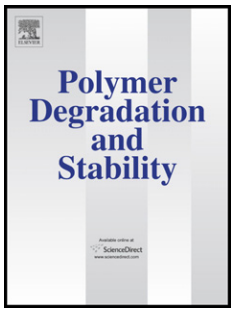

Influence of polymer processing technique on long term degradation of poly(#-caprolactone) constructs

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Influence of polymer processing technique on long term degradation of poly(ε-caprolactone) constructs

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Abstract

Films, fibers, sponges and disks, based on poly(ε-caprolactone), PCL were prepared using solvent-casting, electrospinning, supercritical fluid processing and melt-compression, respectively. The extent of degradation was determined by measuring the change in morphology, crystallinity and molecular weight (MW). The influence of processing method, MW and drug presence on degradation rate was also evaluated. The different processing techniques produced samples of various morphology and crystallinity. Nevertheless, the differences in degradation rate were not so significant during the advanced stage (18 to 36 months), while some differences existed during the initial stage (up to 18 months). MW had an important effect on degradation rate, while drug did not. The low MW disks had a degradation rate that was lower by one order of magnitude than high MW constructs.

Keywords: poly(ε-caprolactone), hydrolytic degradation, solvent-casting, melt compression, electrospinning, supercritical fluid

1. Introduction

Solvent-casting, melt compression, supercritical fluid (SCF) processing and electrospinning are well known techniques to produce materials for tissue engineering and controlled drug delivery (CDDS) applications [1, 2, 3, 4]. Poly(ε-caprolactone), PCL and other polyesters are usually the materials of

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choice for the preparation of scaffolds for tissue engineering applications and of implants/matrices for CDDS applications [5]. These polymers are commercially available, inexpensive, biocompatible and biodegradable (which ensures scaffold/implant integration at the site of implantation). Moreover, they can be easily processed using diverse techniques, that allow control of scaffold/implant morphology and/or control of drug loading and distribution and subsequently release profile.

Degradation profile has to be carefully controlled because it will directly influence the in vivo performance of the scaffold or CDDS. Usually, during degradation several simultaneous physical (water uptake, dissolution) and chemical phenomena (thermolysis, oxidation, hydrolysis) take place that will lead to a change in material properties and induce a certain in vivo response. For a scaffold, the degradation period of the polymer has to be manipulated in a such a way that the scaffold ensures mechanical support to three-dimensional tissue formation and then it gradually disappears in order to integrate the new tissue at the implantation site. For a CDDS, the degradation period has to match the drug release period and it can also determine the release profile [5].

Several factors that influence the degradation process of polyesters were studied such as polymer chemical stability, polymer molecular weight (MW), sample size and geometry, surface-to-volume ratio, degradation medium (type, temperature and pH), blending, end-group chemistry, hydrophilicity, crystallinity, drug presence, drug loading, polymer processing, sterilization [6].

Blending or copolymerization of hydrophlic compounds/polymers/blocks was shown to produce an increase in degradation rate due to an enhancement in water uptake [7]. Other authors have not found such a correlation between hydrophilicity and degradation [8]. The shape or the size of the samples was shown to influence degradation, with larger particles degrading faster than smaller ones due to an enhancement in autocatalytic effect [9], while in other works no evidence was found for internal catalysis [10].

Degradation kinetics was also shown to be highly dependent upon the MW of the polymer. An increase in MW resulted in a decrease in the degradation rate [11], while other authors found an opposite relationship between degradation and MW, with higher degradation rate for high MW polymer [12]. A higher crystallinity was indicated as a reason for the decrease in degradation, because degradation rate of amorphous regions is higher than that of crystalline regions. Other works found that samples with initial higher crystallinity degraded faster due to the formation of a highly microporous

structure [6].

Porosity is another factor that was found to influence degradation, with more porous sponges degrading faster than less porous films, due to a higher surface area in the former case [13]. In many degradation studies, no attempts were made to determine the degradation kinetics. Thus, it is not surprising to find differences between degradation profiles: MW variation was found to follow an exponential decay [14], while other authors presented a linear variation [15].

Careful consideration of processing method is necessary when comparing results from various works, because the physical properties of the material have a huge influence on degradation kinetics. Moreover, during degradation, several material properties change simultaneously, which makes the assessment of factor influence on degradation kinetics difficult. Thus, in this work, various constructs based on PCL and poly(oxyethylene-b-oxypropylene-b-oxyethylene) were prepared using different processing techniques (solvent-casting, melt compression, SCF processing and electrospinning) so that samples of specified morphology and composition were obtained. Moreover, two MW of PCL were used as well as drug incorporation in some of the constructs. This approach allowed the assessment of the processing method, polymer MW and drug presence influence on degradation profile.

