J Mater Sci (2010) 45:1284–1292
DOI 10.1007/s10853-009-4080-9

In vitro degradation and drug release from polymer blends based on poly(DL-lactide), poly(L-lactide-glycolide) and poly(ε-caprolactone)

Paul F. McDonald · John G. Lyons · Luke M. Geever · Clement L. Higginbotham

Received: 12 November 2009 / Accepted: 24 November 2009 / Published online: 10 December 2009

Abstract Bioresorbable materials are extensively used for a wide range of biomedical applications. Accurately modifying and evaluating the degradation rate of these materials is critical to their performance and the controlled release of bioactive agents. The aim of this work was to modify the physical properties, degradation rate and drug delivery characteristics of thin films for medical applications by blending poly(DL-lactic acid) (PDLLA), poly (L-lactide-co-glycolide) (PLGA) and poly(ε-caprolactone) (PCL). The thin films were prepared using solvent casting and compression moulding and the in vitro degradation study was performed by immersing the films in a phosphate-buffered saline at elevated temperature for a period of 4 weeks. The degradation rate of the materials was analysed by differential scanning calorimetry, tensile testing and weight loss studies. The thermal analysis of the blends indicated that the presence of PLGA or PDLLA in the film resulted in increased degradation of the amorphous regions of PCL. It was observed that the samples consisting of PDLLA with PCL demonstrated the greatest weight loss. The decrease in mechanical properties observed for both sets of polymer blends proved to be similar. The solvent cast technique was selected as the most appropriate for the formation of the polymer/drug matrices, due to the potentially adverse thermal processing effects associated with compression moulding. It was found that modulation of drug release was achievable by altering the ratio of PCL to PDLLA or PLGA in the thin film blends.

P. F. McDonald · J. G. Lyons · L. M. Geever · C. L. Higginbotham (✉)
Materials Research Institute, Athlone Institute of Technology, Dublin Rd, Athlone, Co., Westmeath, Ireland
e-mail: chigginbotham@ait.ie

P. F. McDonald
e-mail: paulmcdonaldeire@yahoo.com

J. G. Lyons
e-mail: slyons@ait.ie

L. M. Geever
e-mail: lgeever@ait.ie

Introduction

Resorbable and degradable polymers have been extensively studied throughout the last few decades. A resorbable material can be broken down and the degradation by-products eliminated from the body [1]. In polymers, the resorbability occurs mainly through enzymatic or non-enzymatic hydrolysis followed by the metabolism or excretion of the degradation products. Aliphatic polyesters have found prominence among synthetic resorbable polymers for implants, the most extensively studied amongst this family of polymers are poly(L-lactide), poly(glycolide), poly(ε-caprolactone) and copolymers based on L/DL-lactide, glycolide, trimethyl carbonate and ε-caprolactone [2]. The benefits of using resorbable or degradable materials as implanted in vivo biomedical materials are evident as they degrade after serving their purpose. This has been utilised in the preparation of controlled drug release systems, in sutures and in orthopaedic implants [3]. Polymers with ester linkages in their main chain are ideal candidates for a range of temporary biomedical applications, not in the least for drug delivery, as the need for surgical removal of the depleted device is eliminated. Controlled release of therapeutic agents remains one of the biggest challenges in drug delivery. Repeated administration of a drug so as to maintain drug concentration within a therapeutic window may cause serious side effects, which in many cases necessitates the patient to stop taking the medication [4].

With conventional dosage forms, high peak blood concentrations may be reached soon after administration with possible adverse effects related to the transiently high concentration.

Suitable drug delivery candidates must therefore not only be biodegradable and biocompatible, but must also exhibit control over the release rate of the active moiety. The family of aliphatic polyesters has been by far the dominating choice for materials in degradable drug delivery systems [5]. The advantages of poly(ε-caprolactone) are the high permeability to small drug molecules and its failure to generate an acidic environment during degradation [6, 7]. Many researchers have documented the biodegradation, biocompatibility and tissue reaction associated with poly(lactide) and poly(lactide-co-glycolide) and noted that the opportunity exists to effectively combine the desirable properties of these materials by blending [8, 9].

After the discovery of the major commodity and engineering plastics materials in the early to mid part of the 20th century, the cost of bringing a new polymer material to market began to rise dramatically. In many cases, improvements in physical and mechanical properties can be imparted more rapidly and cost-effectively by mixing available polymers rather than developing new chemistry. As a result, both the polymer industry and academia began to focus on developing polymer blends with novel and valuable properties, in order to enlarge the spectrum of available polymers. Currently, blending aims at securing sets of specific properties required for an envisaged application [10]. The final properties of such blends depend on the chemical structure of the original components, the mixing ratio of the constituent polymers, the interaction between the components and the processing steps to which they have been subjected [11, 12].

