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A comparative study on Poly(ε-caprolactone) film degradation at extreme pH values

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ABSTRACT

The present paper studies the effect of pH on hydrolytic degradation of Poly(ε-caprolactone) (PCL) Degradation of the films was performed at 37ºC in 2.5 M NaOH solution (pH 13) and 2.5 M HCL solution (pH 1). Weight loss, degree of swelling, molecular weight, and calorimetric and mechanical properties were obtained as a function of degradation time. Morphological changes in the samples were carefully studied through electron microscopy. At the start of the process the degradation rate of PCL films at pH 13 was faster than at pH 1. In the latter case, there was an induction period of around 300 h with no changes in weight loss or swelling rate, but there were drastic changes in molecular weight and crystallinity. The changes in some properties throughout the degradation period, such as crystallinity, molecular weight and Young's modulus were lower in degradations at higher pH, highlighting differences in the degradation mechanism of alkaline and acid hydrolysis. Along with visual inspection of the degraded samples, this suggests a surface degradation at pH 13, whereas bulk degradation may occur at pH 1.

Keywords— PCL, hydrolytic degradation, pH, hydrolysis.

1. INTRODUCTION

Polycaprolactone (PCL) is a bioabsorbable, semi-crystalline polymer (Tm ≈ +60 °C) with a low glass transition temperature (Tg ≈ -60 °C), which can be degraded by microorganisms, as well as by hydrolytic mechanisms under physiological conditions[1]. Because of its low glass transition temperature, the PCL amorphous phase displays high molecular mobility at body temperature. In comparison with the other commercially available bioresorbable polymers, PCL is one of the most flexible and easy to process materials[2]. Because of its significant degree of crystallinity and substantial hydrophobicity, high molecular weight PCL has shown remarkably long *in vivo* degradation times, in some instances as long as 2 years [3]. As for its tissue compatibility, PCL is known to elicit a rather mild inflammatory response[4].

Polycaprolactone (PCL) was one of the earliest polymers synthesized by the Carothers group in the early 1930s [5] and a resurgence of interest during the 1990s and 2000s has stemmed from the realization that PCL possesses superior rheological and viscoelastic properties over many of its resorbable-polymer counterparts, which renders it easy to manufacture and manipulate into a large range of scaffolds. Surprisingly, despite more than 1000 papers being published during the last decade in the biomaterials and tissue-engineering literature on PCL-based-scaffolds, only a small number of groups have included a study of the degradation and resorption kinetics of PCL scaffolds [6].

The most important role of the use of scaffold *in vivo* is that it persists in a robust state for sufficient time to allow the formation of new tissue, but also ultimately degrades and is replaced by this tissue. Hydrolytic degradation is of crucial importance [7,8] for its successful implementation in applications such as surgical sutures, drug delivery systems, and tissue engineering scaffolds. The rate of degradation has been attributed to a number of polymer characteristics. It is believed that the access of water to the ester bond, rather than intrinsic rates of ester cleavage, govern the time it takes for a polymer to degrade [9]. Water access to the ester bonds is determined by the combined effect of the hydrophobicity of the monomers, the crystallinity of the sample, the molecular weight, the glass transition temperature and the bulk sample dimensions [10–12]. Some studies have also shown the effect of porosity on degradation of PCL samples [13,14] and on degradation of samples based on other polyesters [15,16]. High porosity with a large specific surface could increase the hydrolysis rate and produce large amounts of acid byproducts and also provide a better inter-connective pore structure and enhanced fluid permeability [14]. Natu et al. have shown that the processing method does not have a significant effect on the long term degradation of PCL constructs, although there were some differences in the degradation profile for samples prepared by different processing methods of up to 18 months, these differences tended to disappear during the advanced stage (18-36 months) [17].

A closer look at the degradation of polyester materials has revealed that there are still many unsolved problems that hinder us from taking full advantage of these materials

[18]. Most of what we know about degradation mechanisms dates back to the early 1980s, when degradable polymers were classified into surface eroding and bulk eroding [19]. Several mathematical models have been developed to predict the degradation of the aliphatic polyesters in an aqueous environment [18,20–23].