2. Materials and methods

2.1. Construct preparation

Poly(ε-caprolactone) of two MW (65000 g/mol, PCL and 15000 g/mol, PCL10 from Sigma-Aldrich) and poly(oxyethylene-b-oxypropylene-b-oxyethylene) or Lutrol F 127 (9000-14000 g/mol, 70 % by weight of polyoxyethylene, Lu from BASF) and dorzolamide hydrochloride (Chemos GmbH) were used to prepare drug-loaded disks (33.3 % w/w theoretical dorzolamide loading) and control disks (no drug) by melt compression as already described [16]. The ratio of polymers in the blends was : 0/100, 25/75, 50/50 % (w/w) Lu/PCL. The same polymer and the same ratios were used to prepare films (by solvent-casting), fibers (by electrospinning) and sponges (by supercritical fluid processing, SCF) as previously reported [17, 18]. In Table 1, an overview of the samples is presented. The dimensions of the constructs are presented in Table 2. The samples were used as such in degradation experiments.

Processing method	Sample type	Drug present	Composition (w/w, Lu/PCL)
Solvent-casting	Films	no	0/100
		no	25/75
		no	50/50
Melt compression	Disks	no	0/100
		no	25/75
		no	50/50
		yes	0/100
		yes	25/75
		yes	50/50
Electrospinning	Fibers	no	0/100
		no	25/75
		no	50/50
Supercritical fluids	Sponges	no	0/100
		no	25/75
		no	50/50

Table 1: Sample description

Sample	Film	Fiber	Disk	Sponge
Length (mm)	10	10	-	5
Width (mm)	10	10	-	5
Diameter (mm)	-	-	5	-
Thickness (mm)	0.5	0.2	1	6
Volume (mm^3)	50	20	19.6	150
Surface area (mm^2)	220	208	55	170
Average weight (mg)	15	13	4	11
Surface/weight ratio (mm^2/mg)	14.7	16.0	13.7	15.5

Table 2: Sample dimensions used in the degradation experiment

2.2. Crystallinity determination

The relative crystallinity of the constructs was determined by differential scanning calorimetry (DSC, equipment Q100 from TA Instruments, 4-5 mg of sample, hermetic pans, temperature ramp: 10 °C/min, temperature range: 25 to 350°C, nitrogen flow rate: 100 mL/min) and calculated as previously described [17, 19], considering the melting enthalpy of 100 % crystalline PCL ($\Delta H_{f,100\%PCL}$=142 J/g) and 100 % crystalline Lu ($\Delta H_{f,100\%Lu}$=181 J/g).

2.3. Morphology

The morphology of the constructs was examined using scanning electron microscopy (SEM, equipment JSM 5310 from Jeol, copper coating) as previously described [17].

2.4. Molecular weight determination

The extent of hydrolytic degradation was evaluated by determining the change of MW in time. Samples were immersed in 4 mL PBS with 0.001 % sodium azide, at 37°C. The changes in the MW and polydispersity index (PI) were measured by size exclusion chromatography (SEC), using chloroform as mobile phase (1 ml/min, 30 °C) and a PLgel MIXED-C column (300 mm×7.5 mm, 5 μm, Varian). PL-EMD 960 (Polymer Laboratories) evaporative light scattering detector was used to acquire the data. Universal calibration was performed using polystyrene (PS) standards and Mark-Houwink parameters k_{PCL}=1.09 $\times 10^{-3}$ dl/g, α_{PCL}=0.60, k_{PS}=1.25 $\times 10^{-4}$ dl/g, α_{PS}=0.71. Peak integration was performed using Clarity chromatography software (DataApex).

2.5. Statistics

All values are presented as mean and standard error of the mean (SEM). Experiments were performed in triplicates. Statistical analysis (linear regression, independent two-tailed T test, one-way ANOVA and Tukey HSD test) was done using OpenOffice.org Calc 3.2 and OOoStat Statistics Macro 0.5. The results were considered statistically significant when $p \leq 0.05$.

3. Results and discussion

The effect of processing method on construct degradation was assessed by recording the change in morphology, crystallinity and MW. The surface/weight ratio of the sample was kept constant (Table 2) so that material

differences influence on degradation rate is evaluated without interference from sample geometry.

3.1. Morphology

In this section, images showing the morphology of the non-degraded and degraded constructs are presented. Initially, the films present large pores (Fig. 1(a)) or fine grooves (Fig. 1(c)) due to solvent evaporation. Fine grooves are formed for blends instead of pores probably because of phase separation after solvent casting. PCL chains can not aggregate intra-molecularly because of the presence of Lu and as such the solvent can easily exit the polymer phase without producing large pores. With aging, spherulites (that are composed of lamellae spreading from nuclei) separated by large pores (≥ 10 μm) are formed due to polymer re-crystallization in PCL films (Fig. 1(b)) or pores (~ 1 μm) obtained due to Lu leaching are formed in blend films (Fig. 1(d)).

