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Effects of material thickness and processing method on poly(lactic-co-glycolic acid) degradation and mechanical performance

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Abstract

In this study, the effects of material thickness and processing method on the degradation rate and the changes in the mechanical properties of PLGA material during simulated physiological degradation were investigated. Two types of PLGA materials were considered: 0.12 mm solvent-cast films and 1 mm compression-moulded plates. The experimental results presented in this study were compared to the experimental results of Shirazi *et al.* [1] for 0.25 mm solvent-cast films. These experimental observations were used to validate the computational modelling predictions of Shirazi *et al.* [2] on critical diffusion length scale and also to refine the model parameters.

The specific material processing methods considered here did not have a significant effect on the degradation rate and the changes in mechanical properties during degradation; however, they influenced the initial molecular weight and they determined the stiffness and hardness of the PLGA material. The experimental observations strongly supported the computational modelling predictions that showed no significant difference in the degradation rate and the changes in the elastic modulus of PLGA films for thicknesses larger than 100 µm.

Keywords: Experimental; Modelling; Poly(lactic-co-glycolic acid); Mechanical properties; Degradation; Compression moulding; Solvent casting; Thickness.

1. Introduction

Biodegradable polymers such as PLGA have been used in a wide range of biomedical applications [3, 4]. Degradation of PLGA is due to the hydrolytic reaction which causes cleavage of the ester bonds of the polymer chains. Optimising the degradation rate of biodegradable polymers is one of the major challenges in designing degradable devices. Length scale plays an important role in determining the degradation rate. In materials with a long diffusion length, acidic polymer fragments which are due to the hydrolytic reaction remain inside the polymer matrix which leads autocatalysis of the hydrolytic reaction [2]. The autocatalytic effect becomes more pronounced as the degradation proceeds and causes heterogeneous degradation which is faster in the centre than at the surface [1, 5]. Fast degradation may cause negative effects such as local or systemic toxicity [6] and loss in cell viability [7] due to the acidic effect of degradation products. Therefore, it is important to determine a length scale above which the device undergoes heterogeneous degradation.

Despite extensive experimental studies on the effect of thickness on the degradation rate in various biodegradable polymers [8-12], there is no consensus in the literature on the critical thickness at which the effect of autocatalysis becomes pronounced. Computational modelling has been used in an effort to provide insightful interpretation of experimental results [13-16] and can be very useful when attempting to quantify the thickness dependence of degradation. Reaction-diffusion models have been developed and have significant potential to assess and predict the rate of degradation and to aid the design of biodegradable devices [17]. Diffusion transport plays a critical role when developing a model of polymer degradation behaviour, especially in determining the type of degradation, given that autocatalysis is the fundamental reason for the size dependence [15].

The change in the mechanical properties of biodegradable polymers during degradation is another critical design factor. Biodegradable devices are intended to degrade over time and, from a mechanical perspective, the design requirement for an implanted device is that it must have appropriate mechanical properties and an adequate degradation rate to maintain the mechanical integrity over the desired lifetime. PLGA material retains its mechanical integrity until the molecular weight of the polymer chains reaches a critical molecular weight [1, 18]. Based on this, a computational modelling framework was used in a previous study by Shirazi *et al.* [2] to predict the reduction in the molecular weight and the changes in the elastic modulus of PLGA structures during degradation. The results of the computational simulations indicated a length scale (e.g. film thickness) in the range 2-100 μm above which heterogeneous degradation occurs.

It has been shown that the mechanical properties of biodegradable polymers are significantly influenced by the material processing method [19, 20]. Shirazi *et al.* [20] showed that solvent-cast PLGA material is more elastically compliant and plastically softer than compression-moulded material and it also shows lower work hardening characteristics. Given that the material processing method affects the mechanical properties, it is important to consider the influence of material processing method on the mechanical performance of biodegradable materials during degradation.

The first objective of the present study is to investigate the effects of material thickness and the processing method on *in-vitro* degradation and the mechanical performance of PLGA material during simulated physiological degradation. *In-vitro* experiments are performed for a 0.12 mm solvent-cast film and a 1 mm compression-moulded plate. The experimental results generated here are compared with the experimental results of Shirazi *et al.* [1] for a 0.25 mm solvent-cast film. The second objective of this study is to assess the predictive performance of, and to calibrate, the computational modelling framework developed by Shirazi *et al*. [2]. The assessment of this model is achieved here based on the experimental observations for the molecular weight degradation and the changes in the elastic modulus of PLGA material for three different thicknesses.

2. Methods

2.1 Experimental methods

2.1.1 Materials and sample preparation

DL-lactide-glycolide copolymer with a molar ratio of 50:50 (PURASORB PDLG 5010) was supplied by Purac Biomaterials (Gorinchem, Netherlands). Dimethylformamide (DMF), chloroform ($CHCh_3$), and phosphate-buffered saline (PBS) tablets were purchased from Sigma Aldrich (Missouri, USA). The PBS solution was prepared by dissolving one tablet in 200 ml of deionised water.

PLGA samples used in this study were prepared by solvent casting and compression moulding. A compression-moulded plate was supplied by Proxy Biomedical Ltd (Co Galway, Ireland). The plate was cut into 20 × 20 mm^2 test pieces with thickness of 1.082 ± 0.006 mm. The density of the compression-moulded material was 1.20 ± 0.02 g cm^{-3}.

To prepare the samples by solvent casting, a concentration of 0.1 g ml^{-1} was prepared by dissolving the polymer in $CHCh_3$. Using a pipette, 2 ml of the polymer solution was then cast onto a glass Petri dish with a dimeter of 40 mm. To prevent the formation of air bubbles, the Petri dishes were covered by glass lids. The samples were put into a desiccator for 48 h at room

temperature and then dried in a vacuum for a week. The thickness and the density of the solvent-cast films were 0.120 ± 0.002 mm and 1.06 ± 0.06 g cm^{-3}, respectively.

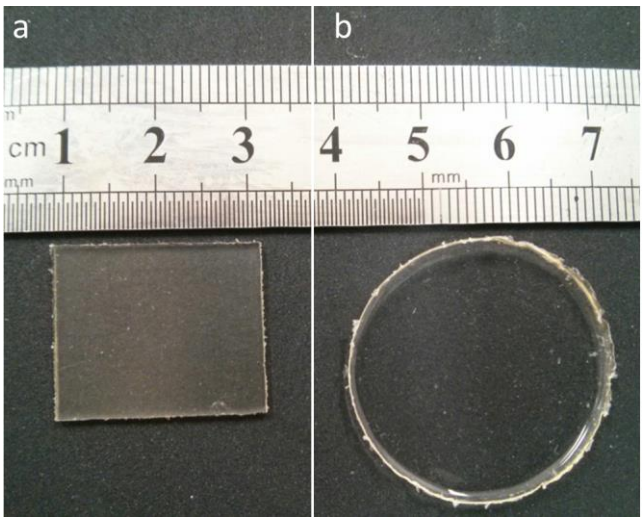


Fig. **1** shows optical images of the prepared solvent-cast film and the compression-moulded plate in the as-received condition.

2.1.2 *In-vitro* degradation

To simulate *in-vitro* degradation conditions, the samples were placed in the PBS solution with a pH of 7.4. The 1 mm plates were immersed and exposed to the PBS solution on both sides, whereas the 0.12 mm films were cast onto dishes and exposed to the solution at one side only. The mass ratio of the PBS solution for each specimen was 100:1 according to the ASTM F1635-11 standard [21]. Individual sterilized containers were used for each sample with sealed lids to prevent evaporation of the PBS solution. The containers were placed in an oven at 37°C during degradation. The samples were removed from the PBS at each time point (5 time points for the compression-moulded plate (day 5, 9, 15, 17, and 19) and 6 time points for the solvent-cast film (day 5, 9, 13, 17, 19, and 21)). The mass remaining and the water uptake of the samples were calculated as follows:

$$\text{Mass remaning (\%)} = 100 - \frac{m_{ini} - m_d}{m_d} \times 100$$
$$\text{Water uptake (\%)} = \frac{m_w - m_d}{m_d} \times 100 \qquad (1)$$

where m_{ini} is the initial weight of the samples and m_w and m_d are the weights of the samples in the wet and dry conditions, respectively. The dry mass m_d was measured after the specimens had been vacuum dried to a constant weight. Three samples were used for each degradation time point to calculate the mass remaining and water uptake according to Eq. (1).

2.1.3 Surface roughness

The surface roughness of the PLGA samples was measured using a Dimension 3100 atomic force microscopy (AFM) (digital Instrument Veeco Metrology, Santa Barbara, CA) in non-contact mode at scan rate of 1 Hz. All samples were examined in scanning areas of 10 µm × 10 µm.

2.1.4 Crystallinity

The crystallinity of the PLGA samples was determined by X-ray diffraction (XRD) using an Intel Equinox 3000 diffractometer (Stratham, USA). Diffraction patterns were recorded between the angular ranges of 5° to 80° (2θ) using Cu K_α radiation of wavelength 1.54 Å (30 kV, 20 mA).

2.1.5 Molecular weight determination

The average molecular weight of PLGA samples was determined by a gel permeation chromatography (GPC) system consisting of a Viscotek DM 400 data manager, a Viscotek VE 3580 refractive-index detector, and two Viscotek Viscogel GMH_{HR}-M columns. The samples were removed from the PBS solution and dissolved in DMF (5 mg ml^{-1}). Then, 100 µl of the solution was injected into the GPC using an auto-sampler. Measurements were carried out at 60°C and at a flow rate of 1.0 ml min^{-1} using HPLC-grade DMF containing 0.01 M LiBr as the eluent. The columns were calibrated using twelve polystyrene standards with molecular weights ranging from 376 to 2,570,000 g mol^{-1}; therefore, the average molecular weight of the samples was measured with respect to polystyrene. The polydispersity index (PDI) was determined as the ratio of the weight average molecular weight M_w to the number average molecular weight M_n. Three samples were used for each degradation time point to determine the average molecular weight.

2.1.6 Mechanical properties

The mechanical properties of PLGA samples were evaluated by the nanoindentation technique using a Nano Hardness Tester (CSM instruments SA, Switzerland). Indentation tests were carried out at room temperature using a Berkovich indenter tip. The PLGA samples were removed from the PBS solution at each time point and blotted dry prior to mechanical testing. They were then mounted on a glass coverslip by a clear double-sided tape. A linear force-controlled mode was used for loading and unloading. The contact load was first increased to a maximum load of 7 mN at a constant rate of 14 mN min^{-1}, kept at this force for 60 s, and finally decreased to zero at the same rate as for the loading [1]. A matrix of 5 × 5 indents was used to perform a single batch of identical indentations with spacing of 100 µm between indents to avoid overlapping the elastic field of each indent. From the 25 indents, any curves with a negative force (pull-off adhesion force) in the force-displacement

curve were removed to avoid the effect of adhesion in the measurement [22]. The average of 20 indents was then used to determine the elastic modulus E_s and hardness H_{IT} of the samples based on the Oliver and Pharr method [23] as described previously in Shirazi *et al*. [1, 20].

The results obtained for the mass loss and water uptake, the molecular weight, and the mechanical properties were compared with the results of the earlier experimental study of Shirazi *et al.* [1] on 0.25 mm solvent-cast PLGA films.

2.2 Computational

2.2.1 Simulation procedure

The coupled computational modelling framework described by Shirazi *et al.* [2] was applied here in order to predict the reduction in the average molecular weight and the elastic modulus of the PLGA films and plate during degradation. The changes in the number average molecular weight M_n of the polymer during degradation were predicted using the outputs of the molecular weight model [2], i.e., the mole concentration of polymer ester bonds C_e and the mole concentration of monomers C_m. In this model, the hydrolytic reaction can be described by the non-catalytic and autocatalytic reaction constants, k_1 and k_2, respectively. The intrinsic diffusion coefficient D_0 is necessary to determine the effective diffusion coefficient, which describes the diffusion of monomers through the polymer. The molecular weight model was implemented in COMSOL Multiphysics (v4.3b, COMSOL Inc., MA, USA). The numerical solution of the model was obtained at each time step in each finite element using an implicit backward differentiated formula (BDF) method, with the maximum order of 2.

The changes in the elastic modulus E during degradation were predicted using MATLAB (R2014a, Mathworks Inc., MA, USA) based on the relationship between the number average molecular weight and the elastic modulus obtained from the mechanical properties model [2]. In this model, the number of polymer chains N_{chains} is determined based on the initial distribution of the polymer molecular weight. The ratio of random scissions to end scissions $R_{scissions}$ determines how often each type of scission occurs. The critical molecular weight M_n^{crit} determines the number average molecular weight of the polymer chains below which the polymer chain does not contribute to the polymer stiffness.

Shirazi *et al*. [2] calibrated the parameters of the molecular weight model (k_1, k_2, and D_0) and the mechanical properties model (N_{chains}, $R_{scissions}$, and M_n^{crit}) based on the experimental results of 0.25 mm films presented by Shirazi *et al.* [1]. These model parameters are refined here in order to obtain a set of parameters which give a good fit to the experimental data for the molecular weight and the changes in the elastic modulus of the 0.12 mm and 0.25 mm films and the 1 mm plate during degradation.

