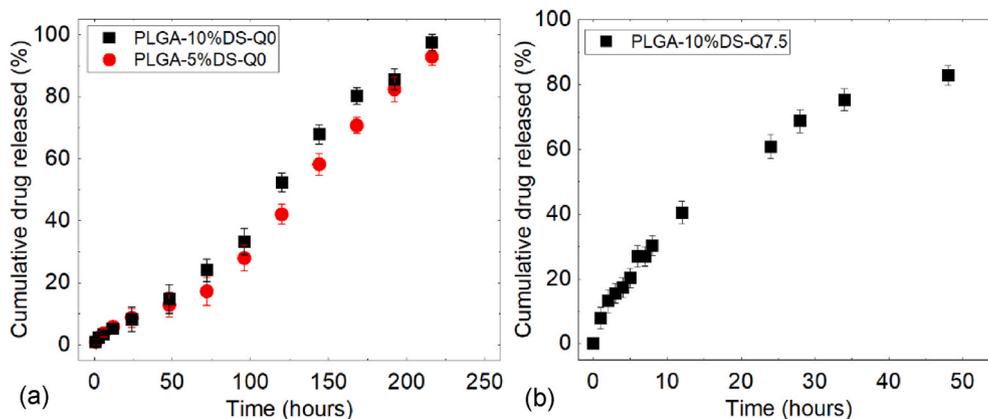


Fig. 16. Cumulative drug release from (a) PLGA-5%DS and PLGA-10%DS at Q = 0 ml/s and (b) PLGA-10%DS at Q = 7.5 ml/s.

However, by moving forward in time, the variance is becoming considerable. Understanding the importance of the amount of water absorption in drug carriers in order to release the drug, leads us to analyze the water absorption data (shown in Fig. 17). The results obtained from the amount of water absorbed by the two polymer films with 5 and 10% of the drug do not significantly difference until 24 h. In a period of 24–48 h, the results show an increase in the amount of water absorbed in the polymer with 10% of the drug compared to 5% of the drug. This rate of increase in water absorption is followed by the possible mechanisms of the drug release from the polymer normally through the water-filled pores [43] to increase the amount of drug released after 24 h for two polymers loaded with 10 and 5% of the drug (shown in Fig. 16 (a)). In this regard, initially the film is dry then it is exposed to the aqueous environment and the diffusion starts to happen where the film starts the swelling since the dry core of the film induce a compressive stress to the wet side, reduce the diffusion. However due to the initial thin thickness of the samples it is not a long time process. When the samples is completely wet due to the water absorption the swelling continue in all the direction and increase the width, length and thickness of the film, where diffusion will increase until a decrease in the concentration [44].

Also, the microscopic results showing the formation of the pores during the release, specially higher quantity of the small pores [35] in the PLGA-10%DS is the reason for higher release rate of the PLGA-10% DS to the PLGA-5%DS.

Considering Fig. 16, about 78.77% of drug was released from PLGA-10%DS at the flow rate of 7.5 ml/s in the first 48 h, while PLGA sample with 10% of drug at 48 h releases 17.79% at the static state. It is worth noting that the time needed for maximum release of the drug under the static state is about four times more than the continuous state. The results obtained from the amount of water absorbed (shown in Fig. 17(a) and (b)) and the rate of physical degradation (such as erosion) of the polymer show that these values under the dynamic state are more than the static state, in which these two parameters describe the increase in drug release rate under the dynamic state rather than static. It is worth mentioning that according to studies, the presence of flow rate has increased the penetration of the fluid into the carrier which will increase the amount of water absorbed. The water penetrated to the polymer films results in the dissolution of the drug particles and also swelling of the polymer layer, thereafter the active substance leaves the polymer layer by the probable mechanisms of diffusion, osmotic. Degradation is another important mechanism for this type of polymer but according to the literature studies the incidence of the chemical degradation in the short duration of the test is far from the expect, however the physical degradation such as erosion or environmental stress results in the cracking can be another reason of the release, notably with the presence of the flow.