The degradation rate also depends strongly on pH. However most degradation studies are usually done in a physiologic saline solution of pH 7.4. After shifts in pH, reaction rates of esters may change some orders of magnitude due to catalysis. Ester hydrolysis can therefore either be acid or base catalyzed [24]. It is therefore important to understand the pH dependent degradation of biomaterials, because they should be able to retain adequate properties under all possible physiologic and pathologic conditions. It is known that the pH of gastric juice in the stomach can go as low as 0.9-1.5, while the pancreatic juice in the duodenum ranges from 7.5 to 8.2 [25]. Hydrolytic degradation of Poly(glycolic acid) has been reported at three different pHs [26]. The comparison of the effect on mechanical properties of pH levels ranging from 5.25 to 10.09 on the hydrolytic degradation of polyglycolic acid and poly(glycolide-lactide) suture materials has also been reported [25]. Accelerated degradation studies in an alkaline medium have previously been reported by a small number of groups for PCL- based polymeric films and devices [27–30]. Tsuji and Ishizaka studied the enzymatic and alkaline degradation of porous PCL films [31]. The degradation of PCLs in acidic and basic media have been studied by Jung et al., who reported variations in the relative viscosities at various pH as a function of time [32].

The objective of this study is to further investigate the hydrolytic degradability of PCL films by assessing the effects of extreme pH (1 and 13) on weight loss, degree of swelling, molecular weight, and calorimetric and mechanical properties, as well as morphological changes, to better understand the influence of the pH medium on the process of degradation and the relationship between bulk and surface characteristics during the degradation period.

2. MATERIALS AND METHODS

Materials

Poly(caprolactone) films

(PCL) [Polysciences (M_w 43,000-50,000)] in the form of powder was used without further purification. The solvent, tetrahydrofuran (THF) from Aldrich was used as received. Films were prepared from a solution of PCL in tetrahydrofuran (THF) by evaporation of THF at room temperature (for 7 days).

Degradation solutions

Sodium hydroxide, NaOH, and hydrochloric acid, HCL, from Sharlab were used as received. Distilled water with 10µS conductivity was used as a solvent. 2.5M degradation solutions were prepared from HCl (pH 1), and NaOH (pH 13).

Methods

Incubation

The resultant films were cut into discs (diameter, 6 mm; thickness, 2.5 mm) and used for the degradation experiments. After placing the films (≈70 mg) into test-tubes, degradation solution was added at either pH 1 or pH 13; the ratio sample/degradation medium was 1/50 in mass. Triplicates were prepared for each period of degradation for both pH settings to minimize the effects of random errors. After the addition of degradation solution, the test tubes were placed in an oven at 37.0°C for incubation. At predetermined time intervals three sample replicates were taken out of the solution, washed twice with distilled water, wiped, weighed, and subsequently vacuum dried prior to posterior analyses.

pH

The pH measurements in the degradation medium were carried out using a pH meter equipped with an Ag/AgCl electrode. The instrument was calibrated using buffer solutions at pH 4 and pH 7.

Degree of swelling and weight loss

The degradation process was followed by determining the water absorption and mass loss of the materials. Samples were washed with distilled water and gently wiped with paper. Wet weight was determined in order to evaluate the evolution of the samples' hydrophilicity. The degree of swelling was determined by comparing the wet weight (w_w) at a specific time with the dry weight (w_d) according to Eq.1

$$\text{degree of swelling}\,(\%) = \frac{w_w - w_d}{w_d} \times 100 \quad (1)$$

The percentage of weight loss was determined after drying the samples in a vacuum by comparing dry weight (w_d) at a specific time with the initial weight (w_0) according to Eq.2

$$\textit{weight loss}\,(\%) = \frac{w_0 - w_d}{w_0} \times 100 \quad (2)$$

A balance (Mettler Toledo) with a sensitivity of 0.01 mg was used to weigh the samples.

Scanning Electron Microscopy (SEM)

To investigate the surface and cross section morphology of dried samples, SEM pictures of degraded and non-degraded samples were taken using a JEOL JSM-5410 scanning electron microscope.