2.2.2 Boundary condition

The solution of the molecular weight model described above was achieved for a one-dimensional problem for the 0.12 mm and 0.25 mm films and the 1 mm plate using appropriate boundary conditions. Contact on the outside of the film with the PBS solution was represented by assuming the concentration of monomers C_m at the boundary of the film is zero which means that all the monomers which reach the surface are immediately convected away from the surface (

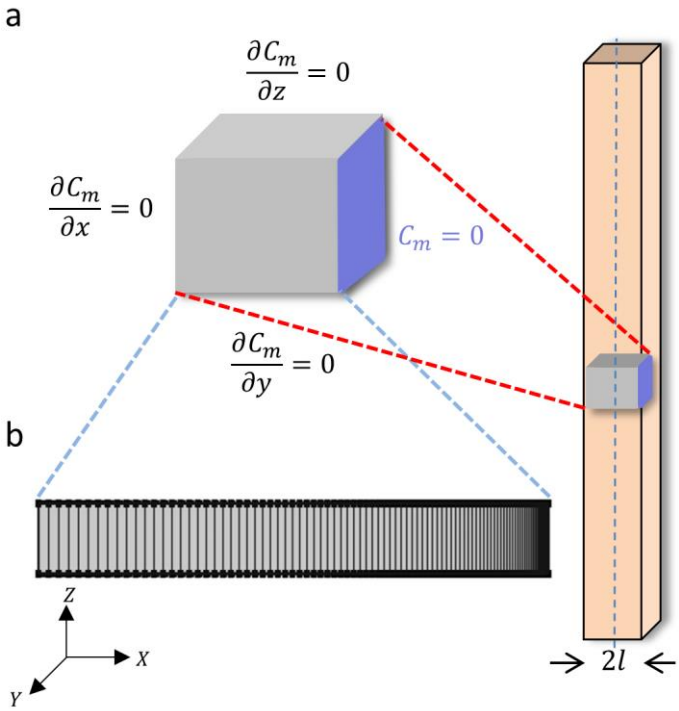


Fig. **2**a). The flux of monomers at all other boundaries, including the interface between the film and the substrate, was set to zero. The plate was represented in terms of half its thickness with a symmetry (zero flux) boundary condition at the mid-

plane, resulting in the same set of boundary conditions as for the film model (refer to

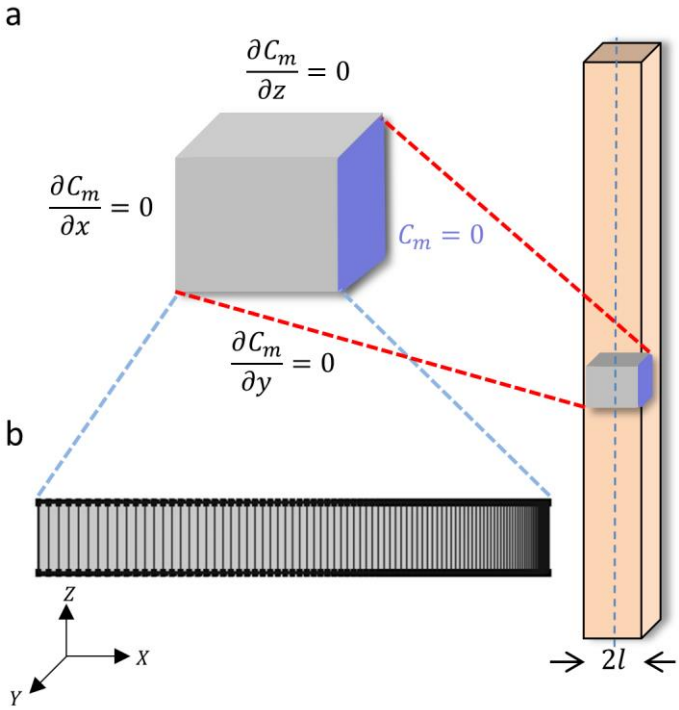


Fig. **2**a); consequently, a 0.5 mm thick film was used to represent the 1 mm plate exposed to the PBS solution on both sides.

A simple mesh of hexahedral elements was used through the film and plate thickness, and thinner elements were used at the surface where higher gradients in the solution variables occur (

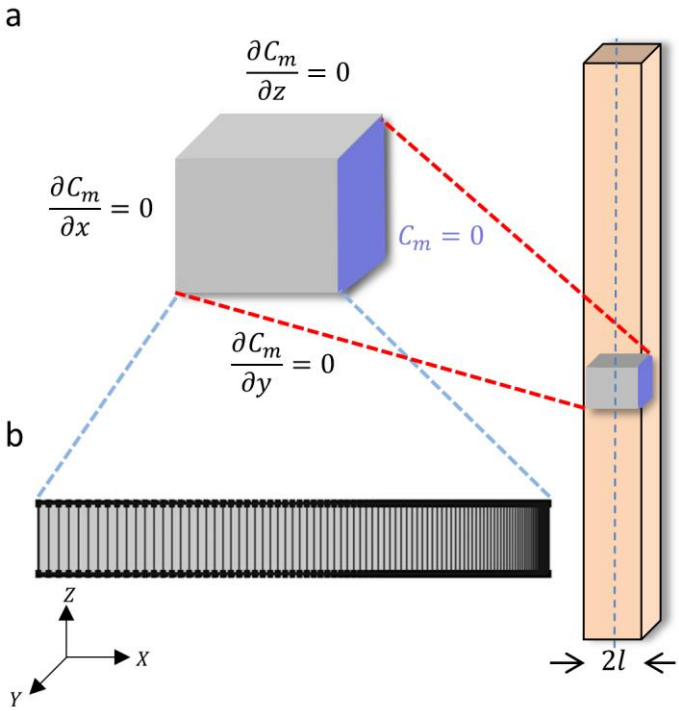


Fig. **2**b). The same number of elements was used for the 0.12 mm and 0.25 mm films and the 1 mm plate.

3. Results

3.1 Mass loss and water uptake

The changes in the water uptake and mass remaining of the 0.12 mm and 0.25 mm solvent-cast films and the 1 mm compression-moulded plate during degradation are shown in

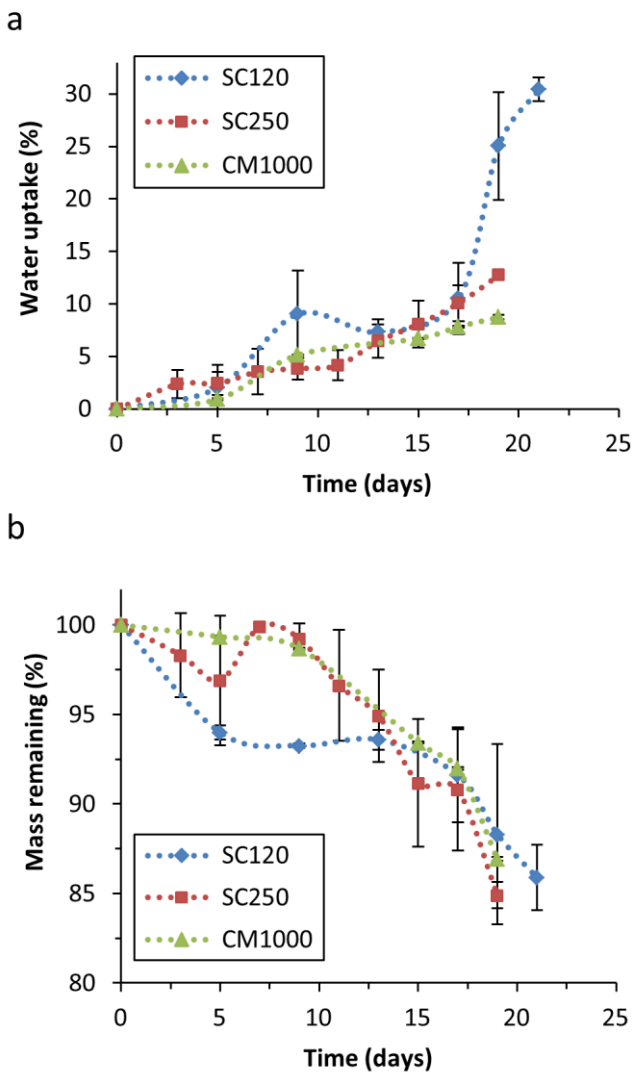
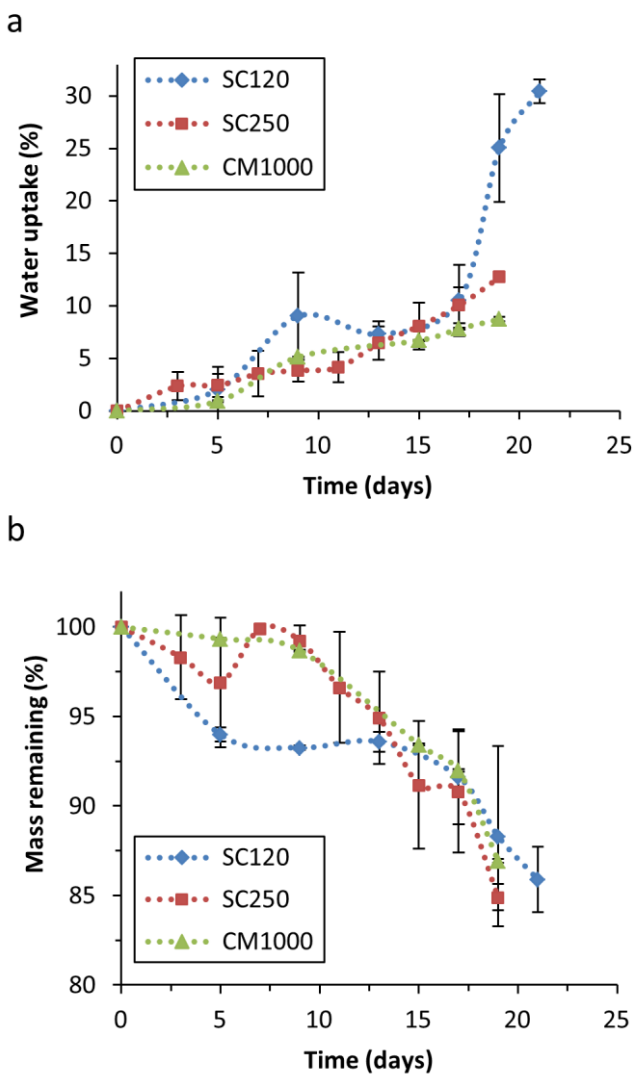


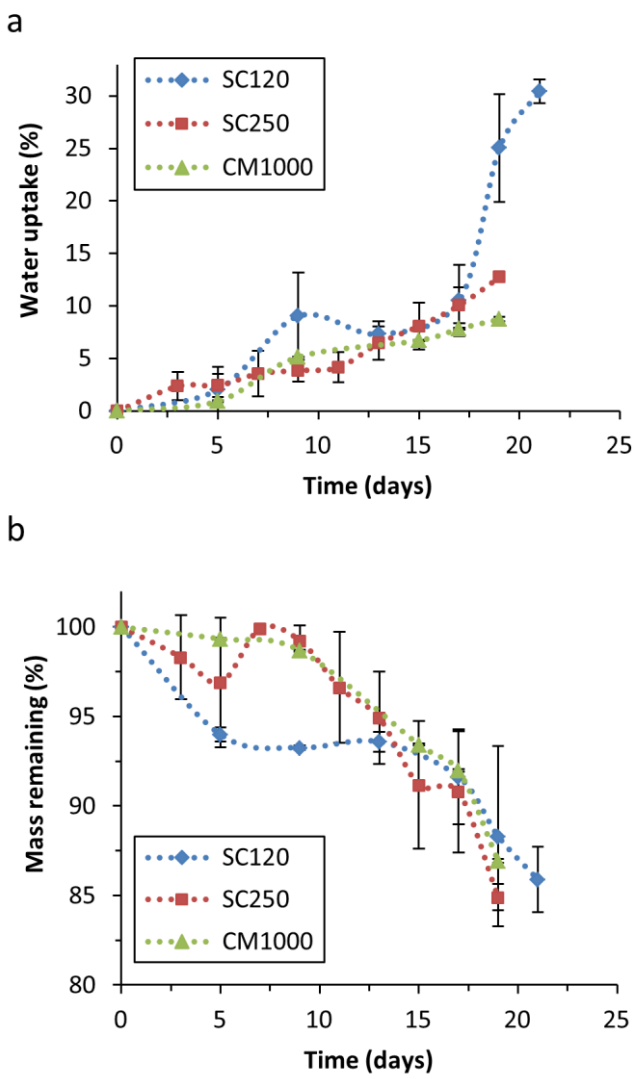
Fig. **3**. The results show that there was no significant difference between water uptake for the films and the plate at the



earlier stages of degradation (

Fig. **3**a). Water uptake increased to 30.4 ± 1.1% for the 0.12 mm film after 21 days of degradation; however, the water uptake of the 0.25 mm film and the 1 mm plate were 12.7 ± 0.1% and 8.7 ± 0.2%, respectively, after 19 days.

The results show that the rate of decrease in the weight of the 0.12 mm film was more than that of the 0.25 mm film and the



1 mm plate for the initial 7 days of degradation (

Fig. **3**b). However, following this the rate of mass loss for the 0.25 mm film and the 1 mm plate increased, and the materials had lost 15% and 13% of their initial masses, respectively, after 19 days. The 0.12 mm film had lost 14% of its initial mass after 21 days of degradation.