Applying different release mechanisms [34] to the DS release profiles from PLGA films showed that the release profiles under the static state with two different percentages of drug are following the zero order

release with the R value of 0.99 (stated in Table 2). It is drawn from the release curve that the release is happening with a rather constant rate of release in which the rate does not change with the increase or decrease in the concentration of the drug during the release [37,45]. In addition, when the percentage of the drug is increased the kinetic of the release for zero order is increased, but it is not significant, therefore, it is notable that even by increasing the initial concentration of the drug, release from these samples follow the same mechanism with almost the same rate of release. Release profile of the PLGA film with 10% of the initial drug up to 76% of release also follows the zero-order release where the release rate is constant during a period.

Comparing the results of release for the samples of 10% of drug at two different flow rates of 0 and 7.5 ml/s, is noticeable that integration of the flow rate causes in the increasing of the kinetic of release.

However, the regression results with Korsmeyer-Peppas shows good correlation where for the  $n > 1$  obtained under the static state indicates super case II transport, which describe the rapid increase in the absorption of the solution in the polymer where it results in the forces exerted by the material with the swelling property [46]. Moreover, the value  $n = 0.73$  for the 10% of the drug at continuous state shows the degradation of the polymer film during the release period, where it seems that integrating the erosion has intensified the kinetic of the degradation.

### 3.4. Drug release and polymer properties

In drug delivery systems several aspects should be considered. The presented results showed the relationship of all the characteristics of the material with together and with the drug release. The term of material refers to the polymers and here in this study PLGA. As it is evident all the polymers have glass transition temperature range where the polymer shifts from a rigid glassy material to a soft (not melted) material, and is usually measured in terms of the stiffness or modulus. This glass transition temperature range could be varied when the polymer exposed to water or etc. The latter can change some physical and mechanical properties of used polymer. In fact, during drug release studies the interaction between the polymer and fluid such as PBS medium or water should be considered.

The results confirm that by increasing the time of immersion, the glass transition temperature is decreased (presented in Fig. 3). One can note that the physical and mechanical properties are changed. For example, by increasing the time of in-vitro test, molecular mobility, and flexibility of PLGA are decreased. However, PLGA presents high strength and Young's modulus. Fig. 18 shows the schematic of the variation of the polymer properties during and after drug release. In this figure the applied test temperature and the zone of the variation of the glass transition temperature, moreover some mechanical and physical properties were illustrated.

One can notice that the relation of microstructure and properties of

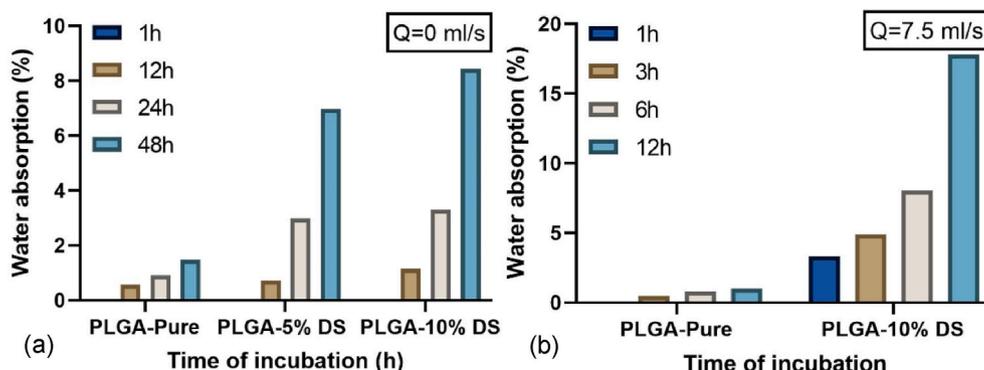
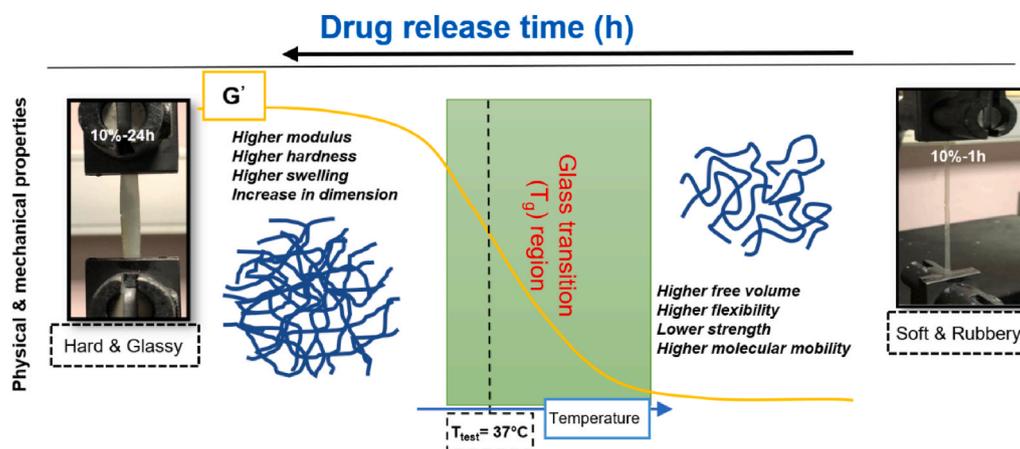