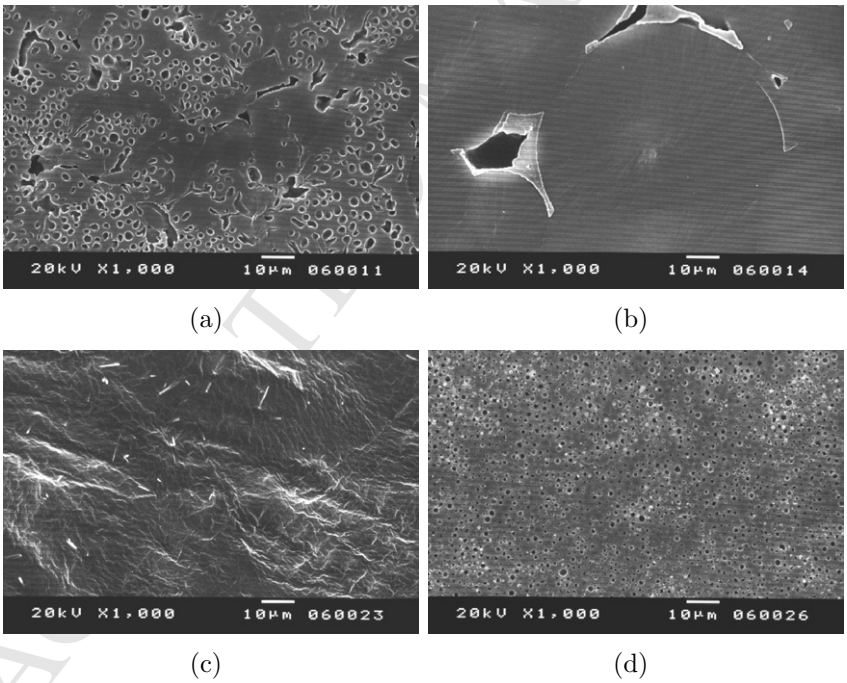


Figure 1: Films a) PCL as prepared, b) PCL degraded during 12 months, c) 50/50 Lu/PCL as prepared, d) 50/50 Lu/PCL degraded during 12 months

With aging, the fibers lost their structural integrity: large diameters fibers

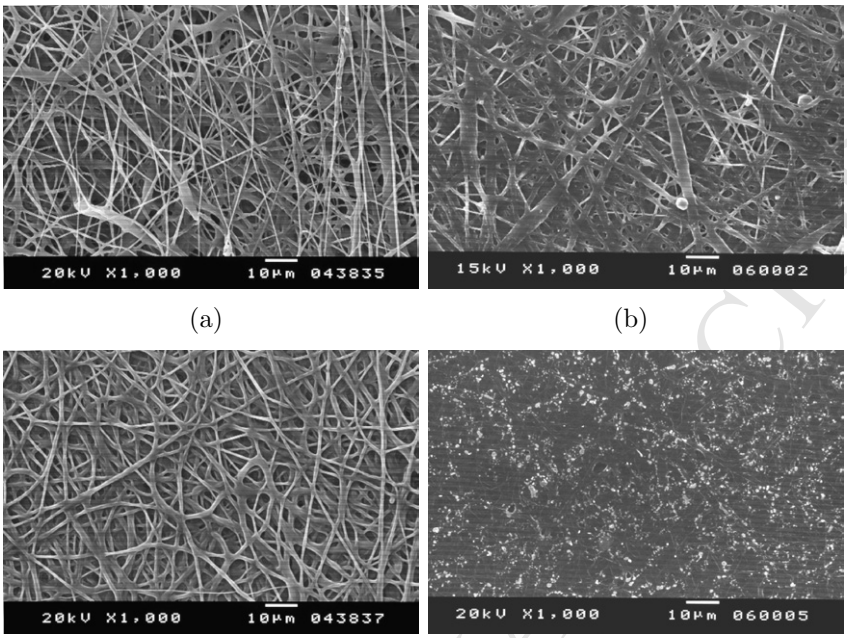


Figure 2: Fibers a) PCL as prepared, b) PCL degraded during 12 months, c) 50/50 Lu/PCL as prepared, d) 50/50 Lu/PCL degraded during 12 months

collapsed and small diameter fibers "glued" on the larger ones in PCL samples (Fig. 2(b)), while for blend samples, the fiber mat was almost transformed into a film, with fine grooves showing the position of the initial fibers (Fig. 2(d)).