3.2 Surface roughness

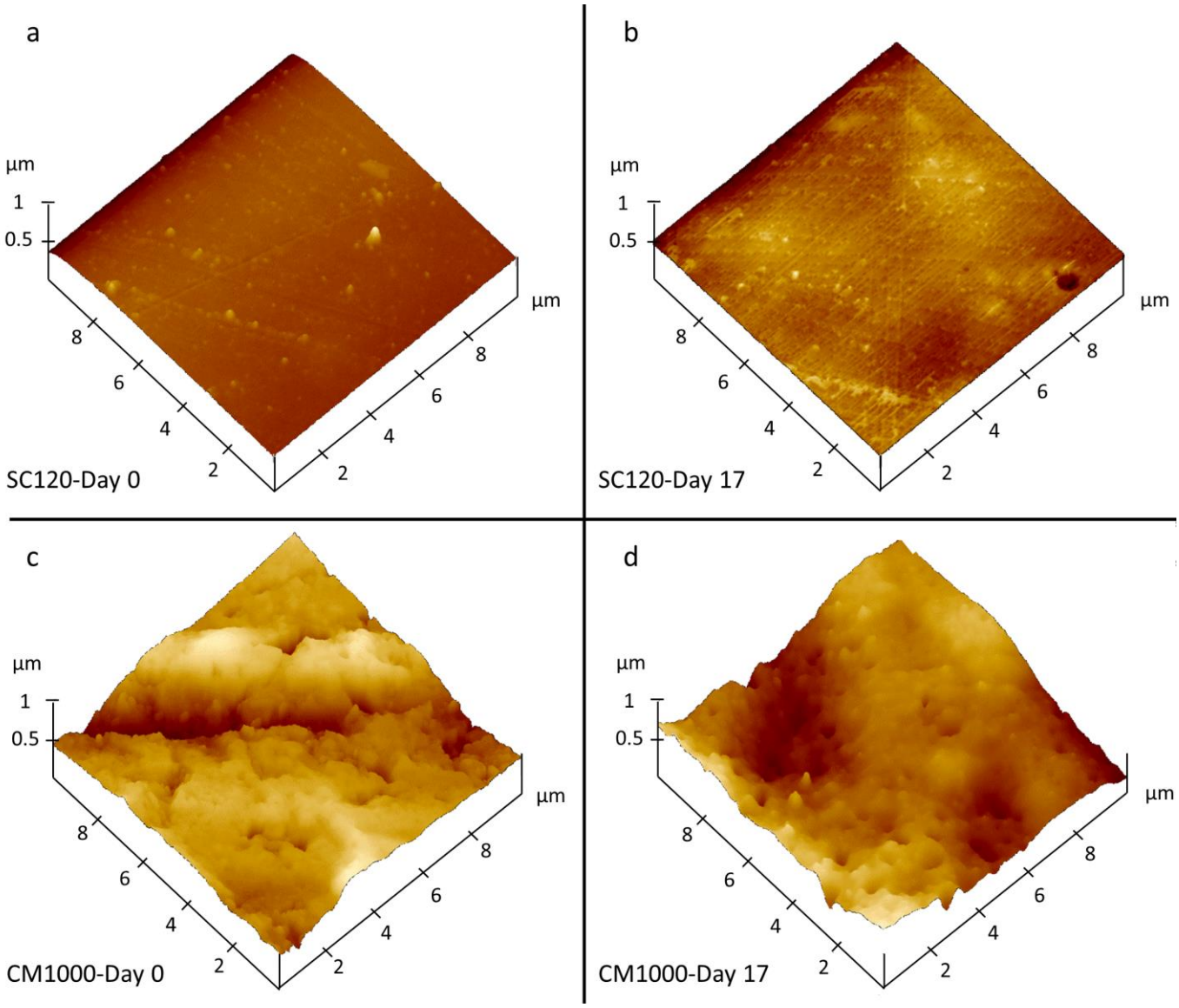


Fig **4** shows the three-dimensional AFM images of the 0.12 mm solvent-cast film and the 1 mm compression-moulded plate before and after immersion in PBS for 17 days. Moreover, the average roughness of the samples presented with R_a values was applied to describe the surface roughness are shown in Table 1. The results show that the compression-moulded material was much rougher than the solvent-cast material before and after immersion in PBS.

Table 1 Values of the average surface roughness, R_a, for the 0.12 mm solvent-cast film (SC120) and the 1 mm compression-moulded plate (CM1000) before and after immersion in PBS for 17 days (mean ± SD; n = 3)

Samples	SC120-Day 0	SC120-Day 17	CM1000-Day 0	CM1000-Day 17
Roughness R_a (nm)	10.04 ± 3.90	12.71 ± 5.29	54.18 ± 8.16	53.29 ± 30.05

3.3 Crystallinity

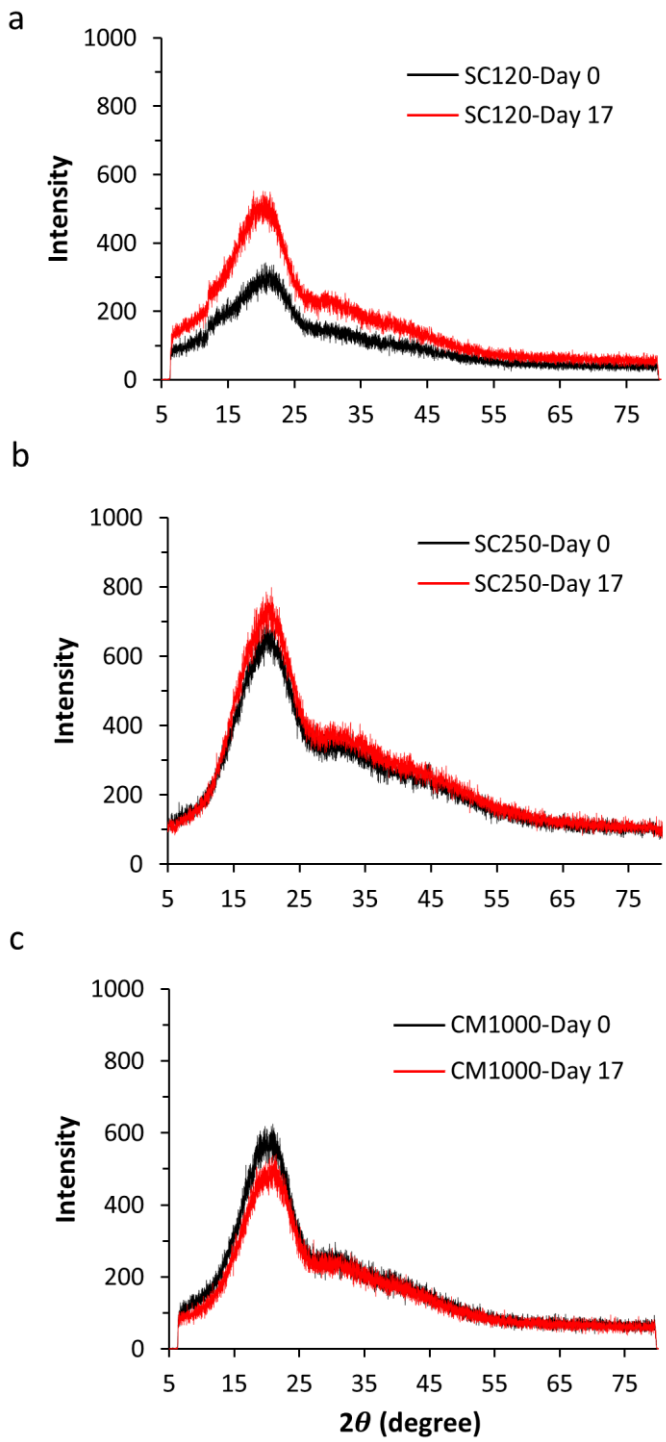


Fig **5** shows the XRD patterns of the 0.12 mm and 0.25 mm solvent-cast films and the 1 mm compression-moulded plate before and after immersion in the PBS for 17 days. The broad peak between 15° and 25° for all samples indicated the amorphous property of PLGA materials.

3.4 Molecular weight

The changes in the average molecular weight and polydispersity of the 0.12 mm and 0.25 mm solvent-cast films and the 1 mm compression-moulded plate are shown in

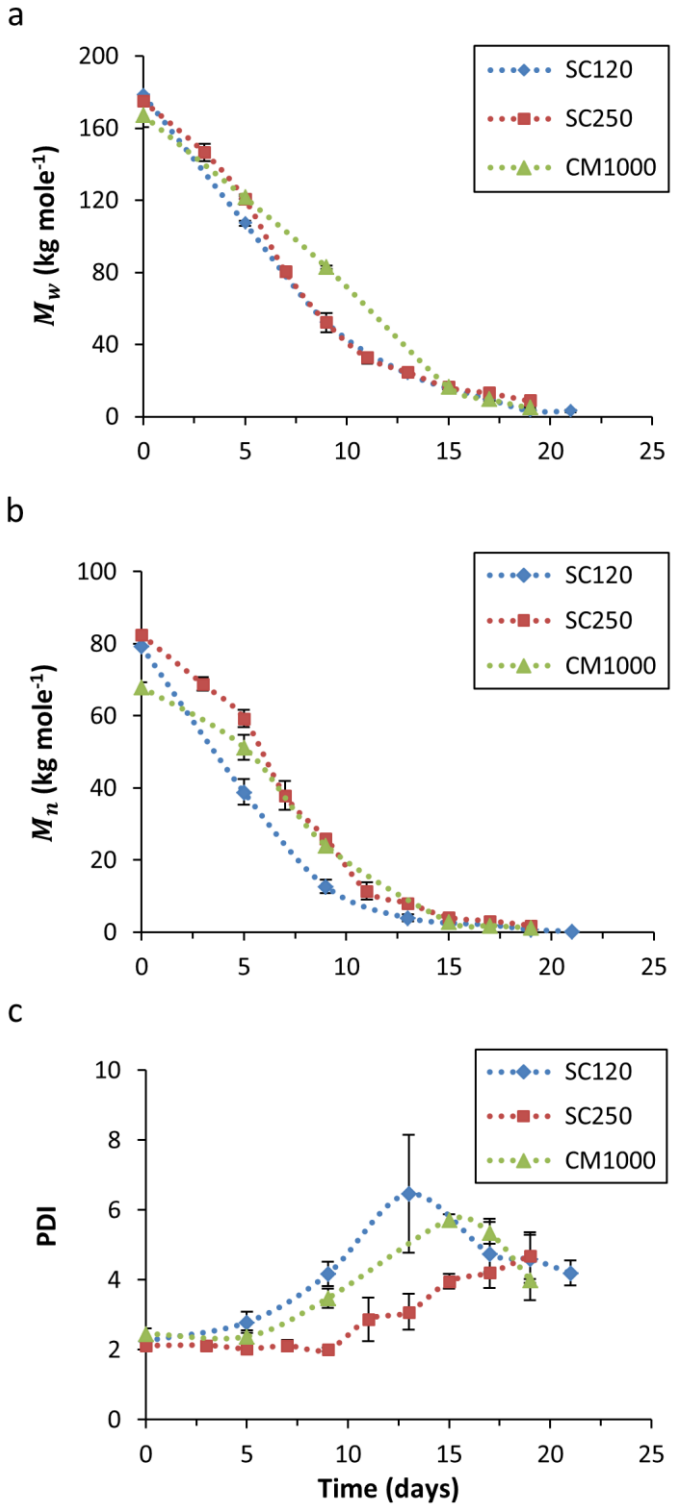
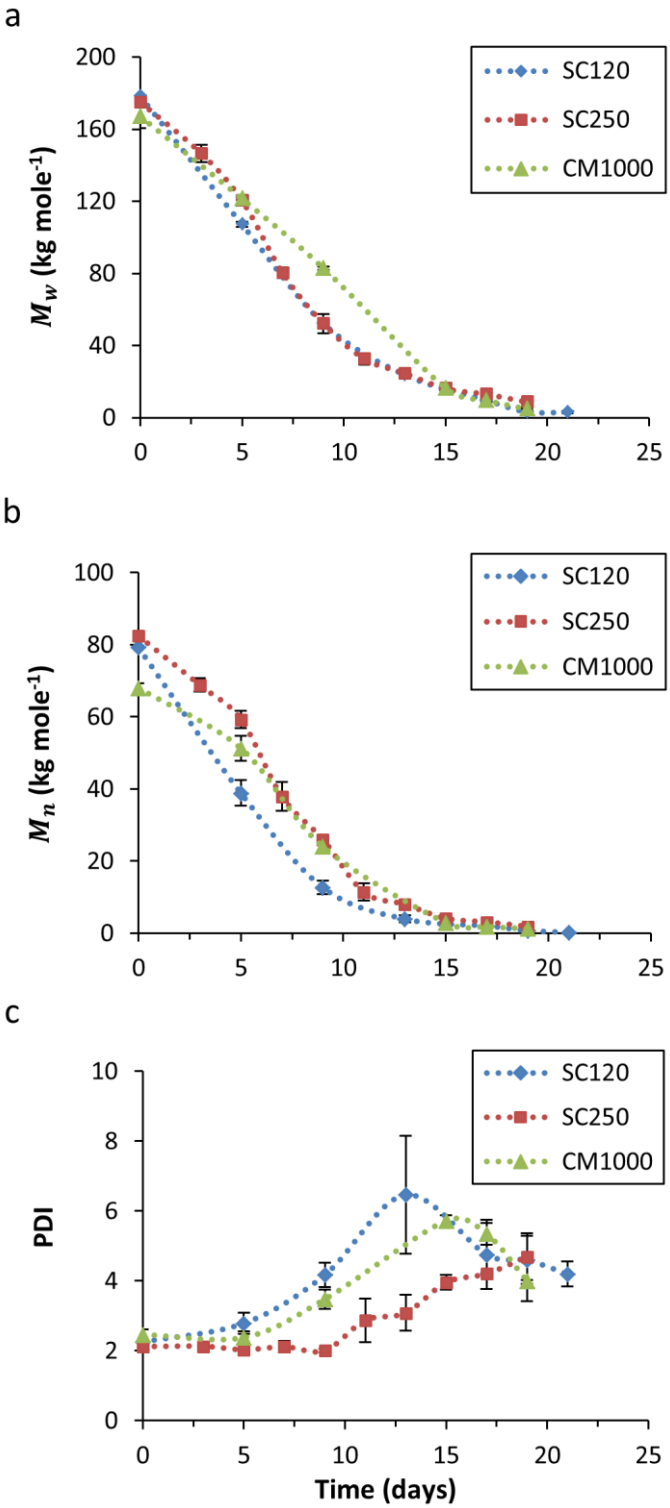