The aim of this study was to modify the physical properties, degradation rate and drug delivery characteristics of thin films for medical applications by blending poly(DL-lactic acid) (PDLLA), poly(L-lactide-co-glycolide) (PLGA) and poly(ε-caprolactone) (PCL).

Experimental

Materials

The poly (ε-caprolactone) (brand name Tone Polymer, P-676 TM) was supplied by the Dow Chemical Company, the poly (L-lactide-glycolide) copolymer with a molar ratio of 83/17 (brand name Purasorb PLG) was obtained from Purac Biochem Bv Gorinchem, while the PDLLA (brand name Galastic, PABR-L-68) was obtained from Galactic Laboratories (a division of Brussels Biotech), all in granular form. The active agent used was acetylsalicylic acid (aspirin, supplied by Aldrich). HPLC grade dichloromethane, tetrahydrofuran, ethyl acetate, chloroform, acetone, hydrochloric acid and methanol solvents were supplied by Aldrich.

Solvent casting procedure

The solvents investigated for dissolving the base polymers (PLGA, PCL and PDLLA) were dichloromethane, tetrahydrofuran, ethyl acetate and chloroform. Different ratios of polymer to solvent were initially investigated, with the optimum ratio found to be 5 g polymer to 50 mL solvent. It was observed that chloroform was the most efficient solvent at room temperature for the base polymers, thus this solvent was chosen for all solvent cast blend preparation. A two-step procedure was developed for the solvent casting of the thin films. The first step involved dissolving the polymer or polymer mixtures: 5 g of the polymer or polymer mixtures were weighed and placed into a glass beaker, 50 mL of chloroform was added and the polymer/solvent mixture was agitated using a magnetic stirrer for a period of between 2 and 4 h until the polymers were fully dissolved. The second step involved removal of the solvent and formation of the film: the polymer/solvent solution was poured into a flat glass container, the solvent was removed via evaporation at room temperature under a fume hood for a period of 24 h and for 12 h in an oven at a temperature of 40 °C. The mixing ratio of the thin film polymer blends prepared by both the solution casting and compression moulding techniques are presented in Table 1. Note that for all experimental works in this study, weights were measured using a Sartorius scales capable of being read to five decimal places.

Compression moulding procedure

During initial trials, it was found that the compression moulding technique did not provide adequate mixing of the blends. As a consequence, a pre-mixing step was deemed

Table 1 Mixing ratio of thin film polymer blends based on PDLLA, PLGA and PCL

Polymer blend (percentage polymer)	PDLLA (%)	PLGA (%)	PCL (%)
PDLLA5/PCL95	5	–	95
PDLLA10/PCL90	10	–	90
PDLLA20/PCL80	20	–	80
PLGA5/PCL95	–	5	95
PLGA10/PCL90	–	10	90
PLGA20/PCL80	–	20	80

necessary prior to the compression moulding process. The technique identified as most suitable was precipitation mixing, which involved the following steps: 5 g of the polymer or polymer mixture was weighed, placed into a flat-bottomed flask containing 50 mL of acetone, the flask was placed on top of a heating mantle magnetic stirrer apparatus with a reflux condenser attached and the mixture was heated to 35 °C. The polymer/solvent mixture was agitated until the polymer(s) had dissolved. The heated solution was poured into a glass Petri dish and 20 mL of methanol was added (addition of the methanol and cooling of the mixture forces the polymers out of solution). Finally, the solvents were removed via evaporation at room temperature in a fume hood for a period of 24 h.

A Daniels compression press, flat mould and a pressure of 1000 psi was used for the fabrication of the polymer films. Following processing trials, a sample weight of 1 g, a moulding cycle time of 1 min and a temperature of 170 °C were chosen, as these parameters produced thin films with optimum properties. Additionally, teflon sheets were used to avoid polymer adhesion to the mould, while all samples were pre-heated for a time period of 1 min on a hotplate set at a temperature of 100 °C, prior to the compression moulding cycle. The final steps involved taking the sample from the mould, cooling at room temperature, and removal of the thin film from the teflon sheets. The thickness of the thin films produced was recorded using a digital micrometer.