With SCF processing (supercritical carbon dioxide), in the depressurization step, carbon dioxide passes from the supercritical to the gas state and exits the polymer matrix, creating pores (Fig. 3(c)). Due to the fact that the SCF decreases the melting temperature of PCL, this sample melts during SCF processing and solidifies at depressurization. Thus, PCL sample shows a slightly different morphology than blend samples, with smaller pores (Fig. 3(a)). During degradation, all the samples preserve their initial morphology (Fig. 3(b) and fig. 3(d)).

In Fig. 4(a), circular structures can be observed probably corresponding to spherulites. The drug-loaded disks present a rougher morphology due to drug crystallization and phase separation from the polymer phase (Fig. 4(c) and Fig. 4(e)). With aging, the morphology of PCL disk without drug

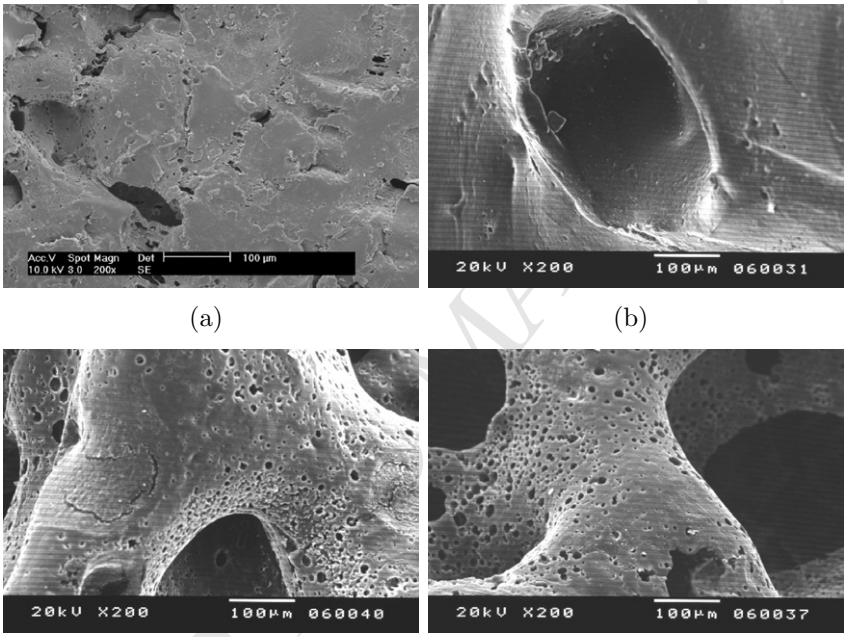


Figure 3: Sponges a) PCL as prepared, b) PCL degraded during 12 months, c) 50/50 Lu/PCL as prepared, d) 50/50 Lu/PCL degraded during 12 months

does not change much with the exception of the appearance of some pores (Fig. 4(b)). On the other hand, the surface of drug-loaded shows significant modification: a filament-like structure composed of "channels" created by drug elution and Lu leaching is shown by PCL (Fig. 4(d)) and blend disks (Fig. 4(f)), while PCL10 disks present various pores, cracks and spherulitic structures (Fig. 4(h)).

3.2. Evolution of crystallinity degree during degradation

Table 3 presents the evolution of crystallinity degree and of T_m during degradation. For semi-crystalline polymers, crystallinity can change during processing and/or during degradation. Usually, during degradation, there is an increase in crystallinity due to mainly two mechanisms: on one hand, solvent-induced crystallization of non-degraded polymer (water uptake allows polymer chain rearrangement and subsequent crystallization) and, on the other hand, crystallization of degraded fragments (oligomers) trapped in the non-degraded polymer bulk. Thus, an increase in crystallinity is expected during degradation. This trend is, in general, observed for all PCL samples regardless of the processing method. Interestingly, fiber blends samples showed a decrease in crystallinity with ageing (22% decrease for 50/50 Lu/PCL and 18% decrease for 25/75 Lu/PCL). This behaviour might be related with the presence in the blend of a water-soluble polymer. Lu dissolution produces a decrease in crystallinity because it can cause the fragmentation and erosion of non-degraded crystalline regions [7].

PCL films presented the lowest initial crystallinity, while fibers and sponges showed the highest initial crystallinity from all the constructs. In electrospinning, polymer chain alignment takes place during the stretching of the polymer solution jet in a similar fashion to crystallinity increase after fiber drawing. On the other hand, sponges are highly crystalline due to SCF-solvent induced crystallization during processing, since SCF swells and plasticizes polymers [21]. We will discuss how the crystallinity will influence degradation rate in section 3.3.

Table 4 presents the change in crystallinity degree for samples with different MW and for samples loaded with drug. Low MW disks showed higher initial crystallinity than PCL disks as shorter PCL chains are expected to crystallize in a higher proportion than longer PCL chains during processing. The presence of the drug caused a decrease in initial crystallinity due to crystallization restriction of the polymer.