Fig. **6**. The results show that the average molecular weight of the undegraded compression-moulded material was smaller



than that of the undegraded solvent-cast material (

Fig. **6**a, b). During degradation, the molecular weight decreased gradually; there was no significant difference between the rates of reduction for the weight average molecular weight M_w of the three materials (

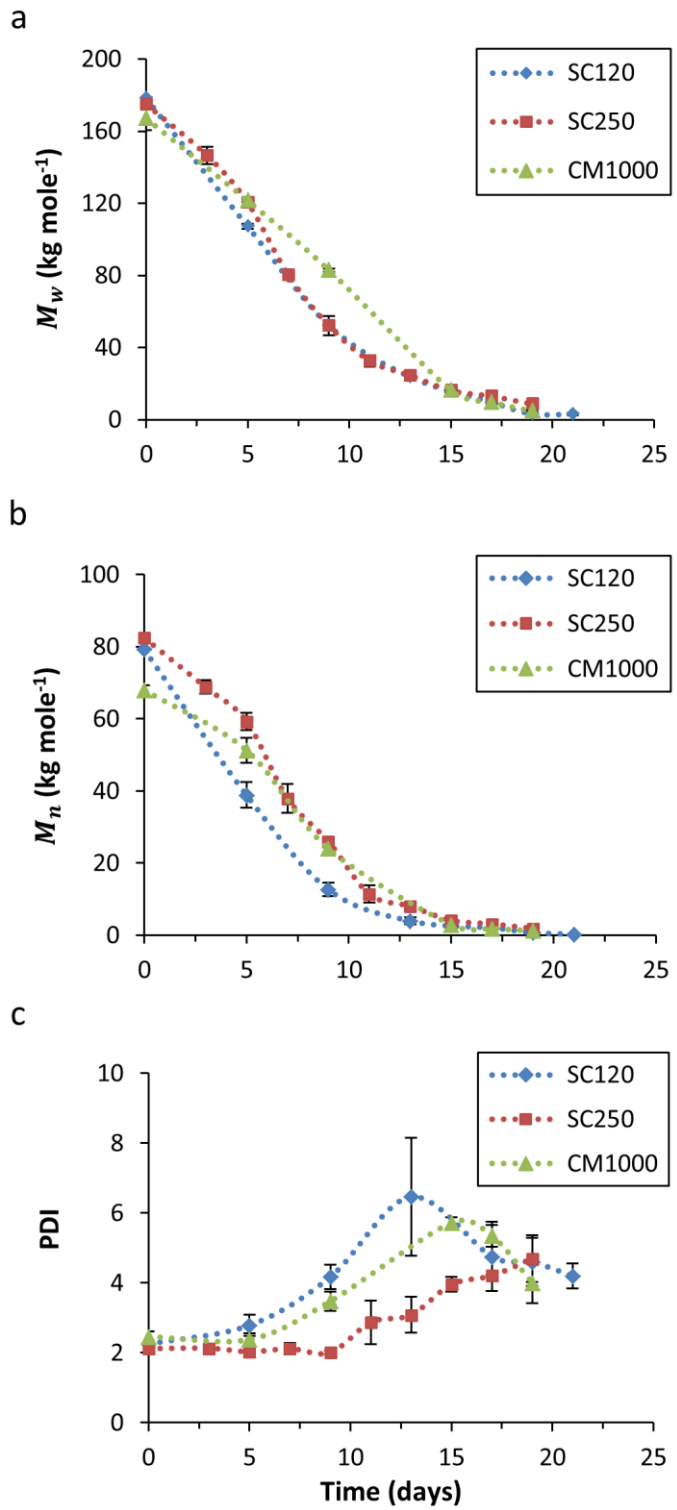
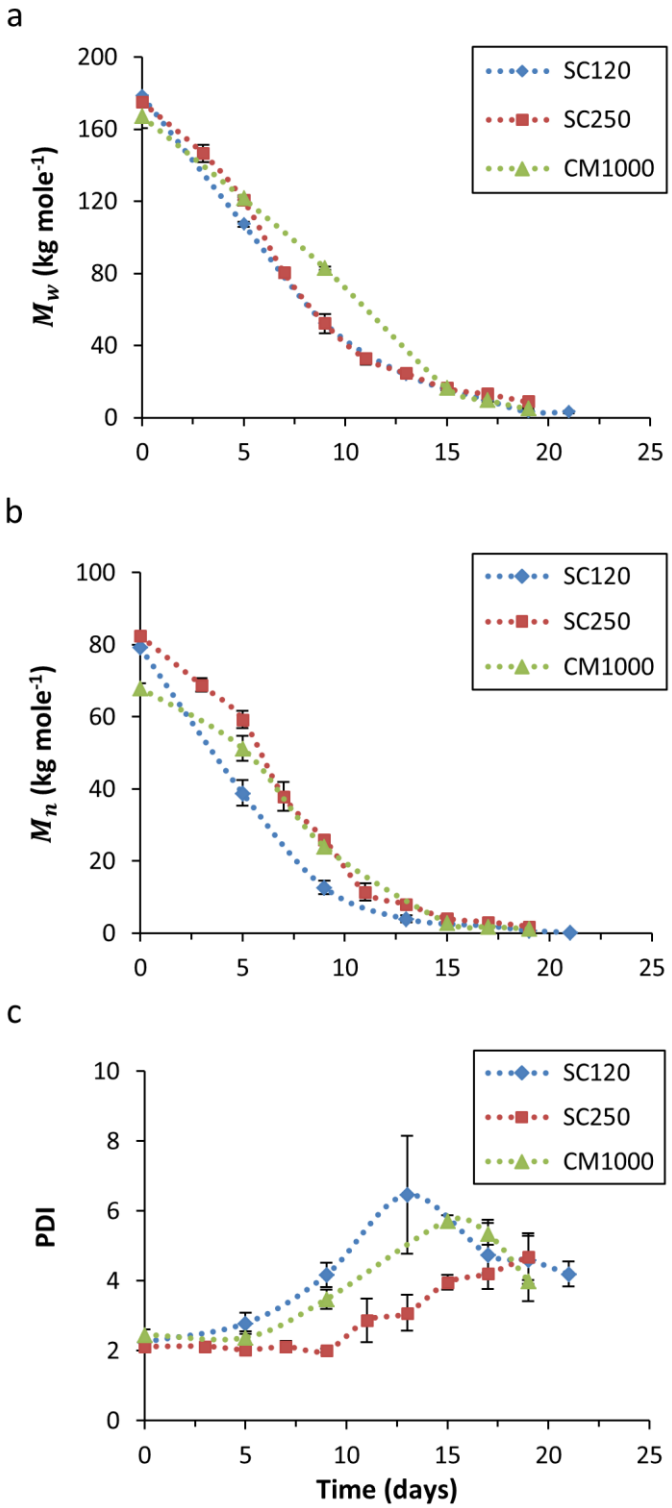


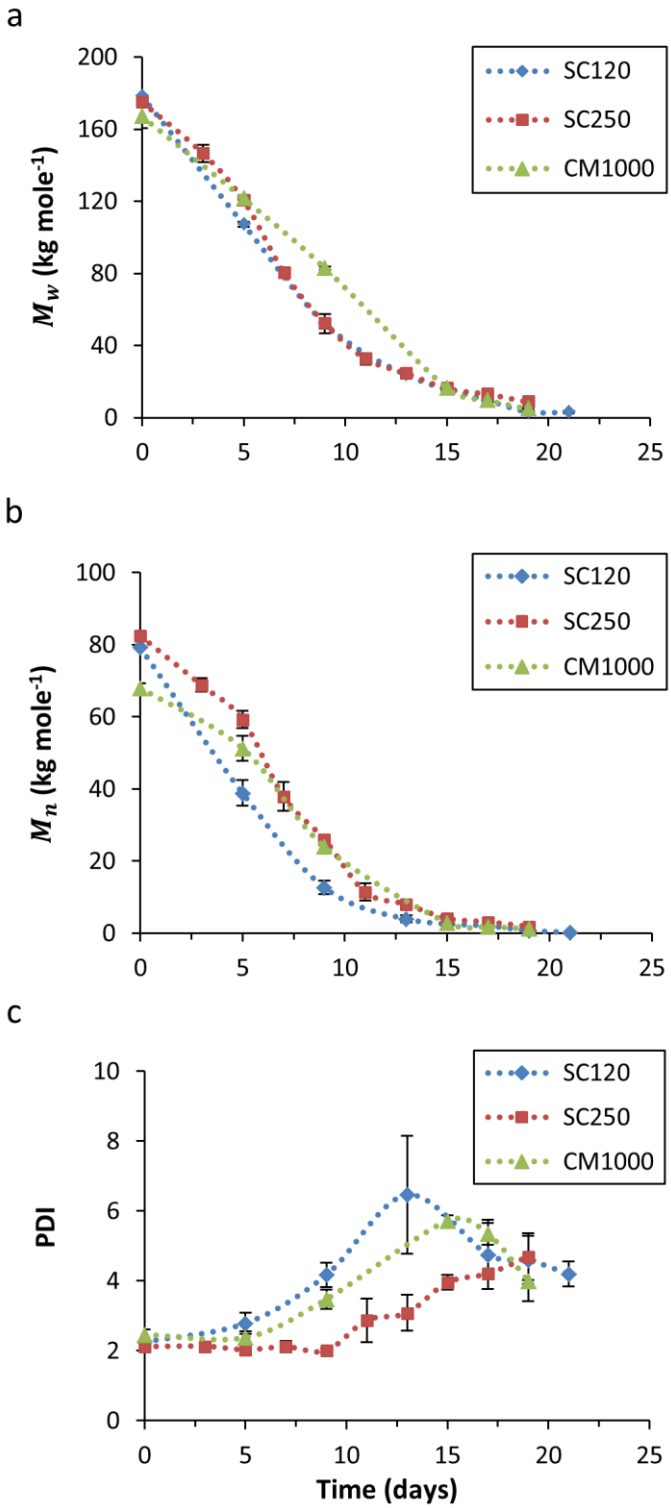
Fig. **6**a). However, the rate of decrease in the number average molecular weight M_n of the 0.12 mm film was slightly faster



than that of the other two materials (

Fig. **6**b).

For the 0.12 mm film and the 1 mm plate, the polydispersity increased for the first 13 days of degradation and then it



decreased (

Fig. **6**c); however, the polydispersity of the 0.25 mm film was constant until day 9 and then it increased reasonably linearly.

3.5 Mechanical properties

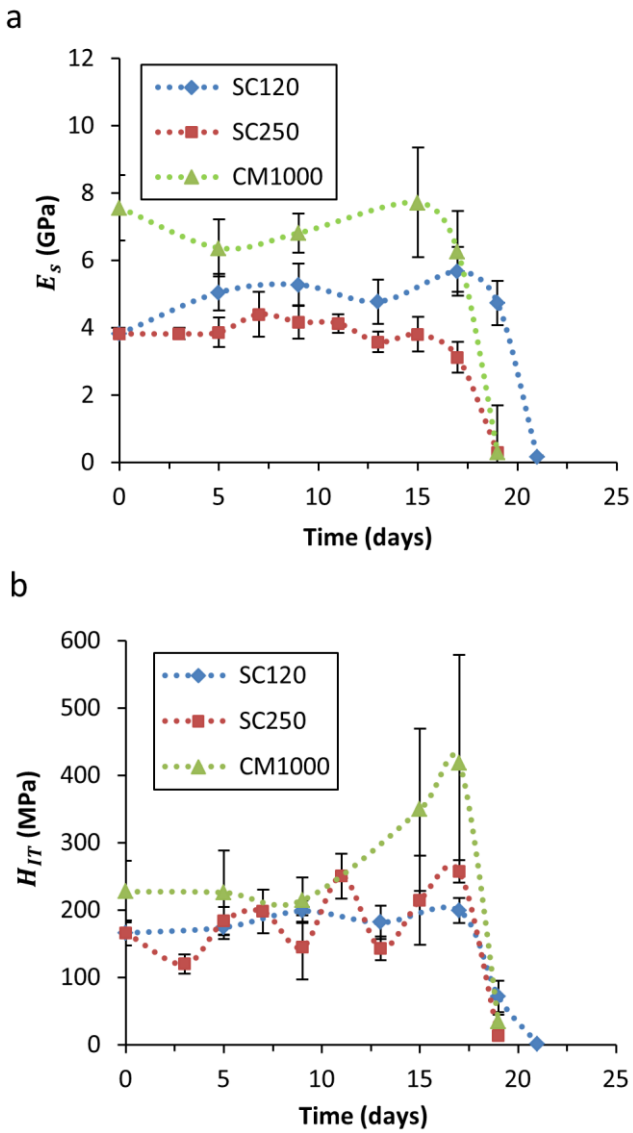
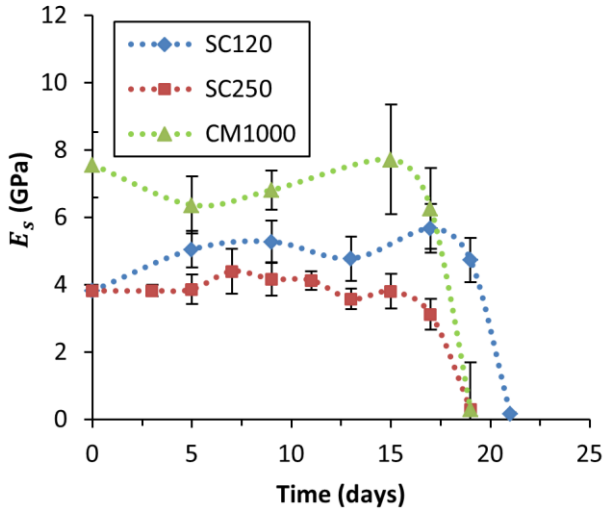