Molecular Weight Analysis by gel permeation chromatography (GPC)

The weight average molar mass of the samples was determined with a gel permeation chromatographer at 30ºC using a Waters Breeze GPC system with a 1525 Binary HPLC

pump (from Waters Corporation, Milford, MA) equipped with a 2414 refractive index detector and Waters Styragel HR THF columns. THF was used as the eluent at a flow rate of 0.5 mL/min. The calibration curve was prepared by using monodisperse polystyrene standards from Shodex (Showa Denko K.K., Kawasaki, Japan).

Differential Scanning Calorimetry (DSC)

The thermal properties of the samples were measured by using a Mettler Toledo differential scanning calorimeter (DSC) calibrated with indium. The measurements were carried out at a scan rate of 10 ºC/min between –10 ºC and 100 ºC. Crystallinity was calculated assuming proportionality to the experimental heat of fusion, using the reported heat of fusion of 139.5 J/g for the 100% crystalline PCL [33].

Mechanical testing

A monotonic ramp performed at a 0.01 mm/s cross-head velocity was carried out using an Instron MicroTester 5548 machine with a precision of 0.0001 N and 0.001 mm in force and displacement respectively, provided with a 50 N load cell. The dimensions of the sample were measured before and after the test. Five replicates for each degradation time were measured. Experiments were performed at room temperature.

3. RESULTS AND DISCUSSION

As defined by Gopferich in 1996, “The process of ´degradation´ describes the chain scission process during which polymer chains are cleaved to form oligomers and finally to form monomers and/or other low molecular weight degradation products [8].

The degradation process of aliphatic polyesters is based on a hydrolytic cleavage of the ester bonds on their backbone chains [34]. When the water molecules attack the ester bonds in the polymer chains, the average length of degraded chains becomes shorter. Eventually, the process results in short fragments of chains that become soluble in water. There are reports in the literature that indicate that molecular weights that are suitable for renal clearance are in the range of 10-50 kDa [35,36].

Weight loss and degree of swelling

The weight loss profile measured in PCL films at 37°C as a function of time is shown in Figure 1 (left). The specimens degraded at pH=13 showed a faster rate of degradation than those degraded at pH 1. At pH 13 it is apparent that there were two weight loss rates. From 0 to 600 hours, when the weight loss is approximately 60%, a more or less linear and steep degradation profile was observed, after which the degradation process slowed down. The weight loss was around 98% at 2110 hours. The weight loss of the samples degraded at pH 1 presented a clear induction period of around 300 hours, after which the mass decreased continuously to a weight loss of around 97% after 2300 hours.

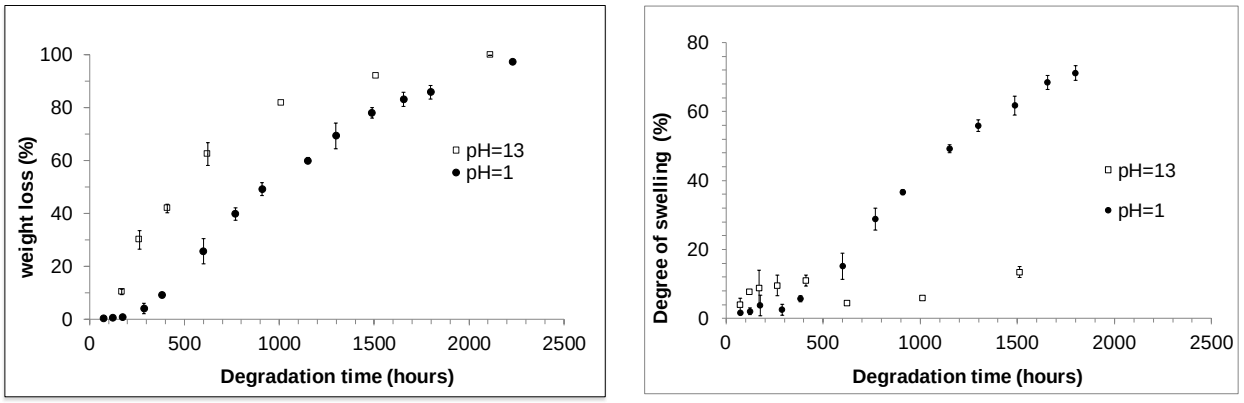

Figure 1. Weight loss profile (left) and degree of swelling (right) as a function of degradation time. Error bars represent standard deviation.