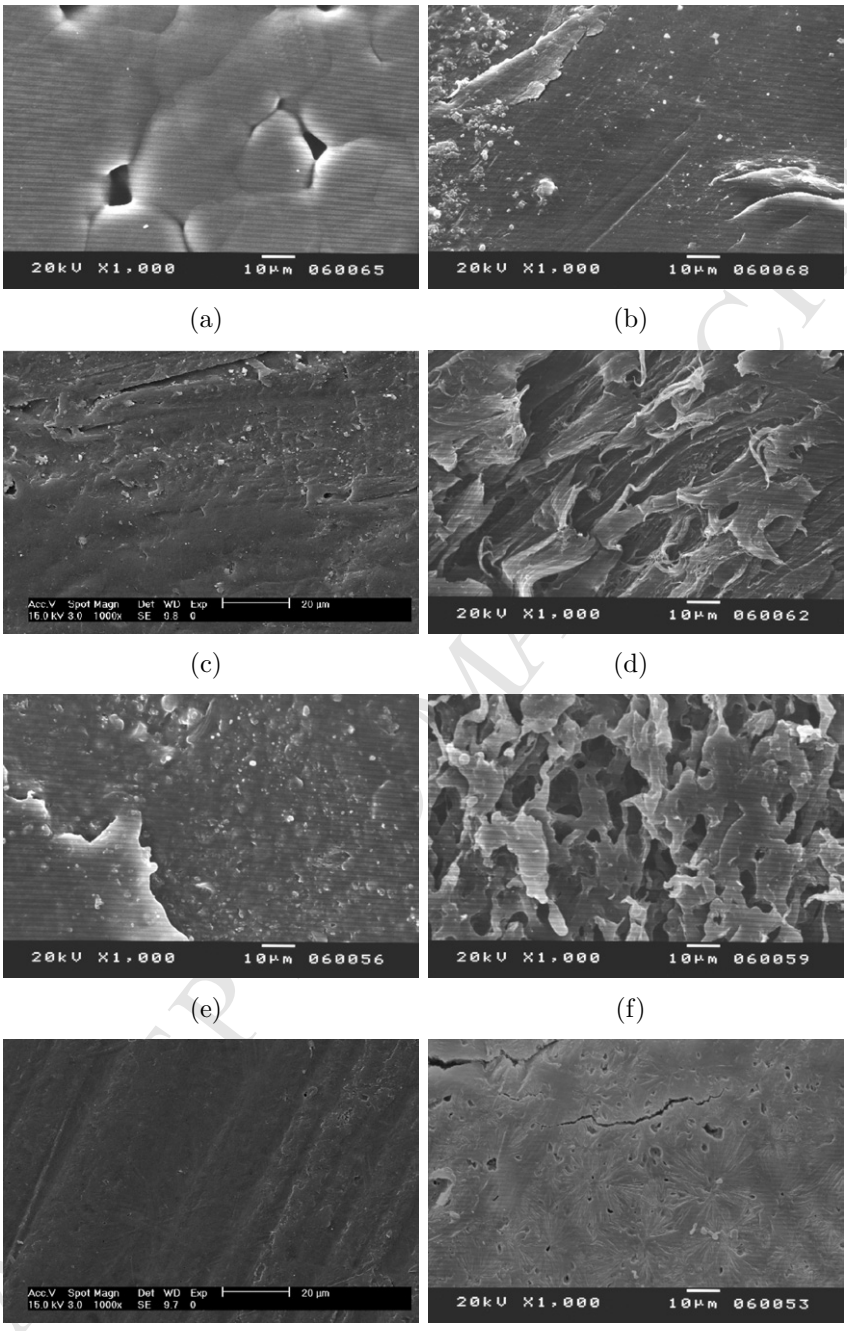


Figure 4: Disks a) PCL as prepared, b) PCL degraded during 12 months, c) PCL+drug as prepared, d) PCL+drug degraded during 12 months, e) 50/50 Lu/PCL+drug as prepared, f) 50/50 Lu/PCL+drug degraded during 12 months, g) PCL10+drug as prepared, h) PCL10+drug degraded during 12 months

	Relative degree of crystallinity (%)			
Time (months)	Disks	Films	Fibers	Sponges
0	50.26 (0.33)	41.95 (0.60)	49.76 (2.87)	52.28 (1.28)
6	47.5 (0.35)	54.79	50.58 (2.23)	51.88
18	53.2	52.11 (2.69)	51.77 (0.54)	56.08
30	na	58.51	52.76 (1.57)	na
	Melting temperature (°C)			
Time (months)	Disks	Films	Fibers	Sponges
0	61.26 (0.31)	57.09 (0.19)	60.06 (0.29)	63.25 (0.13)
6	63.79 (0.00)	63.73	62.27 (0.12)	65.45
18	65.77	66.41 (0.63)	63.05 (0.24)	66.59
30	na	65.87	63.77 (0.11)	na

Table 3: Relative degree of crystallinity and melting temperature evolution for PCL samples (40 kDa, no drug)

There is a higher increase in crystallinity for high MW samples (40% average increase) than for low MW samples (31% average increase). The sample without drug showed only a modest increase in crystallinity (6% increase). The highest increase in crystallinity was presented by 50/50 Lu/PCL disk with drug (51% increase). Lu and drug elution produce high porosity in the sample which enhances water uptake and subsequently polymer plasticization that will cause chain rearrangement and crystallinity increase over time.