Fig. **7** shows the changes in the elastic modulus E_s and hardness H_{IT} of the 0.12 mm and 0.25 mm solvent-cast films and the 1 mm compression-moulded plate during degradation. The elastic modulus of the compression-moulded and solvent-cast

materials was 7.5 ± 0.9 GPa and 3.8 ± 0.1 GPa, respectively, before immersion in PBS (

a



b

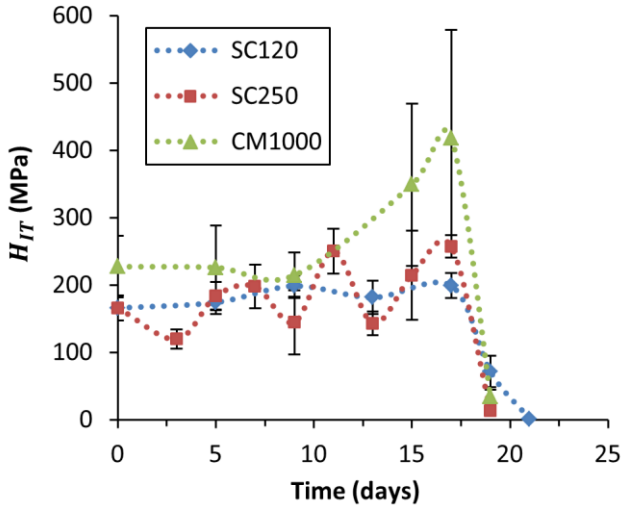
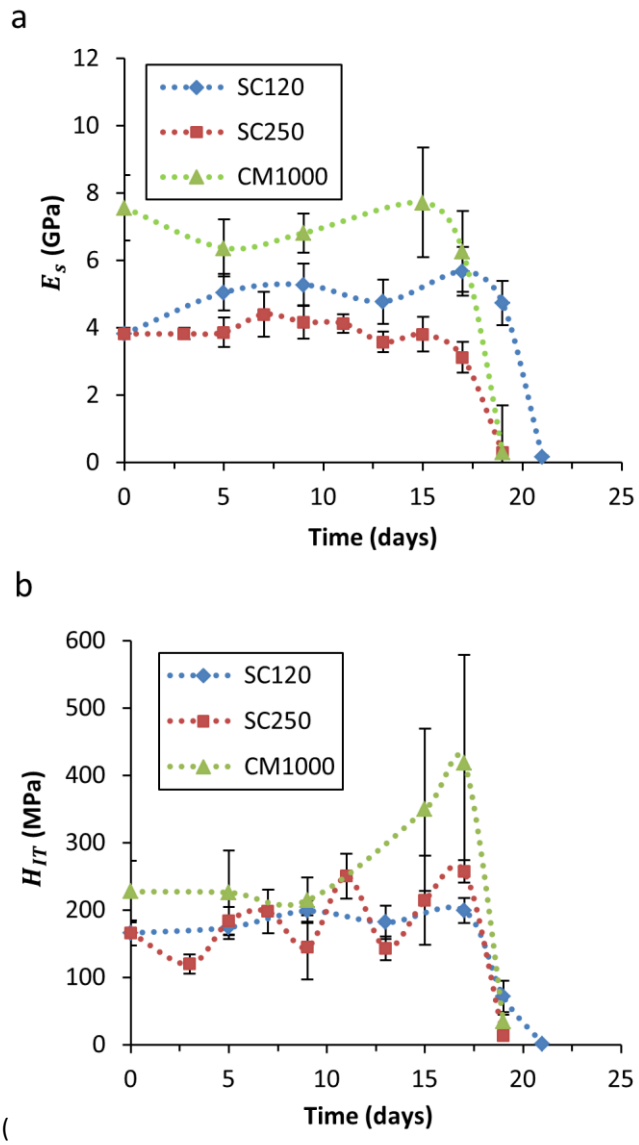


Fig. **7**a). The hardness of the compression-moulded and solvent-cast materials was 227.29 ± 46.19 MPa and 157.9 ± 14.3



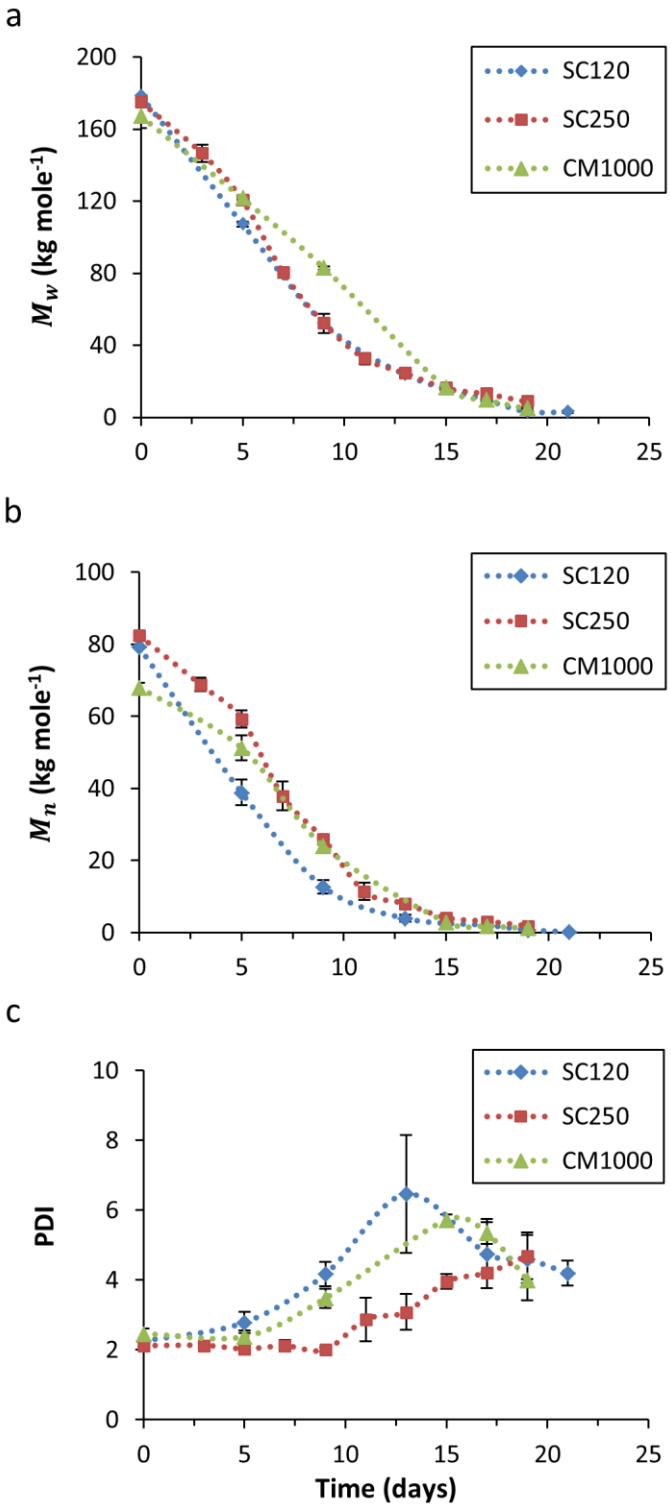
MPa, respectively, before immersion in PBS (

Fig. **7**b). The elastic modulus and hardness were obtained for indentation depths of 1170.59 ± 119.64 nm and 1299.86 ± 68.42 nm for the compression-moulded and the solvent-cast materials, respectively. These values are ~0.1% and 1% of the thickness for the compression-moulded and the solvent-cast materials, respectively, which is significantly less than the recommend 10% [24]; therefore, the effect of substrate is avoided in the measurements.

Apart from the increase in the hardness of the 1 mm plate after 9 days, the changes in the hardness and elastic modulus of the 0.12 mm and 0.25 mm films and the 1 mm plate were not significant over the first 17 days of degradation. Beyond that, the elastic modulus and hardness of the 0.25 mm and 0.12 mm films and the 1 mm plate decreased, indicating that a significant degradation occurred.

3.6 Model calibration

The changes in the number average molecular weight M_n of PLGA were predicted using the molecular weight model described above [2]. The initial number average molecular weight M_{n0} was assumed to be 79,000 g mol^{-1} and 68,000 g mol^{-1} for the 0.12 mm film and the 1 mm plate, respectively. These values were obtained from the experimental GPC results



presented in

Fig. **6**b. The initial number average molecular weight of the 0.25 mm solvent-cast PLGA film was assumed to be 82,000 g mol^{-1} based on the experimental study reported by Shirazi *et al.* [1]. The initial concentration of ester bonds C_{e0} was set at 17,300 mol m^{-3} [15, 2].

A wider range of parameters (k_1, k_2, and D_0) relative to that identified in Shirazi *et al*. [2], corresponding to the 0.25 mm film, was considered here in order to obtain a set of parameters which give a good fit to the experimental data for the three material thicknesses. The values of k_1 and k_2 were set in a range between 0.0006 and 0.2. The values of D_0 were set in a range between 10^{-12} and 10^{-9}.

The mechanical properties model [2] was calibrated based on the experimentally observed relationship between normalised E and M_n. The best model fit to all experimental data was achieved using the number of polymer chains N_{chains} equal to 3000 and the critical number average molecular weight M_n^{crit}equal to 1500 g mol^{-1} [2]. For less than 3000 polymer chains (300, 500, or 1000), the molecular weight of the chains in the simulation did not match the experimental GPC data. For more than 3000 polymer chains (10,000 or 20,000), similar results to the 3000 polymer chains were achieved. Different values of random to end scission ratios $R_{scissions}$ (3:1, 1:1, 1:12 or 1:50) did not have any significant effect on the results.

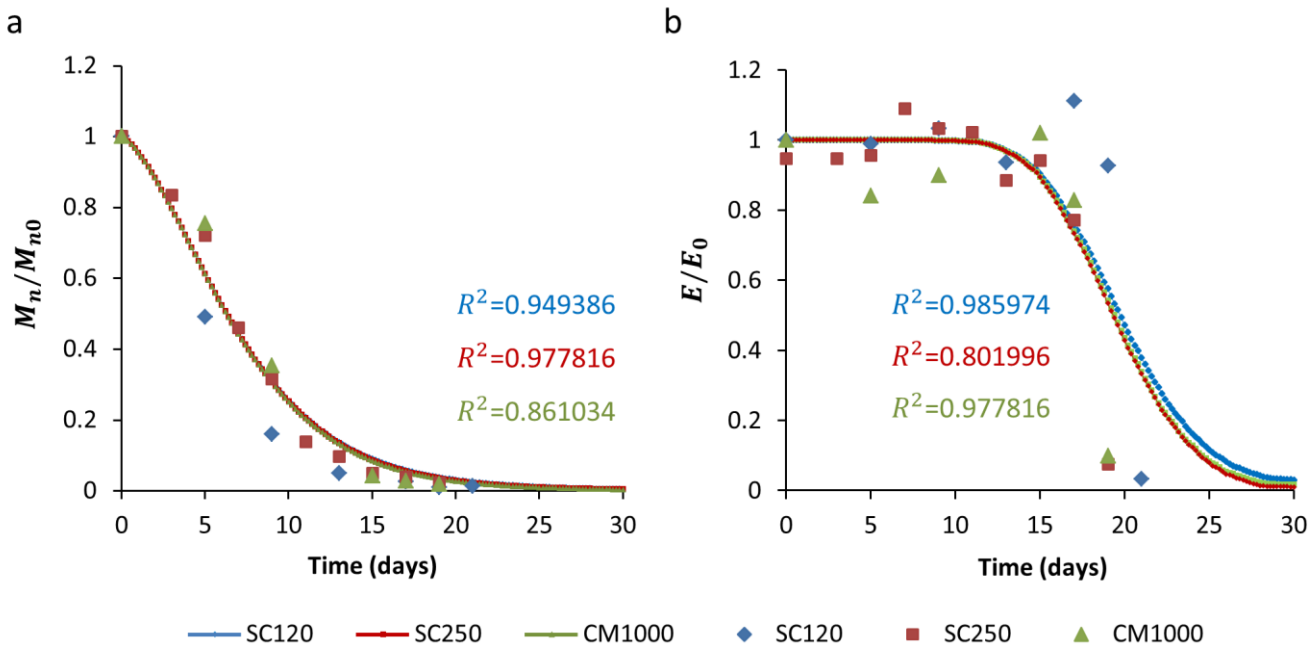
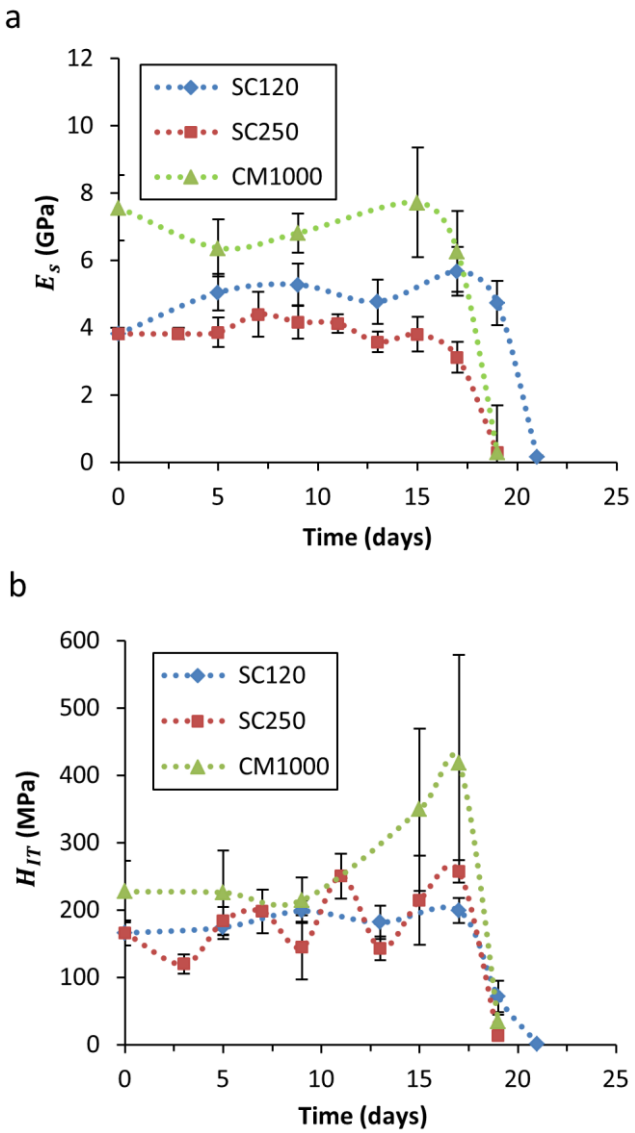