In vitro degradation

The temperature typically used in degradation studies of biodegradable polymers is 37 °C, i.e. the temperature of the human body. In order to accelerate the degradation of the polymers, the films were subjected to a test temperature of 50 °C, similarly to Hukins et al. [13]. Temperature is a critical factor in chemistry and thus plays an important part in polymer degradation where the rate of degradation generally increases with temperature [14]. The in vitro degradation testing method described herein was based on the ASTM international standard F1635-95 test method for in vitro degradation testing of PDLLA resin. This test method covers poly(L-lactic acid) resin for use in surgical implants. The degradation study was performed by immersing films in a phosphate-buffered saline with a pH of 7.0 in an oven at a temperature of 50 °C for a period of 4 weeks.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to assess the melting points and crystallinity of the base polymers and their blends during the in vitro degradation test. Initial testing was carried out on undegraded samples with further analysis carried out at weeks 2 and 4. Prior to testing, the samples were dried for a period of 24 h at a temperature of 50 °C. The tests were carried out using a Perkin-Elmer, Pyris 6 DSC using samples of between 9.3 and 10.3 mg. All measurements were conducted in crimped non-hermetic aluminium pans with an empty crimped aluminium pan being used as the reference. The samples were heated from a temperature of 20 to 200 °C at a rate of 10 °C per minute and then kept at 200 °C for a period of 5 min. The samples were then cooled down from 200 to 20 °C at a rate of 2 °C per minute. All DSC tests were carried out under a 20 mL/min flow of nitrogen to prevent oxidation. High-purity indium was used to calibrate the DSC cell. Percentage crystallinity of the samples was calculated using data obtained from the DSC thermograms and equations outlined by Sperling [15].

Tensile testing

Tensile testing of the films was used to assess the mechanical properties of the thin film polymer blends and base polymers. The tensile testing procedure used was based on the ASTM international standard D882-02 standard test method for tensile properties of thin plastic sheeting. The samples were cut into tensile samples using a dumbbell cutter, which gave a sample test length of 20 mm and a width of 4 mm. Five samples were tested from each batch using a Lloyd Lrx Tensile tester, with Nexygen software. A crosshead speed of 20 mm/min was used during all tests. To reduce slippage and sample breakage in the jaw area, paper labels were applied to the samples. Initially undegraded samples were tested so as to establish baseline mechanical properties. During the in vitro degradation study, five samples were taken from each batch at weekly intervals. Before tensile testing took place, the samples were dried for a period of 24 h at a temperature of 50 °C.

Weight analysis

Changes in sample weight during the in vitro degradation study were used to assess the rate of degradation of the polymer blends and base polymers. Before the degradation study commenced, all samples were dried for a period of 24 h in an oven at 50 °C. The samples were subsequently weighed prior to the beginning of the in vitro degradation study. Three samples were taken from each batch at weekly intervals. All samples were dried for 24 h at a temperature of 50 °C and weighed. The weight loss was calculated as a percentage using the following equation:

$$(W_i - W_d/W_i) \times 100$$

where W_i is the initial weight of the sample and W_d is the degraded weight of the samples.

Drug release

The processing techniques of solvent casting and compression moulding were initially evaluated for the manufacture of the thin film polymer drug matrices. An important factor in the manufacture of polymer drug matrices is the thermal degradation of the drug or additive during the process. After initial testing, it was concluded that the compression moulding process was unsuitable for the manufacture of the thin film polymer drug matrices as the excessive temperature and residence times required to successfully prepare test specimens was likely to lead to thermal degradation of the active moiety. Dissolution studies were carried out using the polymer blends and base polymer films. For preparation of the samples; batches of 1 g polymer, incorporating 5 wt% acetylsalicylic acid (aspirin) were weighed, the mixtures were dissolved in chloroform and the polymer/drug-solvent mixture was transferred to Petri dishes. The solvent was subsequently evaporated off at room temperature in a fume hood for a period of 24 h and then for 12 h in an oven at a temperature of between 30 and 40 °C to form a thin polymer film.

Dissolution testing was carried out using a Sotax AT7 smart dissolution system from Carl Stuart Ltd. Tests were carried out in triplicate using the Basket method (USP XXV). The dissolution media used in these tests consisted of 0.2 M hydrochloric acid (pH 1.2). All tests were carried out at 37 °C ± 0.5 °C. The stir rate was set to 100 rpm with 600 mL of dissolution media used per vessel. The wavelength and absorption of a 100% drug concentration for the drug (aspirin) was determined using a Perkin Elmer Lambda 40 UV/Vis spectrometer. These values were entered into software calculations prior to commencement of testing. Samples were automatically taken every 15 min, filtered and passed through a Perkin Elmer Lambda 20 UV/Vis spectrometer, before being returned to the dissolution chamber. The dissolution profile was observed from a plot of time versus absorbance.