The degree of swelling shows a different tendency for the samples degraded at different pH values (see Fig. 1, right). Samples degraded at pH 13 showed an initial increase in the degree of swelling, reaching a maximum value of around 10% for a period of 150h and then remained almost constant for the rest of the time interval. It was not possible to handle the samples after 1500 hours of degradation to measure the degree of swelling due to fragmentation. For films degraded at pH 1 the water uptake had an induction period in which the degree of swelling did not significantly change. After 380 hours, water absorption increased steadily, reaching 80% at the end of the degradation period (2250h). The degree of swelling as a function of weight loss is shown in Figure 2. Films degraded at pH 1 exhibited a linear relationship between both parameters (ρ^2=0.9934). However, at pH 13 the degree of swelling slightly increases at the beginning of degradation with no significant changes during the rest of the degradation process.

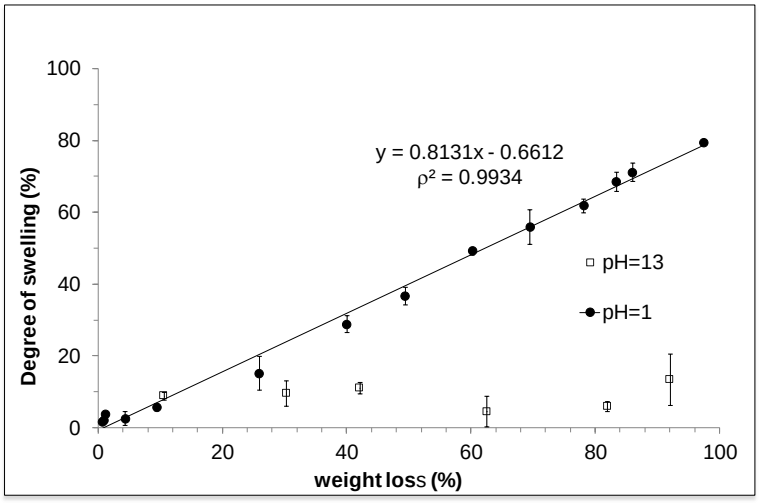

Figure 2. Degree of swelling as a function of weight loss. Straight line represents the linear fit of data corresponding to pH 1.

The extent and mechanism of hydrolysis are determined by the amount, presence and location of water molecules. Thus, the polymers´ chemical composition, hydrophobicity, size and design all play an important role in this interaction with water [28].The differences in the degradation behavior at different pH can be correlated with the effect of pH on hydrophilicity. The polymer at alkaline pH (pH 13) maintains its apolar (hydrophobic) character, probably because hydroxyl ions are entrapped by the ester groups on the film surface, which lowers its absorption capacity. As a result, water cannot penetrate the sample and the weight loss can only be produced by superficial degradation. However, at acid pH the PCL films change from hydrophobic to hydrophilic in character during the stay in the degradation solution. The absorption capacity increases linearly with weight loss. Larger water uptake results in an increased hydrolysis rate as more water penetrates the samples.

Visual Examination and Scanning Electron Microscopy (SEM)

Before hydrolysis all the films were homogeneous and had a smooth and even surface structure. After degradation, samples immersed in acid or basic medium exhibit quite different morphologies (Fig. 3 a) and b)). Films degraded at pH 13, see Figure 3a, present non-uniform superficial erosion. After 168 hours of degradation, mass loss is only 10.6% and to the naked eye presents a rough surface with small cavities. After 621 hours, when the sample has lost 62.5% of its mass, large cavities can be observed on the disk surface. This effect is much higher when the sample has lost 92% of its mass. In contrast, the films degraded at pH 1, see Figure 3b, showed an increase in opacity during the course of the degradation experiment and slowly began to decrease in size after 120 hours of degradation. After 600 hours of degradation, cavities, cracks and fissures appeared, which is consistent with bulk degradation. The whitening observed during hydrolysis is assumed to be an effect of molecular reorganization during degradation and has previously been concluded to be the result of the formation of accelerated spherules in lactic acid based polymers [37,38].

a) pH 13 0h/0% 168h/10.6% 621h/62.5% 1510h/92%

b) pH 1 0h/0% 120h/1% 600h/62% 1650h/80%

Figure 3- Photographs of samples at different degradation time for samples immersed in a) basic pH 13 and b) acid pH 1 media. Labels indicate degradation time in hours and percentage weight loss.