Fig. **8** shows the best fit to the experimental data presented above for the number average molecular weight and elastic modulus of the 0.12 mm and 0.25 mm films, and the 1 mm plate. The values of M_n and E were normalised to their initial

values, i.e. M_{n0} and E_0, respectively, in order to compare the behaviour of the three material thicknesses. The initial elastic moduli were obtained from the experimental results presented in Fig. **7**a.



The goodness of the fitting was established by the R^2 values. A computer code was developed in MATLAB (R2014a, Mathworks Inc., MA, USA) to calculate the R^2 values based on the linear least squares regression method. The R^2 values were calculated for each set of parameters (k_1, k_2, and D_0) and for each of the three materials with different thicknesses. The maximum value of R^2 was then given for the normalised M_n and E versus time. Comparing the maximum values of R^2 for the normalised M_n versus time and those for the normalised E versus time, the best fit was achieved by setting $k_1 = 0.02$

day^{-1}, $k_2 = 0.001$ (m^3 mol^{-1})$^{0.5}$ day^{-1}, and $D_0 = 10^{-12}$ m^2 day^{-1} for all materials. The R^2 values for the best fit are included in

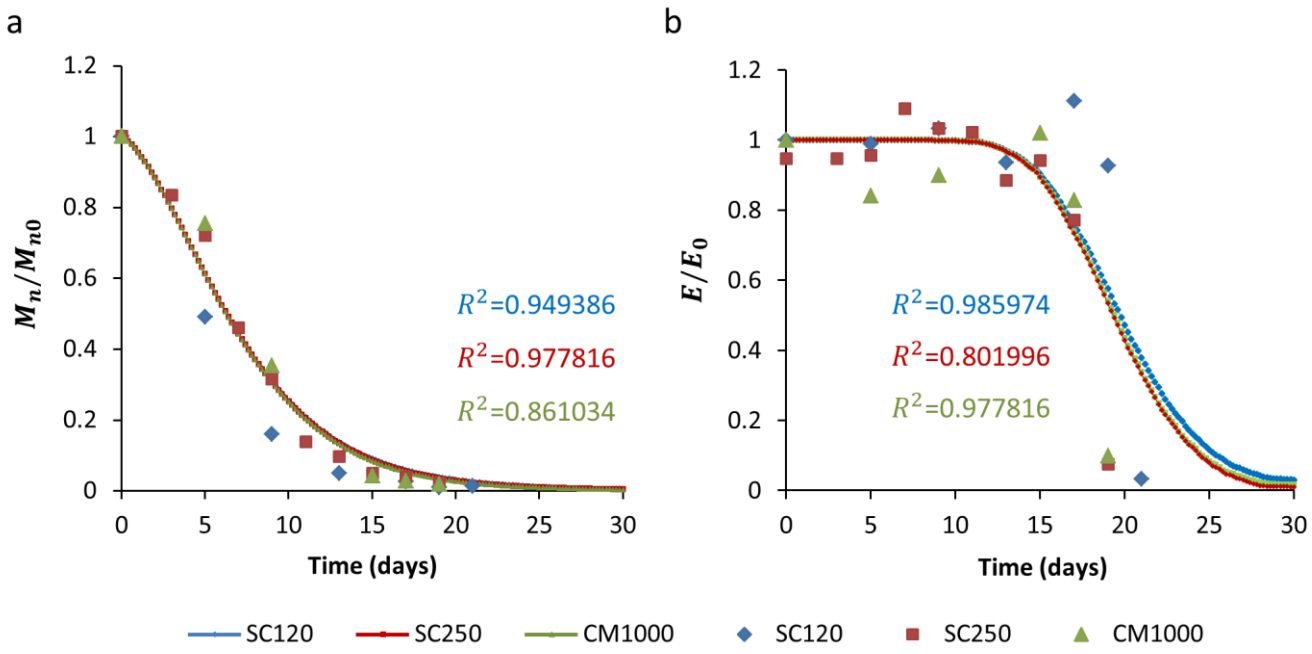


Fig. **8**.

4. Discussion

In this study, the degradation rate and the changes in the mechanical properties of the solvent-cast and the compression-moulded PLGA materials for different thicknesses were considered. The predictive performance of the computational modelling framework developed by Shirazi *et al.* [2] was assessed based on the experimentally observed changes in the molecular weight and the elastic modulus of PLGA for three different thicknesses. The model parameters which were calibrated based on the 0.25 mm solvent-cast film [1] were refined here to give the best fit to the experimental results for the 0.12 mm solvent-cast film and the 1 mm compression-moulded plate.

4.1 Molecular weight distribution during degradation

The present study has demonstrated that there is no significant difference in the degradation rate of PLGA material thicker than 0.12 mm, as indicated by the decrease in the weight average molecular weight (M_w). The significance of specimen thickness and degradation rate is discussed below. Despite the similarities in degradation rate, however, the decrease in the number average molecular weight (M_n) of the 0.12 mm film was faster than that of the 0.25 mm film and the 1 mm plate. The difference between the decrease in M_w and M_n is due to the fact that M_n is strongly influenced by the relatively small number of chains of low molecular weight. The molecules of low molecular weight can be produced as a result of end

scissions, where scissions occur at the final bond at chain ends, resulting in the production of monomers. In contrast, M_w is strongly affected by a relatively small number of chains of large molecular weight. The slightly higher M_w observed on day 9 for the 1 mm plate was not accompanied by higher M_n which suggests that the 1 mm sample retains slightly more long chains during degradation at day 9 than the other two samples. However, this difference is not significant enough to result in a substantially different PDI at day 9 for the compression-moulded sample.

A faster decrease in the weight of the 0.12 mm film at the earlier stages of degradation indicates that a significant number of polymer chains, which were produced as a result of end scissions, were small enough to diffuse from the polymer matrix to the surrounding medium. An initial delay in the reduction of the number average molecular weight and the mass loss of the 0.25 mm film and the 1 mm plate may be related to the small polymer chains being unable to diffuse to the medium due to the larger diffusion length. If this were the case then this would result in the accumulation of the carboxylic acid chain ends of water-soluble oligomers and monomers inside the polymer matrix which would accelerate the hydrolytic degradation and therefore the mass loss at the later stage of degradation. This is consistent with the observations here after 7 days of degradation; however, this effect is not pronounced.

4.2 Critical diffusion length scale

The experimentally observed results for the degradation rate of PLGA materials presented in this study are in agreement with the computational modelling predictions of Shirazi *et al.* [2]. These computational predictions suggested a critical diffusion length scale in a range 2-100 µm, below which degradation is homogenous. This length scale arises from the diffusion of the monomers out of the sample. For larger samples, the monomers are trapped and faster autocatalytic degradation occurs and degradation is heterogeneous.

The values for the dominant model parameters (D_0, k_1, k_2) are refined in this study to give the best fit to the experimental results for PLGA material for three different thicknesses. The value of the diffusion coefficient (D_0) proposed in this study is exactly the same as that presented in the earlier computational study of Shirazi *et al.* [2] ($D_0 = 10^{-12}$ m^2 day^{-1}). The difference in the value proposed in this study for the autocatalytic reaction constant ($k_2 = 0.001$ (m^3 mol^{-1})$^{0.5}$ day^{-1}) relative to the value presented by Shirazi *et al.* [2] ($k_2 = 0.002$ (m^3 mol^{-1})$^{0.5}$ day^{-1}) is not that significant. Compared with the study of Shirazi *et al.* [2], the value proposed here for the non-catalytic reaction constant is substantially larger ($k_1 = 0.02$ day^{-1} versus $k_1 = 0.002$ day^{-1}); however, as shown in [2], this difference does not have a significant effect on the degradation rate of PLGA as the model is much less sensitive to k_1 relative to k_2.

Irrespective of the specific individual parameter values, the effective parameter that characterises the homogeneity/heterogeneity of the degradation of the material is the critical diffusion length l_{diff} that can be determined from the material parameters (D_0 and k_2 only) as follows [2]:

$$l_{diff} = \sqrt{\frac{D_0}{k_2\sqrt{C_{e0}}}} \tag{2}$$

The set of parameters proposed in the present study results in a critical diffusion length equals to 3 µm below which degradation is homogenous. This result is very similar to the critical length scale presented in the computational study of Shirazi *et al*. [2] (l_{diff} =2 µm) but because they are based on the experimental observations over range of thicknesses, the set of model parameters proposed here can be used to characterise PLGA material irrespective of thickness. It should be further noted that k_1 does not appear in Eq. (2) which emphasizes the insignificant effect of non-catalytic hydrolysis discussed above.

Sample thickness is only significant when on the order of the critical diffusion length. For the PLGA materials considered in this study, the thicknesses of the samples are much larger than the critical diffusion length scale suggested by Shirazi *et al*. [2]; hence, it is expected that autocatalytic hydrolysis is the dominant mechanism and that degradation is heterogeneous. It should also be recalled that the 1mm plate was exposed to PBS on two surfaces thus will behave like a 0.5mm film exposed to PBS on one surface. The heterogeneous degradation of 0.25 mm solvent-cast PLGA films was observed in the earlier experimental study of Shirazi *et al.* [1] using scanning electron microscopy. Although the heterogeneous degradation of the 0.12 mm film and the 1 mm plate were not directly inspected here using scanning electron microscopy, the similar degradation rate for the molecular weight of all three thicknesses is consistent with the heterogeneous degradation of PLGA for the thicknesses considered here. Similarly, experimental studies have shown heterogeneous degradation for films of 300 µm [25] and 5-100 µm [12], and for 50-70 µm microspheres [26]. However, there is no consensus in the literature on the length scale for transition between homogenous and heterogeneous degradation.

The experimental results presented in the current study did not consider the degradation of PLGA thinner than 100 µm, where the differences in thickness dependence should be observed; however, the agreement here between the experimental and computational results for the degradation of PLGA thicker than 120 µm suggests that the model has captured the correct behaviour.

4.3 Mechanical properties during degradation

The results of the present study showed that despite the fact that the degradation of PLGA results in a quick decrease in the material molecular weight, the elastic modulus does not decrease until the number average molecular weight of the polymer chains reaches a critical molecular weight of 1500 g mol^{-1}. These results are in agreement with the results of *in-vitro* degradation for 0.25 mm solvent-cast PLGA films presented by Shirazi *et al*. [1].

The results of the present study showed that the rate of change of mechanical properties during degradation was similar for all cases; the modulus remained constant before suddenly dropping after 19 days (the 0.12 mm solvent-cast sample showed a slightly later drop at 21 days). On this basis, the experimental observation further supports the computational predictions of Shirazi *et al*. [2] which showed no significant difference between the changes in the elastic modulus of PLGA films larger than 100 µm. Although the experimental results presented here did not consider the degradation of PLGA thinner than 100 µm, they allow for the assessment of the performance of the model and the verification of its predictive capability.