Results and discussion

Fabrication of polymer blends

Solvent casting and compression moulding are commonplace processing techniques used in the evaluation of biodegradable polymers and manufacture of devices for medical applications [16]. The first technique investigated for the formation of the thin film polymer blends was solvent casting. One of the most important considerations in solvent casting is the choice of solvent. Initial trials were carried out using several commonly used solvents, such as dichloromethane, chloroform, tetrahydrofuran and ethyl acetate, in an attempt to determine the most suitable solvent to dissolve PLGA, PCL and PDLLA. Based on these trials, the most effective solvent proved to be chloroform, in agreement with previous experimental works [17–19].

Three of the most important processing parameters of compression moulding are heat, time and pressure [20]. In order to produce films of consistent thickness, experimental work was carried out to ascertain the optimum process temperature and cycle time. During the initial trials, it was found by visual examination of the blend films that there was little or no mixing of the polymers during the compression moulding process. Therefore, in order to produce consistent and homogenous thin film polymer blends, a pre-mixing step was deemed appropriate prior to compression moulding. An economical lab-scale mixing process was required that did not waste material, thus precipitation mixing was chosen. This is a form of solution blending that is carried out by dissolving the two components in a common solvent and precipitating out the blend by addition of a suitable precipitant [21]. During the precipitation mixing process, the polymers were first dissolved in acetone by heating to approximately 40 °C. Acetone was chosen as it partially dissolves PLGA, PDLLA and PCL at room temperature and requires only gentle heating to fully dissolve the polymers [20, 22, 23]. As the polymer/acetone mixture was allowed to cool, methanol was mixed with the polymer solution. The cooling of the mixture and addition of the methanol forced the polymers out of solution, which resulted in the polymer mix. The solvents were removed by evaporation at room temperature in a vacuum hood for a period of 24 h. Different process settings for heat and time with the same mould pressure (1000 psi) were trialled using the blends. Finally, cycle times of 1 min and a mould temperature of 170 °C were decided upon as films with consistent thickness were produced using these parameters. The thin film samples produced using the compression moulding technique had an approximate thickness of 1.2 mm ± 0.3 mm. In order to gain knowledge of the miscibility and physical properties of the thin film polymer blends at diverse blend percentages, a variety of mixing ratios were investigated as illustrated in Table 1.

Controlled release of drugs, proteins and other bioactive agents can be achieved by incorporating them, either in dissolved or dispersed form, in polymers [24]. An important factor in the manufacture of polymer drug matrices is the thermal degradation of the drug or additive during the process. Solvent casting of film containing active moieties for controlled delivery may be superior to melt processing if the active agent is thermodynamically unstable. As no thermal processing step is involved in the solvent casting

thin film preparation technique, this was the method chosen to manufacture the samples containing the active agent, acetylsalicylic acid.

Differential scanning calorimetry

A thermogram typical of those obtained in this work is presented in Fig. 1. The crystallinity results for the blend materials were calculated based on the presumption that PCL alone contributed to the melting point. For a semi-crystalline polymer such as PCL, the biodegradation usually starts from the amorphous region, and the crystallinity, crystal order and the interaction between the crystals has a great effect on the degradation process. The PDLLA/PCL blends analysed during the degradation study were observed to exhibit similar trends for crystallinity change as those observed for the blends of PLGA/PCL. The solvent cast technique also produced samples with lower levels of crystallinity (48.5%) than the compression moulding method (53.5%) for the homopolymers. A possible reason for this may be the presence of residual traces of solvent in the solvent cast samples, which may have restricted the crystallisation of the PCL [25, 26].

After the first degradation period, an increase in the crystallinity was observed for all samples. This to be expected as the first stage of degradation of PCL involves nonenzymatic, random hydrolytic ester cleavage and autocatalysis by carboxylic acid end groups of the polymer chains in the amorphous regions [25]. As the amorphous regions reduce, the polymer chains align themselves more readily into crystalline regions [27]. Pitt et al. [6] measured a rapid increase in crystallinity of PCL drug delivery devices over the first four weeks post implantation from 45 to 50%, which was assigned to annealing of the polymer at body temperature. The crystallinity gradually increased to a value of approximately 80% after 30 months, which was attributed to crystallisation of tie chain segments from the amorphous phase following chain cleavage, facilitated by the low T_g of PCL. Little et al. [28] found for their PCL control samples, that the degree of crystallinity increased during the 7 months of degradation. The rate of increase in crystallinity during the first month was attributed to the reorganisation (annealing) of part of the amorphous phase to a crystalline phase due to the plasticising effects of the aqueous environment at 37 °C. After the second degradation period, there is a reduction in the crystallinity of the samples. PCL behaves similarly to PGA in that the residual crystallinity increases with time [14]. Reed and Gilding [29] found that by increasing the temperature of the samples, this increases the rate of water diffusion thus promoting the hydrolysis of PGA.