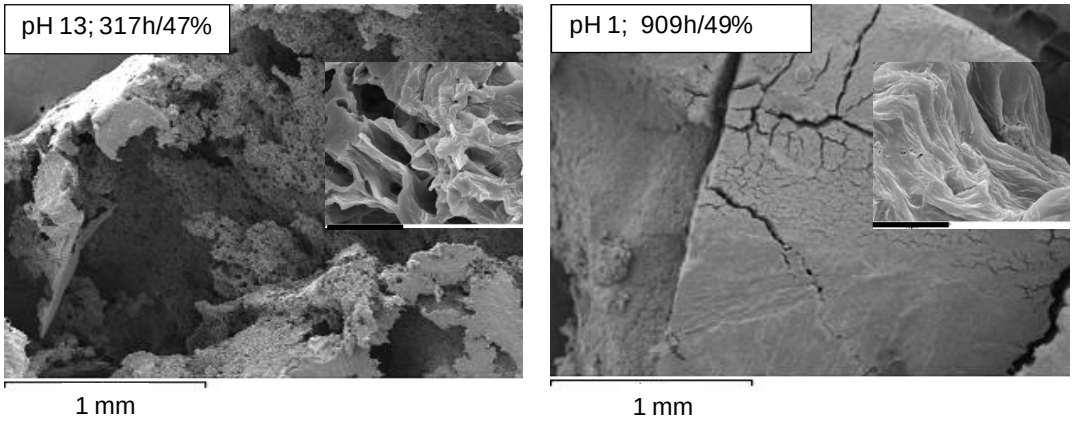

Figure 4. Superficial SEM microphotograps of samples at different degradation times for samples degraded at pH 13 after 317 h and 47% of weight loss (left) and at pH 1 after 909 h and 49% of weight loss (right). The insets show a higher magnification (bar=10µm)

Figure 4 shows the SEM microphotographs of degraded samples with similar weight loss (close to 50%). The sample degraded 317 hours at pH 13 is shown in Figure 4 (left) and presents a porous structure. The insets contain enlargements. Large cavities can be seen together with increasing surface roughness. Figure 4 (right) shows the PCL sample after 909 hours at pH 1. It can be seen that the surface is covered with cracks with small pores.

Molecular Weight Analysis (GPC)

The changes in molecular weight for the two different degradations, at extreme pH, presented different behaviors (Fig.5). At basic degradation of pH 13, it is observed that the molecular weight distribution remains unchanged with time; this phenomenon can be related to erosive degradation [39]. Despite the weight loss of the sample, the core material remains intact and the molecular weight distribution remains constant with time.

On the other hand, in the pH 1 acid medium, the molecular weight distribution is seen to move towards lower values and a double peak distribution is present after 909 h of degradation. Similar behavior of the dependence of the molecular weight distribution has also been found by other authors [40–42].

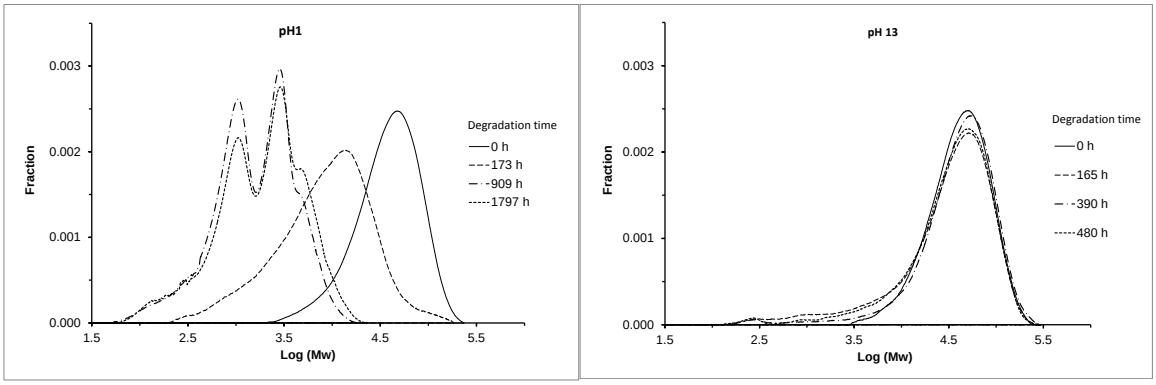

Figure 5 . Molecular weight distribution vs. time degradation in acid medium pH 1(left) and in basic medium pH 13 (right).