4.4 Effect of processing method

The present study has demonstrated that the specific processing method considered here affects the initial molecular weight of PLGA. The smaller molecular weight of the compression-moulded material before immersion in PBS may be related to the heat treatment during the compression moulding process which may cause the degradation of polymer. This result is consistent with the observations of previous studies [27-29]. Gogolewski and Mainil-Varlet [27] showed that the molecular weight of the heat-treated poly(D,L-lactide acid) (PDLLA) orthopaedic pins decreased due to the heat treatment over 50 hours at 135°C under moisture-free argon. Carassco *et al*. [28] observed that extrusion and further injection moulding caused a decrease in the molecular weight of poly(lactic acid) (PLA) due to molecular degradation.

The experimentally observed results in the present study showed that the hardness of the compression-moulded PLGA material is larger than that of the solvent-cast material. Shirazi *et al*. [20] discussed previously that this phenomenon may be due to the heat treatment during the compression moulding process which may cause an increase in the degree of crystallinity of the polymer [30]. In the current study, the XRD patterns show no evidence of crystallinity before or after degradation. However, the surface roughness measurements show greater roughness for the compression moulded samples compared to the solvent cast. The average surface roughness values are ~20 times smaller than the indentation depths and thus within the guidelines recommended by the ISO standard for indentation hardness [31]; however, there is a difference in roughness between the processing methods which may explain the observed increased hardness in the compression

moulded sample. Shirazi *et al*. [20] also discussed that the lower stiffness of the solvent-cast material relative to the compression-moulded material may be due to the residual solvent in the solvent-cast material [19] which may cause an increase in the mobility of the polymer chains.

The present study has demonstrated that the material processing methods considered here do not have a significant influence on the degradation rate and the changes in the mechanical properties of PLGA during degradation. The degradation behaviour of the 1 mm compression-moulded sample was observed to be the same as the 0.12 mm solvent-cast sample. Therefore, as the behaviour of the solvent-cast samples is not sensitive to thickness above 0.12 mm, the processing method does not affect the degradation rate. This can be concluded despite the observed increase in the hardness of the compression-moulded material after 9 days of degradation, which is more likely due to the influence of the surface roughness, indicated by the large scatter in the hardness measurements.

A number of studies have shown the effect of materials processing method on the degradation rate of PDLLA material [32, 33]; although the material considered in these studies are different to that in the present study. Cui *et al.* [32] showed that a PDLLA electrospun fibrous mat degrades more slowly than a PDLLA film prepared by solvent casting. They proposed that the high voltage of electrospinning process may cause the enrichment of hydrophobic methyl group on the surface of the electrospun mat, which results in slower water diffusion rate from the medium in the fibre matrix. This result is in contrast to the observation of the present study, which may be due to the different processing methods to those applied here. Miller *et al.* [33] showed that 10 µm × 3 µm grooves on the surface of PDLLA films degrade faster for compression-moulded films compared with solvent-cast. They attribute this to elevated temperatures during the compression moulding process. This result is in contradiction to the results observed in the present study. Furthermore, Miller *et al.* visually inspect their samples for signs of degradation using scanning electron microscopy, rather than measuring the molecular weight.

It has been shown that any crystallinity present may have an effect on the degradation behaviour [34, 35]. In the case of PLA, a crystallinity of 30% did not affect the initial degradation behaviour, but did alter the water uptake and swelling during the later stages of degradation [35]. In the case of PLGA material, crystallinity can increase the degradation rate [34]; however, the effect of crystallinity on the rate of degradation for the PLGA materials considered here was not significant as the solvent-cast and the compression-moulded PLGA materials remain amorphous during degradation. In the present study, a small difference in water uptake was noted for the 0.12 mm solvent-cast sample, which also exhibited a slightly later drop in modulus; however, no clear relationship between water uptake, crystallinity, and modulus can be concluded as no significant

change was observed in the XRD patterns. The diffusion of water during degradation (possibly with changes in crystallinity) has not been analysed in the present study, but may be related to the observed phenomena.

5. Conclusion

This study investigated the experimental and computational analysis of the degradation behaviour and the changes in the mechanical properties of PLGA material for different thicknesses which were prepared by solvent casting and compression moulding. The experimental results show that the specific material processing methods considered here do not have a significant effect on the degradation rate and the changes in the mechanical properties during degradation; however, it influences the initial molecular weight and it determines the hardness and stiffness of the material. It was shown that the initial molecular weight of the compression-moulded material is smaller than that of the solvent-cast material. The experimental observations strongly support the computational modelling prediction that show no significant difference between the degradation rate and the changes in the elastic modulus of PLGA film larger than 100 µm. The set of parameters proposed here allows for more accurate predictions of the mechanical performance of PLGA material during degradation.

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Figure captions

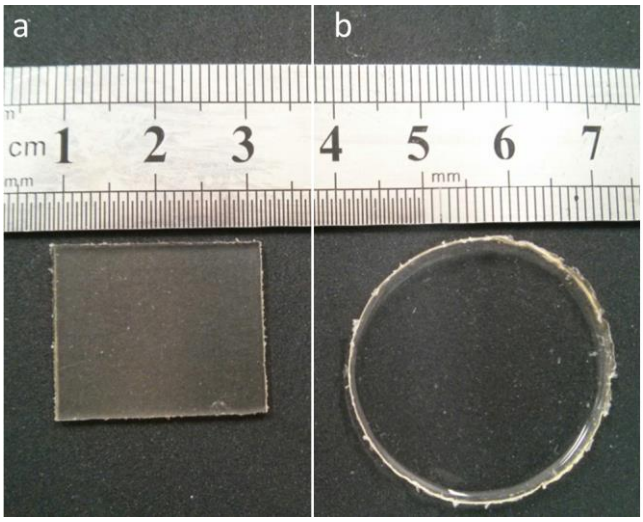

Fig. 1 Optical images of (a) a compression-moulded plate in the as-received condition and (b) a prepared solvent-cast film

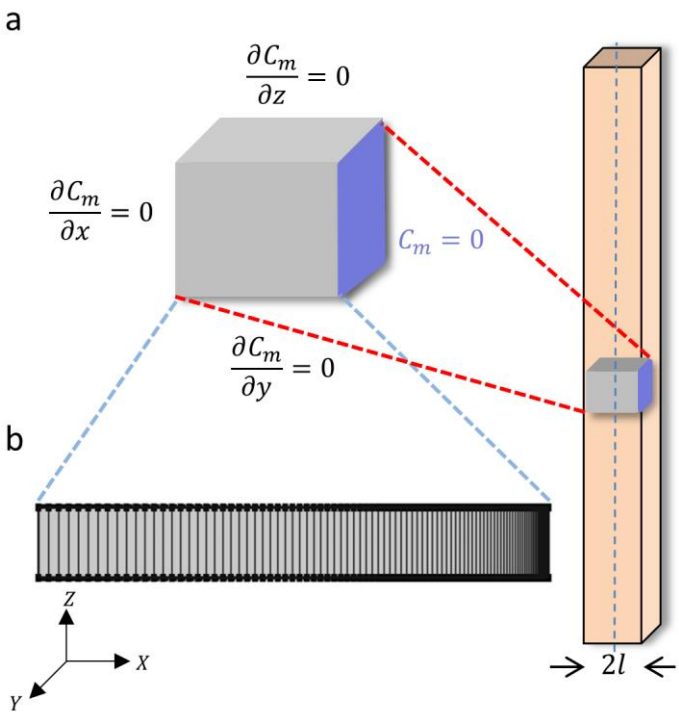

Fig. 2 (a) The boundary conditions of the concentration of the monomers (C_m) applied to predict the changes in the average molecular weight during degradation using the molecular weight model [2] and (b) the mesh element used through the film thickness. The film thickness l is equal to half the thickness of the plate

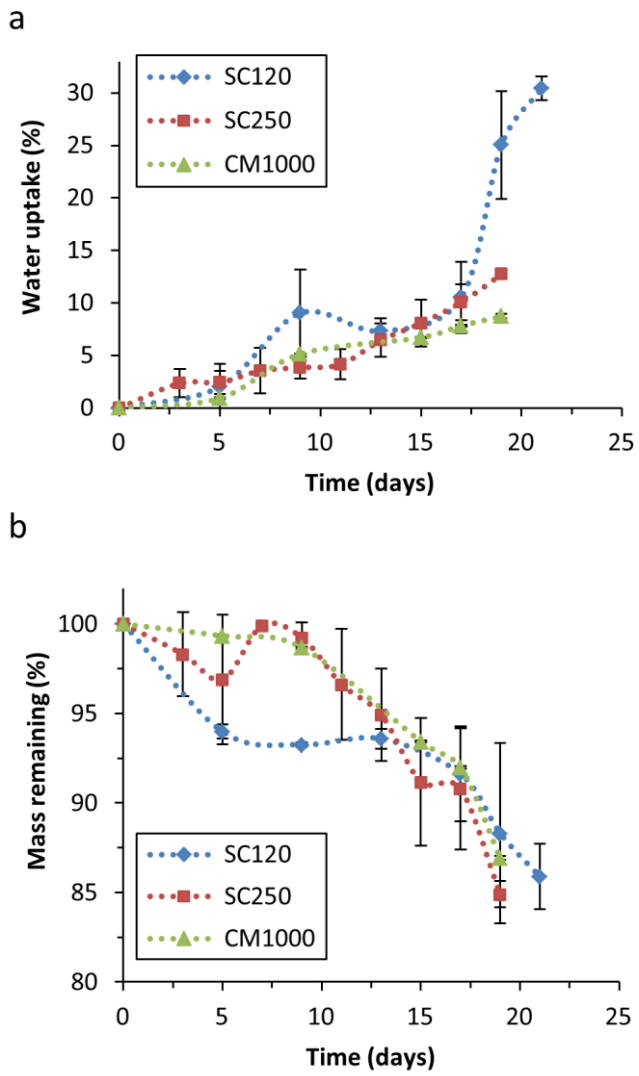

Fig. 3 Changes in the (a) water uptake and (b) mass remaining of the 0.12 mm and 0.25 mm solvent-cast PLGA films (SC120 and SC250, respectively) and the 1 mm compression-moulded PLGA plate (CM1000) during degradation (mean ± SD; n = 3)

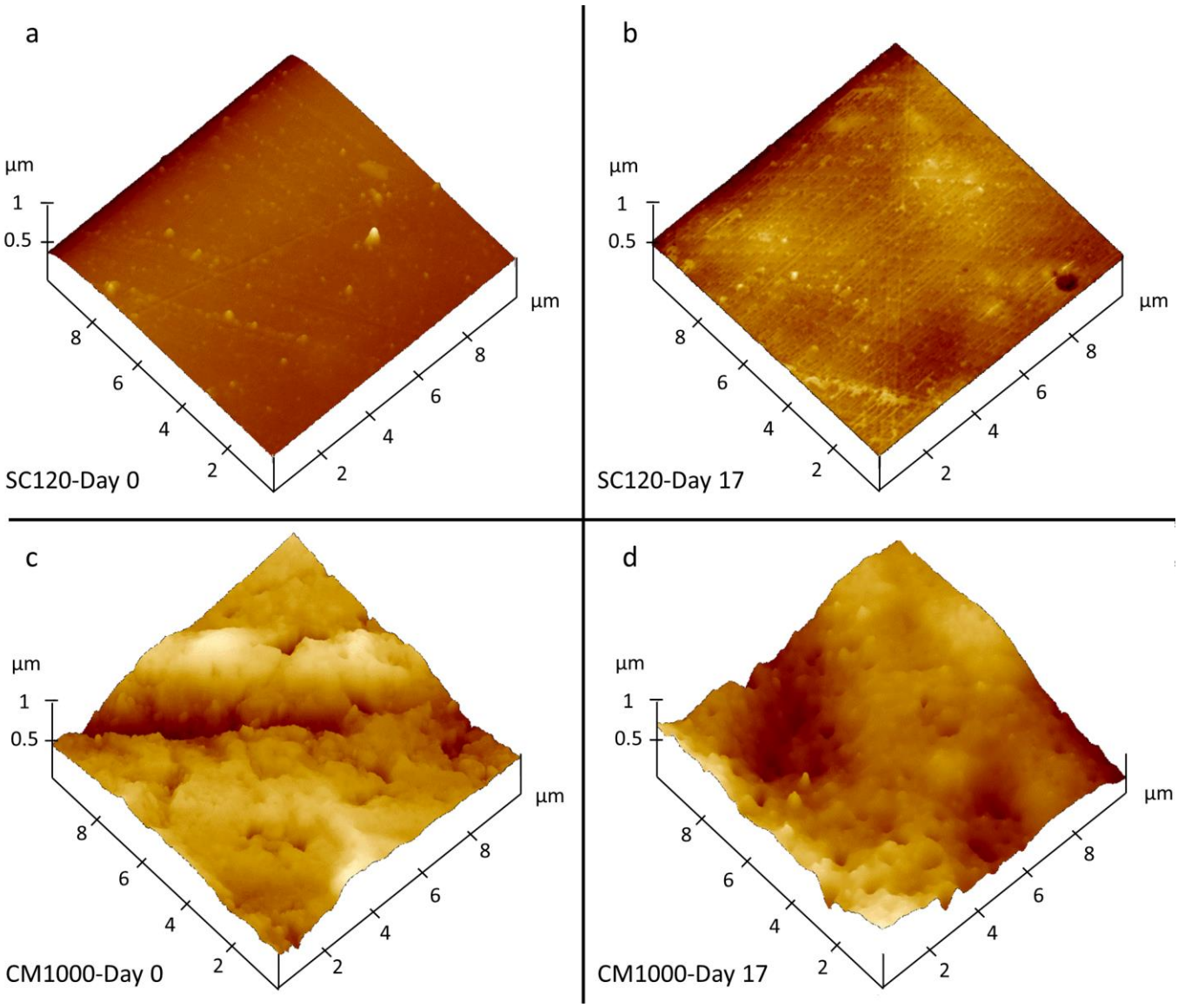

Fig 4 The three-dimensional AFM images of (a, b) the 0.12 mm solvent-cast film (c, d) the 1 mm compression-moulded plate (a, c) before and (b, d) after immersion in PBS for 17 days