Parameters affecting the controlled degradation of blends, apart from the properties of the components, include the composition, preparation method, compatibility and miscibility of the components [30, 31]. During the degradation study, an increase was observed in the crystallinity of the 5%PLGA/95%PCL blend when compared to the PCL homopolymer which may indicate that at low percentages of PLGA, the blends are compatible to a certain extent. When PCL is blended with other partially crystalline polymers, the blends are often crystalline in character. Rather than disrupting crystallinity, it often appears that the crystallinity is enhanced and new interactions take place. Crystalline interactions are found to

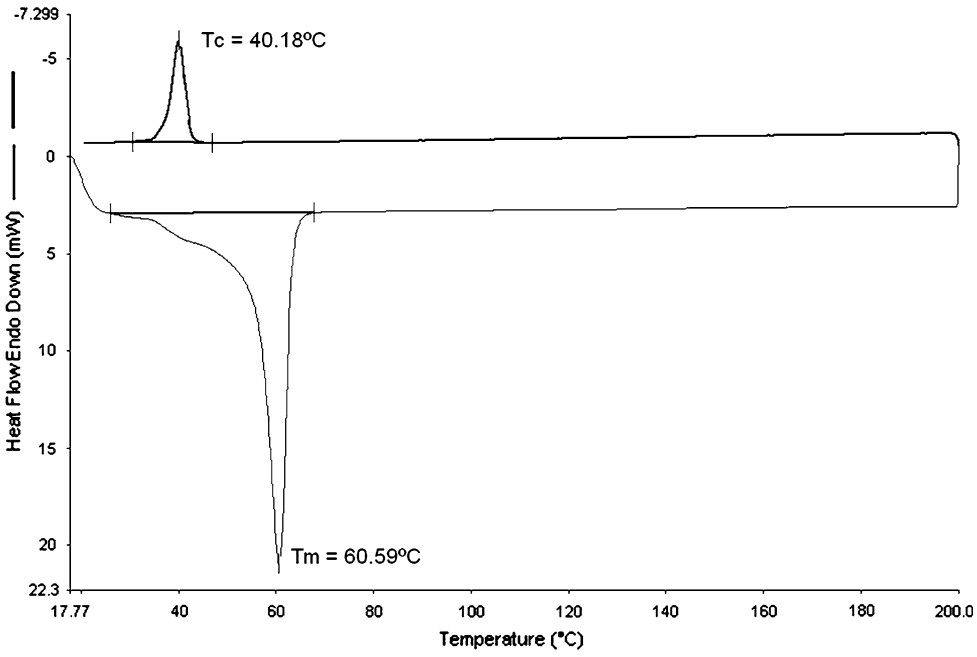

Fig. 1 DSC thermogram of PCL

exist when PCL is blended with polyethylene and polypropylene [32]. The solvent cast and compression moulded 20%PLGA/80%PCL samples were found to have the lowest levels of initial crystallinity (40%) amongst the PLGA/PCL blends. This indicates that as the level of PLGA increases in the blend, the ability of the PCL to crystallise becomes progressively more retarded. These trends could again be attributed to several factors, the degradation of the amorphous regions of PCL, annealing of the PCL and degradation of the PLGA, which may have allowed the crystalline chains of PCL to realign. Whilst the 20%PLGA/80%PCL blend demonstrates a decrease, this could again be related to the high presence of PLGA end groups in the blend, which could have restricted the alignment of the polymer chains. In the 4th week, all of the blends demonstrate a decrease in crystallinity. The PLGA copolymers undergo degradation in an aqueous environment (hydrolytic degradation or biodegradation) through cleavage of its backbone ester linkages [33]. The carboxylic end groups present in the PLGA chains increase in number during the biodegradation process as the individual polymer chains are cleaved: these are known to catalyse the biodegradation process [8]. Thus, the presence of these end-groups could have restricted the alignment of the polymer chains.

Weight analysis

Figure 2 shows the reduction in weight by percentage of solvent cast and compression moulded PCL over the duration of the in vitro degradation test. In the 2nd week, there was an increase in weight loss compared to the 1st week, for both samples. This change in slope is evident for the different polymer blends and unblended thin films prepared by compression moulding and solvent casting techniques. The change in slope could be attributed to the autocatalytic hydrolytic degradation mechanism, where released carboxylic acids contribute to an increased rate of hydrolysis along the polymer backbone [34]. In the 3rd and 4th weeks, there is further weight loss evident; however, the rate of this weight loss has slowed somewhat when compared to the initial 2-week period. The solvent cast polymer has a higher overall percentage of weight loss. The level of crystallinity is an important factor in the degradation rate of the polymer and the associated changes in weight [35]. The calculated percentage crystallinity of PCL obtained for the solvent cast samples was previously found to be lower than the compression moulded samples. The higher percentage of amorphous polymer present in the solvent cast samples may account for the higher weight reduction, in agreement with findings by Kweon et al. [35].