T_m also increased during the period of study suggesting that crystallite growth and preferential hydrolysis takes place in the amorphous regions. Usually, when hydrolysis occurs in crystalline regions, T_m decreases because the crystallites are being destroyed. Only after 25 months, T_m does not increase anymore or starts decreasing, suggesting that only now hydrolysis extends to crystalline regions in agreement to previous works [20].

3.3. Evolution of molecular weight during degradation

The hydrolytic degradation mechanisms of PCL is a random chain scission process. Polymer degradation is a complex process composed of several simultaneous physical (water uptake, swelling, dissolution, crystallization, stress cracking) and chemical phenomena (thermolysis, oxidation, hydroly-

	40 kDa				10 kDa		
Lu/PCL	0/100	25/75	50/50	0/100	0/100	25/75	50/50
Drug	yes	yes	yes	no	yes	yes	yes
Time (months)	Relative degree of crystallinity (%)						
0	33.55 (0.85)	35.43 (2.84)	31.42 (0.72)	50.26 (0.33)	40.06 (0.15)	38.17 (2.33)	38.77 (1.53)
6	39.81	46.77	45.69	47.5 (0.35)	55.16 (1.52)	54.44 (1.13)	50.61 (0.94)
18	44.96 (0.01)	48.73 (1.26)	47.05 (0.91)	53.2	50.32	52.7 (0.63)	50.35
Time (months)	Melting temperature (°C)						
0	61.54 (0.02)	60.11 (0.42)	60.14 (0.48)	61.26 (0.31)	60.67 (0.19)	61.35 (0.64)	60.55 (0.42)
6	63.82	62.95	63.77	63.79 (0.00)	62.8 (0.16)	61.67 (0.05)	61.80 (0.22)
18	66.67 (1.52)	65.15 (0.33)	65.52 (0.07)	65.77	66.41 (2.01)	63.77 (0.25)	63.03

Table 4: Relative degree of crystallinity and melting temperature evolution for disk samples

sis, photolysis). Nevertheless, for polyesters, the most important steps are water uptake/diffusion and hydrolysis [5]. Polyesters can present surface or bulk degradation mechanisms depending on the rate limiting step, which is water diffusion in the first case and hydrolysis in the second case. Mass loss or erosion occurs when water-soluble fragments that form due to hydrolysis, are able to leach out from the polymer matrix. As hydrolysis is a random chain cleavage process, the probability to obtain a water-soluble fragment that is small enough to diffuse from the bulk increases as MW decreases.

In Fig. 5(a), Fig. 5(b) and Fig. 5(c) the change in weight-average MW is presented for samples processed by different methods. It can be noted for PCL samples, at 6 months that there are some differences in terms of MW decrease between processing techniques: films, fibers and sponges showed a decrease of approximately 10%, while fibers showed a smaller decrease (4%).

The differences between samples become smaller after 18 months with 45% decrease in MW for disk, 58% for fiber and 54% for films. This might be explained by water uptake kinetics which is controlled by initial construct porosity. Thus, sponges, films and disks have high initial porosity and high water uptake relative to fibers and show faster degradation at 6 months. PCL fibers are much more hydrophobic, which inhibits water uptake [17]. Developed porosity and subsequently reaction surface is important for the later stages of degradation [14]. Sponges maintain their high initial porosity during aging, while films and fibers do not. This might be the reason why PCL fibers (20% decrease) and films (17% decrease) are less degraded than sponges (46% decrease) at 18 months.

Blend disks show statistically significant differences in MW when compared to sponges, films or fibers only at 6 and 12 months, but not at 18 months. Thus, at 18 months water content of the various constructs is expected to be similar. At 30 months, the different constructs showed similar decrease in MW (for 50/50 Lu/PCL samples: 61% for disks, 71% for films and 69% for fibers). When comparing the degradation curves for different compositions of the same construct, the blends degraded faster than PCL. This might be connected to the change in crystallinity. PCL samples showed a slight increase in crystallinity during ageing, while blends showed a significant decrease in crystallinity in some cases.