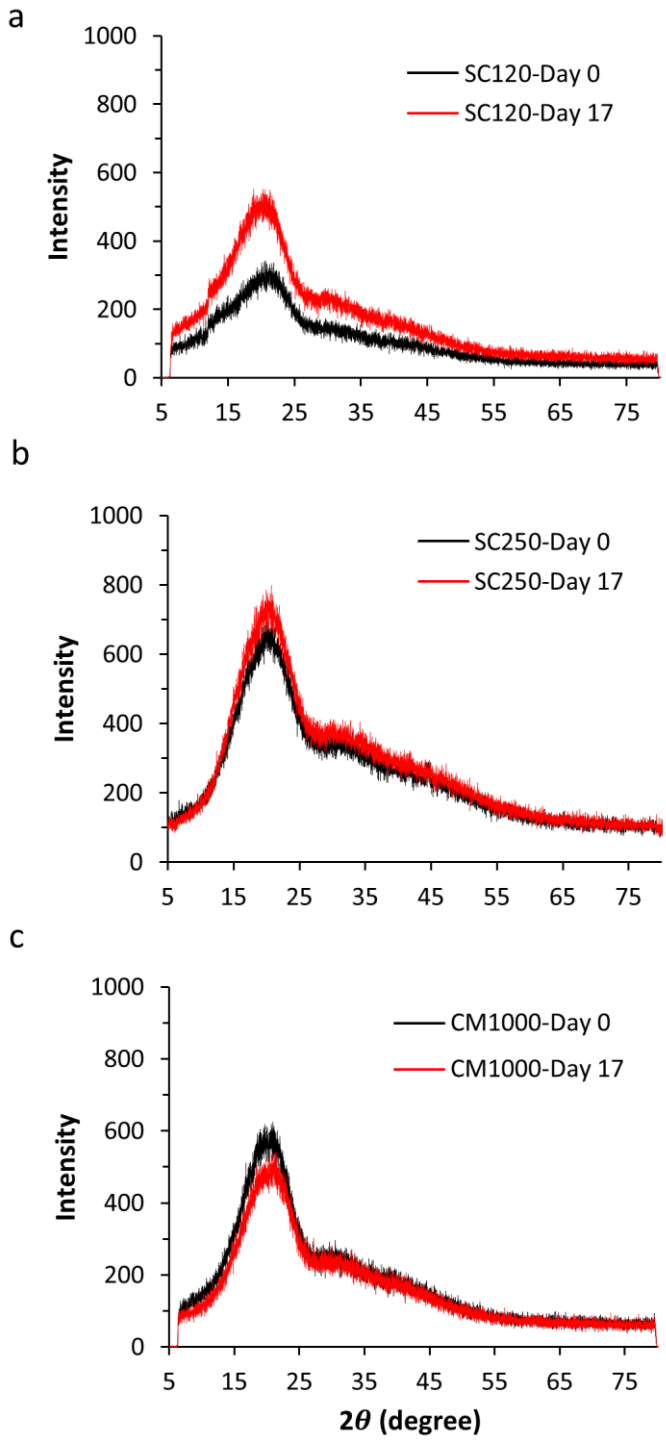

Fig 5 XRD patterns of the (a) 0.12 mm and (b) 0.25 mm solvent-cast PLGA films (SC120 and SC250, respectively) and the (c) 1 mm compression-moulded PLGA plate (CM1000) before and after immersion in PBS for 17 days

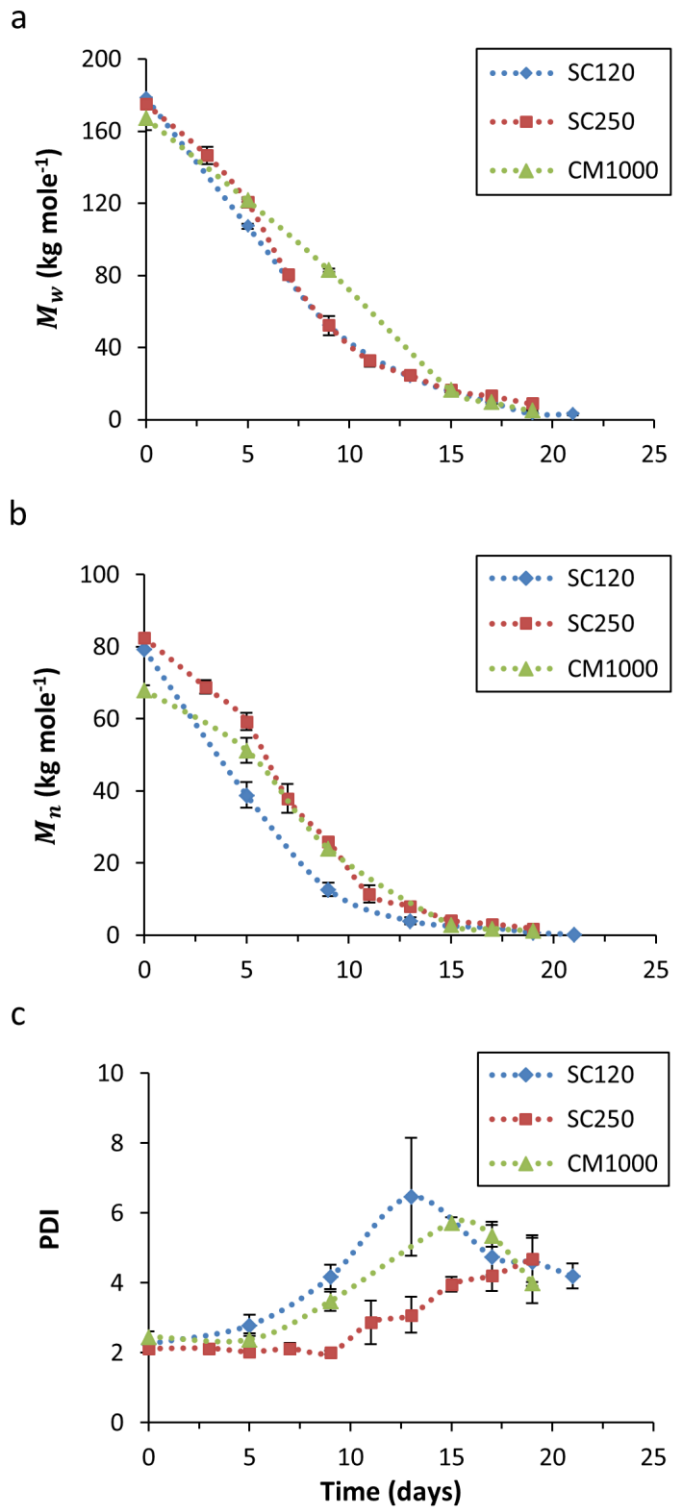

Fig. 6 Changes in the (a) weight average molecular weight (M_w), (b) number average molecular weight (M_n), and (c) polydispersity index (PDI) of the 0.12 mm and 0.25 mm solvent-cast PLGA films (SC120 and SC250, respectively) and the 1 mm compression-moulded PLGA plate (CM1000) during degradation (mean ± SD; n = 3)

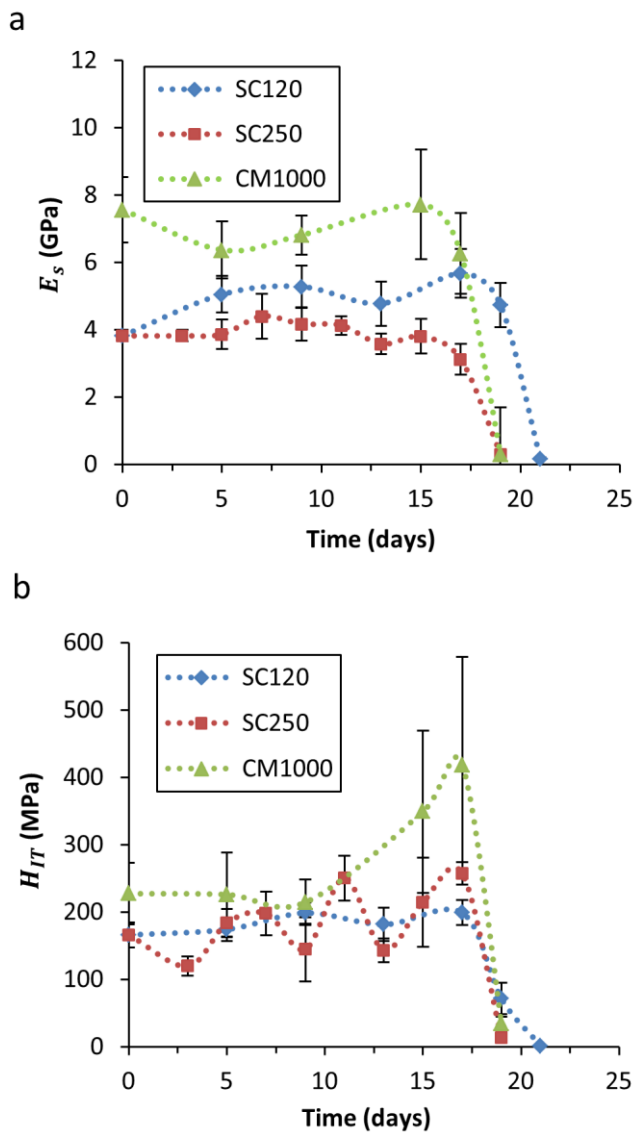

Fig. 7 Changes in the (a) elastic modulus (E_s) and (b) hardness (H_{IT}) of the 0.12 mm and 0.25 mm solvent-cast PLGA films (SC120 and SC250, respectively) and the 1 mm compression-moulded PLGA plate (CM1000) during degradation (mean ± SD; n = 20)

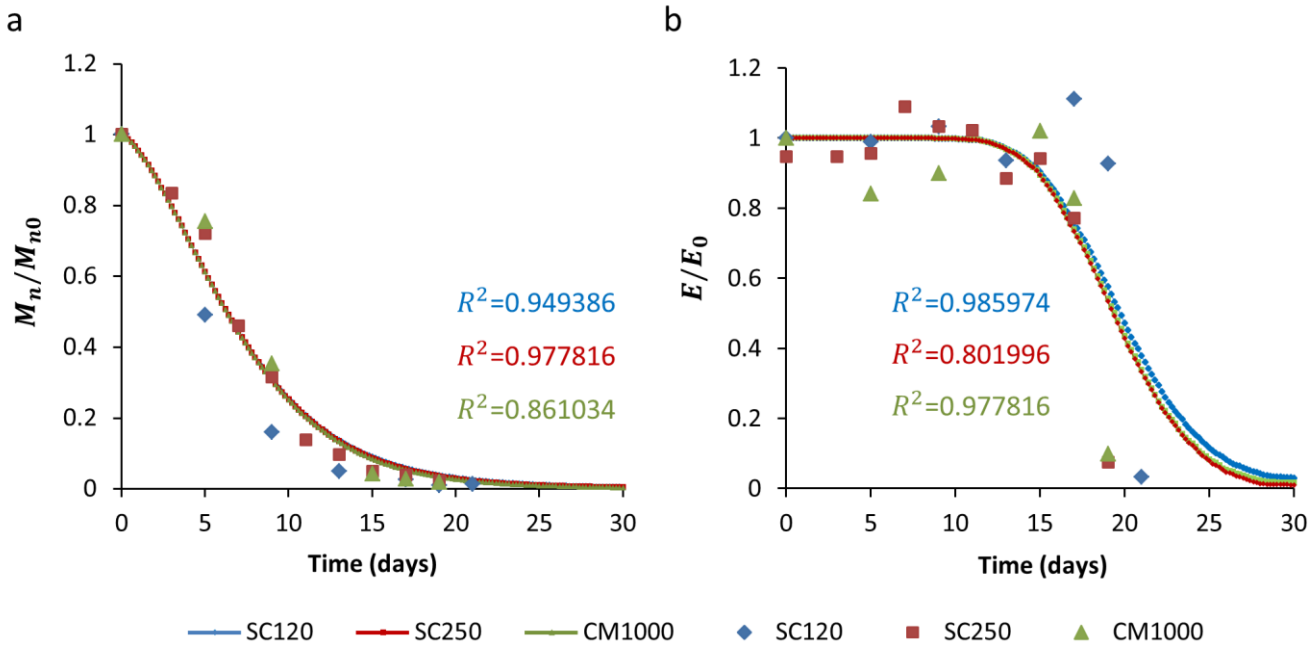

Fig. 8 Model fittings of the normalised (a) number average molecular weight (M_n/M_{n0}) and (b) elastic modulus (E/E_0) to the 0.12 mm and 0.25 mm solvent-cast PLGA films (SC120 and SC250, respectively) and the 1 mm compression-moulded PLGA plate (CM1000). The solid lines and the discrete dots show the model predictions and the experimental data, respectively. The R^2 values show the best fits to the experimental data for SC120, SC250, and CM1000 which are indicated by blue, red, and green, respectively

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