Surface degradation takes place when diffusion is much slower than the degradation of the polymer bonds. Water penetrates into the polymer at a slower rate than hydrolysis; the hydrolysed surface by-products simply diffuse rapidly into the media and there is no opportunity for water molecules to reach the center of the matrix. Degradation occurs purely at the surface. As a consequence, the polymer device experiences a thinning effect and leaves the molecular weight intact, since lower molecular weight surface by-products are diffused out [28].

Bulk degradation occurs when the diffusion of water into the polymer is faster than the degradation of polymer bonds. The medium is able to penetrate through the entire polymer and random hydrolytic chain scissions take place throughout the matrix in a more or less uniform manner. The common hydrolyzed by-products of polyester degradation are typically the hydroxyl and carboxyl end groups. As a result, the formation of these end groups from each ester-bond cleavage produces carboxylic acid, which is a catalyst for hydrolysis [28]. When these by-products are removed from the polymer matrix, chain scission becomes homogeneous; this principally defines bulk degradation when molecular weight reduction is homogeneous. In contrast, when these by-products are not able to diffuse out of the polymer matrix, they form a concentration gradient of carboxylic acid from the center to the surface of the polymer producing an exponential rate of degradation at the core of the material. This phenomenon is known as internal autocatalysis, which produces a bimodal molecular weight distribution [40].

Differential Scanning Calorimetry (DSC)

The changes in thermal properties during degradation were monitored by differential scanning calorimetry (DSC) (see Fig 6). The degree of crystallinity (χ_c) and the melting temperature (Tm) were determined during the first heating scan. The thermal analysis

of films degraded at pH 13 showed no significant change in crystallinity(χ_c), which was only 2% higher after 553 hours of degradation (Table 1). At longer degradation times, the melting temperature increased slightly, from 66.2 to 67.8^{o}C. There were no differences between the calorimetric scans throughout degradation. These results, together with the fact that there was no significant change in molecular weight, are consistent with surface erosion, since DSC curves for different times showed very little difference and the crystallinities of the PCL films did not change. The comparison of weight loss and crystallinity indicates that both the amorphous and crystalline phase samples degraded in a similar way to enzymatic degradation [45,46].

pH 13, 1st scan				pH 1, 1st scan		
t (h)	χ(%)	T_m (^{o}C)		t (h)	χ(%)	T_m (^{o}C)
0	65,90	66.2		0	67,24	66.6
165	66,48	67.0		173	71,58	65.8
390	68,36	67.2		909	88,4	62
553	67,81	67.8		1797	88,4	64.4

Table 1.- Crystallinity and melting temperature determined during the first scan for the degraded samples at pH 13 and pH 1

Thermal analysis of films, at pH 1 showed a 21% increase (from 67.2 to 88.4%) in the degree of crystallinity (χ_c) during the degradation period. After reaching 88.4% crystallinity, there is little change in the remaining period of degradation. This rise can mainly be related to the degradation of the amorphous phase. Besides, when the polymer chains are short enough, the increased mobility of the chains makes it possible for them to reorganize and crystallize [40,43]. The melting temperature for films degraded at pH 1 decreased (from 66 to 64.4 ^{o}C) as a result of the formation of smaller crystals of shorter polymer chains [44].