Additionally, residual traces of solvent may have remained trapped within the solvent cast samples, which could have been released as the degradation study progressed, a theory previously suggested by Yu et al. [26]. Overall, the percentage weight loss is relatively low. This is to be expected as, for medium-molecular-weight PCL, reported weight loss values (i.e. yields of water-soluble monomers and oligomers from PCL) were 25% and 51% when in vivo degradation was continued for as long as 96 and 160 weeks, respectively [6]. However, for high-molecular-weight PCL, a reported weight loss value was as low as 1% even when its hydrolysis at 37 °C was continued for as long as 20 months [36].

The PLGA/PCL blends analysed during the weight loss study exhibited similar trends as those observed for the blends of PDLLA/PCL. Throughout the duration of the test, samples containing PDLLA exhibited the greatest weight losses (Fig. 3). The increase in weight loss of the blends when compared to the change in weight loss of PCL homopolymer film may be attributed to several factors. PDLLA or PLGA have a faster degradation rate when compared to PCL [37] and this is highly dependent on temperature. The hydrolytic degradation of PDLLA was

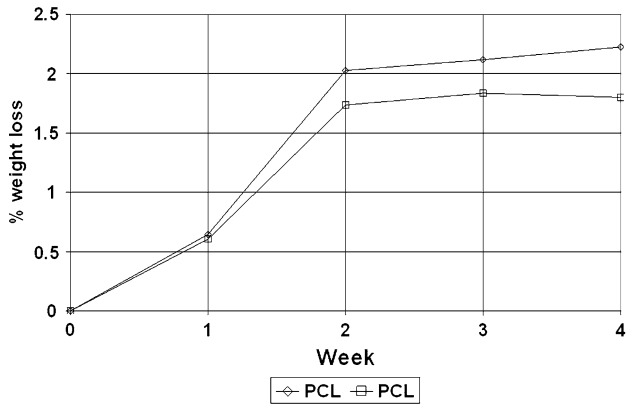

Fig. 2 Changes in weight by percentage of solvent cast PCL and compression moulded PCL

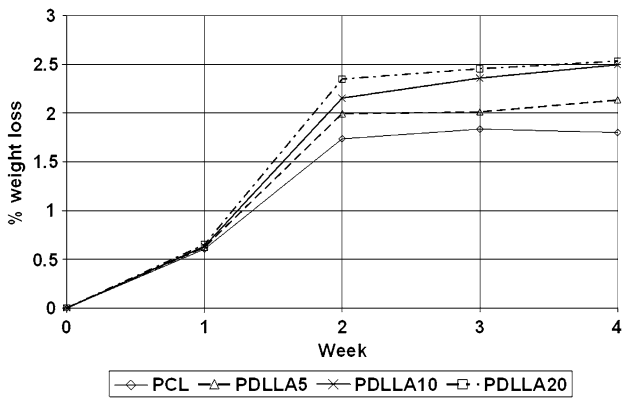

Fig. 3 Changes in weight of PCL and blends of PCL/PDLLA (compression moulded thin films)

investigated by Li and McCarthy [38] in order to evaluate the effects of temperature of the external medium on the degradation characteristics. After 10 days at 60 °C and pH 7, a 50% reduction in weight was observed in the samples of PDLLA. It was concluded that degradation was extremely rapid when compared with degradation at 37 °C [39].

As the increasing level of PDLLA in the blends was observed to reduce the percentage crystallinity, the higher levels of amorphous regions present may also account for the greater levels of weight loss observed. Another factor that may have contributed to the varying levels of weight loss by the different blends could be the higher release of carboxylic acids by the degradation of the PDLLA, which could have contributed to an increased rate of hydrolysis along the polymer backbone [8]. The release of carboxylic acids could have led to a change in pH of the system, thereby catalysing the degradation of the polymers [37]. As previously discussed, the slight difference in weight loss between the solvent cast samples and the compression moulded samples could be related to the effect of the different processing techniques upon the percentage crystallinity and the possible presence of residual solvents, in agreement with work previously carried out by Alexis [39].