A comparison between the degradation profile for samples of different MW is shown in Fig. 6(a), fig. 6(b) and Fig. 6(c). The decrease in MW is much lower for 10 kDa samples than for 40 kDa samples (for PCL, at 18 months, 8% decrease and 38% decrease, respectively). In addition, there are no differences in terms of MW due to composition. First, 10 kDa samples have higher initial crystallinity than 40 kDa samples and this will slow down water uptake (1% water content after 1 month). Additionally, for a short chain polymer, there is a higher probability to obtain water soluble fragments at hydrolysis, that leach out, especially through a porous structure, leading to a decrease in autocatalytic effects. These factors contributed synergistically to the observed degradation delay.

Degradation curves of drug-loaded disks and disks without drug are shown in Fig. 7(a) and Fig. 7(b). Drug-loaded PCL disks showed a 4% decrease in MW, while PCL disks without drug presented a 9% decrease in MW at 6 months. At 12 and 18 months, there were no significant differences in MW decrease between the different PCL samples. The same observation was valid for blend disks that only showed at 6 months a higher decrease in MW for

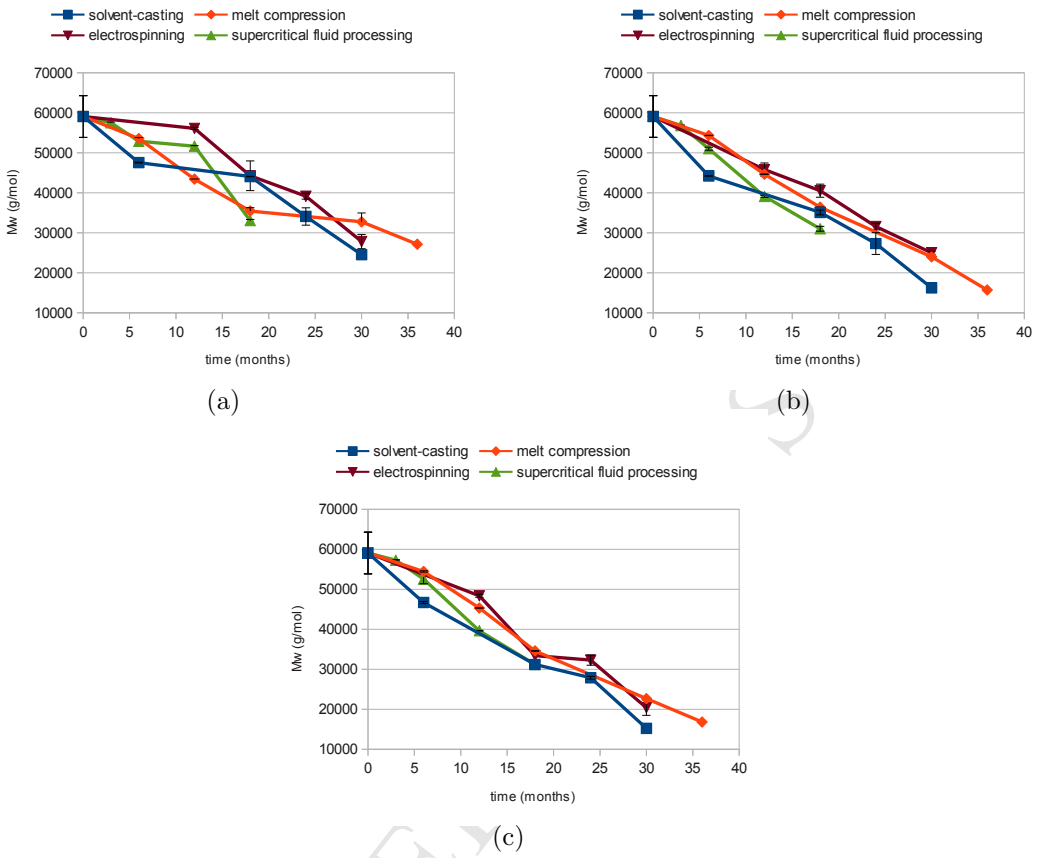


Figure 5: Weight average molecular weight of a) PCL, b) 25/75 Lu/PCL and c) 50/50 Lu/PCL constructs

samples without drug probably due to increased autocatalytic effects. The PCL samples with drug showed a much higher increase in crystallinity and thus degradation will be slower in these samples.

4. Conclusions

Various constructs were prepared based on PCL and Lu, such as films, fibers, sponges and disks using different techniques such as solvent-casting, electrospinning, supercritical fluid processing and melt-compression, respectively. The influence on degradation rate of several factors (processing method, MW, drug presence, composition) was determined.