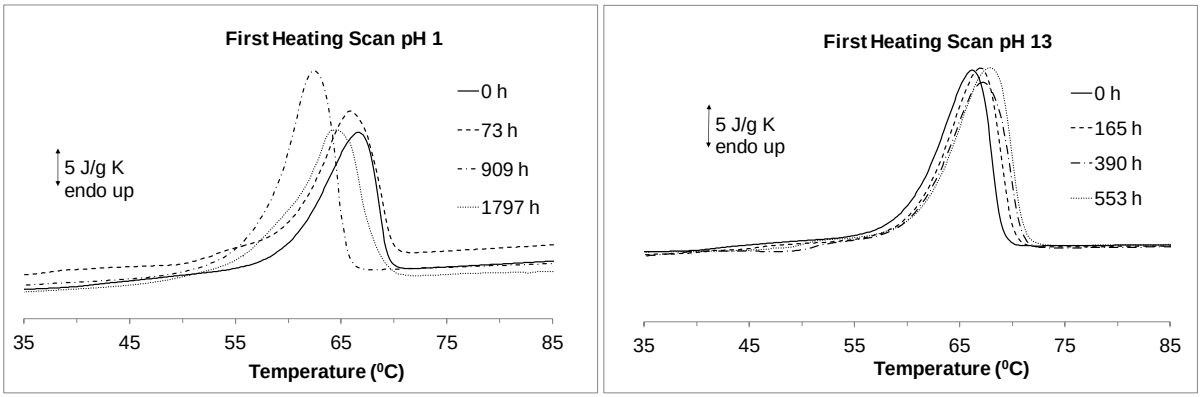

Figure 6. Endothermic DSC curves for the first scan in acid medium, pH 1 (left) and basic medium pH 13 (right)

Other degradation studies of different aliphatic polyesters at different pH [47,48], have shown higher degradations rates in alkaline solution than degradation under acidic conditions, where the rate was comparable to that in neutral buffered solutions [49,50].

Mechanical testing

The controlled decline of mechanical properties is desirable as tissue regeneration progresses; it is believed that the ideal *in vivo* degradation rate is equal to or slightly less than the rate of tissue formation [51].

Figure 7 exhibits the Young´s modulus of films degraded at pH 13 and pH 1. Non degraded films presented an initial Young´s modulus of 12 MPa. During the degradation period the PCL samples showed a rapid decrease in the modulus over time at both pHs. The same value of Young´s modulus (5MPa) was reached after 600 hours of degradation at pH 1, when the mass loss was 25%, and after 500 hours of degradation at pH 13, when the mass loss was 55%. The drop in the Young's modulus of the samples can be related to the increased porosity due to degradation. The dependence of mechanical properties on sample porosity has been reported by Thomson et al. [52] and de Groot et al [53]. More recently, other groups [2,54] have demonstrated the dependence of mechanical properties on scaffold porosity when fabricating scaffolds via rapid prototyping. Logically, as porosity increases the mechanical properties should deteriorate correspondingly. This decline has been found to follow a power law relationship [55]. Samples degraded for longer than 500 hours at pH13 were very difficult to handle and no mechanical measurements were possible.

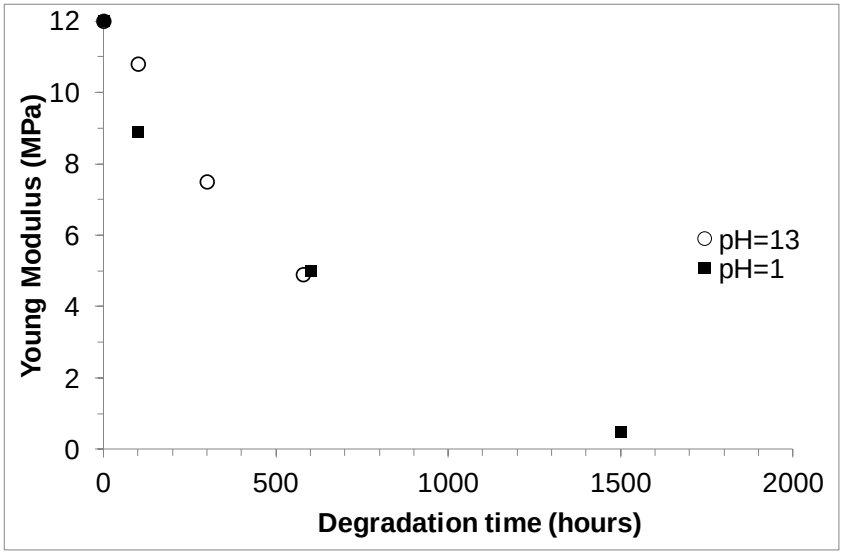

Figure 7. Young´s modulus of films degraded at pH 13 and pH 1 as function of degradation time.