Tensile testing

Mechanical parameters play a crucial role in determining the in vivo performance of biomedical systems. After the 1st week of in vitro degradation, there was a reduction in tensile strength of the PCL films, with the compression moulded samples showing the greatest reduction in percentage tensile strength. After the 2nd week, the percentage tensile strength loss of the solvent cast material drops below the compression moulded sample. This loss of strength correlates with work carried out by Rutkowska et al. [40], where a reduction in strength was reported after a 2-week degradation interval using thin films of PCL with additives in a buffered salt solution (pH 7.2) at 37 °C. The difference in tensile strength loss between the solvent cast samples and the compression moulded samples could be related to the effect of potential residual solvents in the solvent cast blends [39]. When the solvent cast and compression moulded samples of PLGA/PCL and PDLLA/PCL were compared, there was an obvious reduction in percentage strength after the 1st week. After this time, there is no significant loss of strength for the samples. Slight difference in the changes of tensile strength for the blends could be related to the differing levels of polymer degradation associated with the amorphous PDLLA and the semi-crystalline PLGA. Figure 4 displays the changes in tensile strength observed over the degradation period for compression moulded samples of PCL and PCL/PLGA blends.

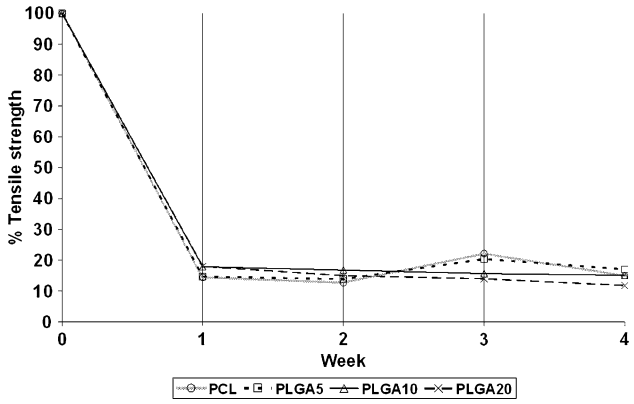

Fig. 4 Decrease in tensile strength of films of PCL and blends of PLGA/PCL over the 4-week degradation period (compression moulded)

Drug release

Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled release device. The diffusion can occur on a macroscopic scale (through pores in the polymer matrix) or on a molecular level (by passing between polymer chains). For both diffusion and degradation controlled mechanisms, the matrix morphology is a determining factor. Figures 5, 6 and 7 compare the drug release curves for PCL, PLGA and PDLLA homopolymers and blends of PDLLA/PCL and PLGA/PCL.

Due to the short-term nature of the drug elution studies described herein, the principal mechanism of drug release may be considered diffusion. PCL eluted approximately 46.6% of the drug loading over the duration of the test, which was the highest of the three base polymers. The high level of drug release during the burst period was expected as the polymer matrices are thin films and this may account

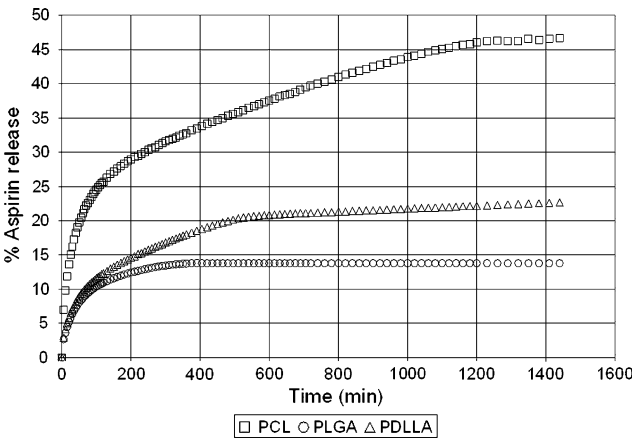

Fig. 5 Drug release curves for thin film polymer drug matrices of PCL, PLGA and PDLLA

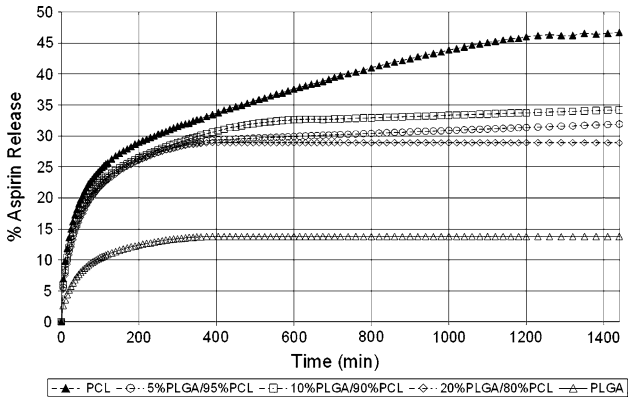

Fig. 6 Drug release curves for thin film polymer drug matrices of PLGA, PCL and PLGA/PCL blends