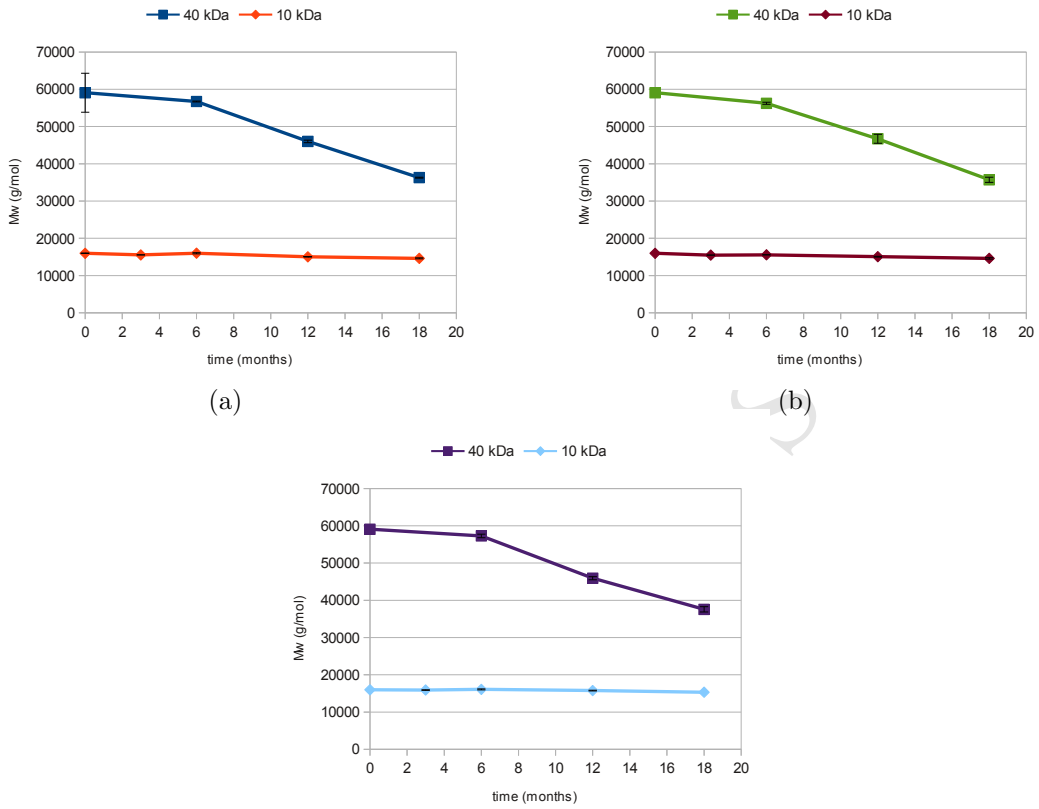
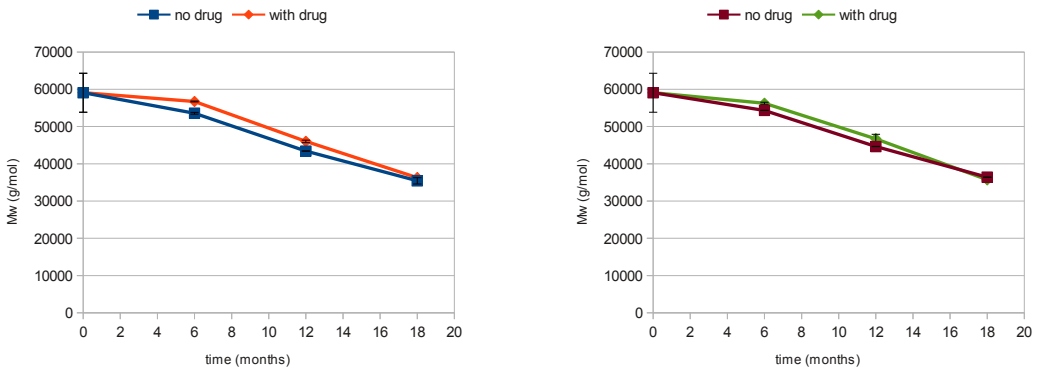


Figure 6: Weight average molecular weight of a) PCL, b) 25/75 Lu/PCL and c) 50/50 Lu/PCL constructs

Overall, there was an increase in crystallinity with degradation in agreement with previous works. MW had an important effect on degradation rate. The low MW disks had a degradation rate that was lower by one order of magnitude than high MW constructs. On the other hand, the drug had little effect on degradation with significant differences only in the initial stage (up to 6 months).

Although there were some differences in degradation profile for samples prepared by different processing methods up to 18 months, these differences tended to disappear during the advanced stage (18 to 36 months). Water uptake kinetics and polymer chain rearrangement will produce significant changes in construct morphology, porosity and crystallinity during the initial



(a) (b)

Figure 7: Weight average molecular weight of a) PCL, b) 25/75 Lu/PCL disks

stage with direct results on degradation rates. Thus, it was shown that processing method does not have such a significant effect on the long term degradation of the PCL constructs.

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