Our results obtained at acidic pH 1, with significant mass loss and increased water uptake during the degradation period, together with the molecular weight results and morphology data, seem to be clearly related to bulk erosion. As we have mentioned above, when water penetrates into the material it causes erosion that affects the whole solid mass. Initially the degradation starts at the amorphous phase, with reduction in

molecular weight but without any loss in physical properties. After the induction phase, the molecules become water soluble, initiating the mass loss of the polymer. In contrast, the results of the degradation at basic pH 13 in molecular weight, mass loss and water uptake, DSC, together with the morphology data, are consistent with the fact that degradation proceeds from the surface to the interior of the sample. As far as we know these results of the degradation of PCL films at extreme pH have not previously been published. In the literature, the majority of the studies on the degradation of polyesters are focused on PLA and its copolymers, which means that the theory of the hydrolytic degradation mechanism of polyesters is mainly based on the results of PLA degradation [22], [37–40], [45]. Our results with PCL samples corroborate the findings of Von Burkersroda et al. [18] for PLA and our data therefore provide experimental support for their theory that a polymer considered bulk eroding according to the literature can be made surface eroding. Every polymer has its own specific critical dimension after which samples exceeding that dimension show surface erosion instead of bulk erosion [18]. We have taken this critical size into account when cutting the samples.

To summarize, from our results on weight loss and degree of swelling (Figures 1 and 2), molecular weight profiles (Figure 5) and the morphology data (Figures 3 and 4), it can be deduced that the degradation pathways proceeded via the surface degradation mechanism at pH 13 and via bulk degradation mechanism at pH 1. Lam et al. [28] studied long-term degradation studies of PCL scaffolds under physiologically simulated conditions using Phosphate buffered saline (PBS) at pH 7.4 and found a bulk degradation pathway. Accelerated degradation aims to accomplish the degradation of polymeric devices within a shorter period of time and could be achieved using an acidic or basic medium. The results of our study also show that accelerated degradation in acidic media better matches degradation under physiologically simulated conditions.

CONCLUSIONS

The hydrolytic degradation of PCL films at extreme pH (1 and 13) were monitored by following mass loss, polymer swelling, changes of molecular weight, thermal and mechanical properties and morphology.

The behavior of PCL films varied according to environmental pH. Initially, degradation was more rapid in a basic medium at pH 13. In an acidic medium (pH 1) an induction period was observed in which no changes occurred, followed by rapid degradation. There were considerable differences in the evolution of the degree of swelling with degradation time. While there were no significant differences in the degree of swelling when degradation occurred in a basic medium (pH 13), the degree of swelling increased monotonically with degradation time in the case of degradation in an acid (pH 1) medium. This, along with visual inspection of the degraded samples, suggests a surface degradation at pH 13, with bulk degradation at pH 1. Our findings are in agreement with other experimental results. Thus, no significant changes were observed in the molecular weight of the degraded samples at pH 13, while there was a decrease in molecular

weight in the case of degradation at pH 1. Similarly, no change was observed in the thermal properties of the material degraded at pH 13, while crystallinity was seen to increase and melting temperature to decrease in the samples degraded at pH 1.

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FIGURE CAPTIONS

Figure 1. Weight loss profile (left) and degree of swelling (right) as a function of degradation time. Error bars represent standard deviation.

Figure 2. Degree of swelling as a function of weight loss. Straight line represents the linear fit of data corresponding to pH 1.

Figure 3. Photographs of samples at different degradation time for samples immersed in a) basic pH 13 and b) acid pH 1 media. Labels indicate degradation time in hours and percentage weight loss.

Figure 4. Superficial SEM microphotograps of samples at different degradation times for samples degraded at pH 13 after 317 h and 47% of weight loss (left) and at pH 1 after 909 h and 49% of weight loss (right). The insets show a higher magnification (bar=10µm)

Figure 5. Molecular weight distribution vs. time degradation in acid medium pH 1(left) and in basic medium pH 13 (right).

Figure 6. Endothermic DSC curves for the first scan in acid medium, pH 1 (left) and basic medium pH 13 (right)

Figure 7. Young´s modulus of films degraded at pH 13 and pH 1 as function of degradation time.