Fig. 17. Water absorption percentages for PLGA-Pure, PLGA-5%DS and PLGA-10%DS at flow rates of (a) 0 and (b) 7.5 ml/s.

**Table 2**

Values related to the Peppas model by fitting the experimental results.

| Model            | Korsmeyer- Peppas |      |                | Zero-order |                | First order |                | Higuch |                |
|------------------|-------------------|------|----------------|------------|----------------|-------------|----------------|--------|----------------|
|                  | K                 | n    | R <sup>2</sup> | K          | R <sup>2</sup> | K           | R <sup>2</sup> | K      | R <sup>2</sup> |
| PLGA.5%DS.Q:0    | 0.06              | 1.36 | 0.99           | 0.42       | 0.99           | 0.022       | 0.81           | 4.69   | 0.88           |
| PLGA.10%DS.Q:0   | 0.17              | 1.18 | 0.99           | 0.46       | 0.99           | 0.022       | 0.56           | 5.22   | 0.90           |
| PLGA.10%DS.Q:7.5 | 6.66              | 0.73 | 0.99           | 2.54       | 1              | 0.16        | 0.32           | 12.4   | 0.95           |

**Fig. 18.** Schematic of the variation of the polymer properties during and after drug release.

PLGA plays an important role in drug delivery systems which use polymer as a drug carrier. Therefore, referring to the case of utilisation, the type of the polymer and its properties should be well understood.

#### 4. Conclusion

The intrinsic properties of the material and their evaluation during the test on the drug release are among the important parameters to better understand and predict the release behaviour of the drug carrier. In this study, the effect of the polymer properties on the release behaviour with considering two different parameters was studied. First the effect of the drug percentage on the properties of the PLGA polymer and second the effect of the flow rate by considering the static and flow rate of 7.5 ml/s on the polymer films were investigated. The results proved the relationship between the characteristics of the material with the drug release. Increasing the drug percentage in the PLGA film, water absorption has increased and as a result quantity of the pores created are also augmented, therefore an increase in the kinetic of the release is observed. This evolution was also similar with increasing the flow rate.  $T_g$  is amongst the important parameters in this regard, where by getting in the time of release  $T_g$  of the samples decreases which helps to more movements of the polymer chains and liberation of the drug particles. Another critical factor which was examined here represents the mechanical strength of the films to analyze its durability. The results presented that by increasing the drug percentage the polymer films become more brittle, importantly by the time of the release. This behaviour is much more significant when the flow rate is rising. As a result, this study revealed us substantial information about the relationship of indicators such as  $T_g$ , free volume fraction, modulus, the stress of the polymer and their variation during release time. These results may encourage in developing a drug release prediction model for this type of drug carrier.

#### CRediT author statement

**Navideh Abbasnezhad:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - original draft, **Nader Zirak:** Validation, Formal analysis, Investigation, Writing - original

draft, **Mohammadali Shirinbayan:** Conceptualization, Supervision, review & editing, **Abbas Tcharkhtchi:** Supervision, **Farid Bakir:** Conceptualization, Supervision, review & editing

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