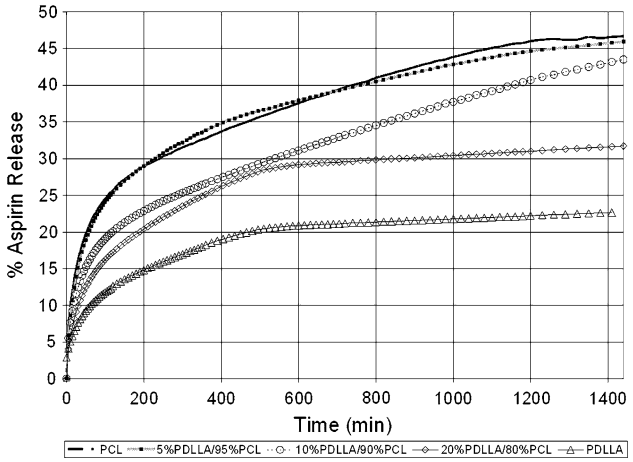

Fig. 7 Drug release curves for thin film polymer drug matrices of PDLLA, PCL and PDLLA/PCL blends

for a proportion of the surface drug. PCL is a semi-crystalline polymer with a high degree of permeability to many therapeutic drugs and has a T_g of −60 °C [41]. Hence, with the test temperature simulating the human body (37 °C), the PCL backbone chains may be presumed to be in a highly flexible state with significant free volume in the PCL/drug matrix. Work carried out by Pitt et al. [42] on capsules of PCL indicates that the release of drug from PCL and PDLLA is diffusion controlled. PDLLA is an amorphous polymer with a T_g of 48 °C and eluted 26.6% of the drug loading over the duration of the test, the second highest percentage drug release.

PLGA is a hydrophobic and semi-crystalline polymer with T_g of 65 °C and proved to be the polymer/drug matrix with the lowest level of drug release at 13.75% over the duration of the experiment. Work carried out by Heya et al. [43] found that after an initial burst release of drug from PLGA, the release rate was controlled by the degradation of the polymer. Further drug release from PLGA requires polymer degradation to break long backbone chains and polymer relaxation to create more free volume. The slow release rate observed may be due to the entrapment of the drug particles in the crystalline regions. The higher T_g of PLGA when compared to PCL and PDLLA could also account for the limited drug release, as at 37 °C reduced free volume may have been available for drug transport through the polymer. The presence of PLGA in the PLGA/PCL blend leads to a decrease in drug release rate, when compared to the PCL homopolymer drug release curve. A similar trend is observed for blends of PDLLA/PCL. However, in the case of the PDLLA blend materials, the decrease in release rate is not as pronounced with decreasing PCL content.

The difference in the release levels of the blends of PLGA/PCL and PDLLA/PCL can be related to the reduction of PCL in the samples. Incompatible blends of PCL and PDLLA were reported by Shen et al. [44] to have faster drug release rates than compatible blends because the phase separation of incompatible blends contributed extra drug release through micro channels formed among the phase-separated domains. The difference between the drug release rates of the two polymer blends may be accounted for by the differing levels of immiscibility. Another factor is the effect of blending PDLLA or PLGA on the percentage crystallinity of PCL. Godinho et al. [45] reported that with blends of PCL and nalidixic acid, the environment for drug diffusion changed according to the crystalline microstructure of the PCL. Blends containing higher concentration of nalidixic acid showed lower release fractions over time as they possessed a higher level of crystallinity, thus exhibiting a tendency towards more sustained release. The difference in the drug release percentage levels between the two polymer blends could also be related to the morphology of the component polymers. The work outlined herein demonstrates that modulation of drug release is achievable by altering the ratio of PCL to PDLLA or PLGA in the thin film blends.

Conclusion

The aim of this work was to modify the physical properties, degradation rate and drug delivery characteristics of thin films for medical applications by blending PDLLA, PLGA and PCL. It was observed that modulation of the blend ratios afforded significant control over the degradation rate of the materials. The presence of PLGA in blend PLGA/PCL leads to a decrease in drug release rate, when compared to the PCL homopolymer. A similar trend is observed for blends of PDLLA/PCL. However, in the case of the PDLLA blend materials, the decrease in release rate is not as pronounced with decreasing PCL content. The

films described in this work present two major advantages: variable degradation rates and tunable release rates and profiles, thus enabling their use in a wide variety of applications where bioresorbable polymers are required.

Acknowledgement This study was supported in parts by grants from both Enterprise Ireland and the Athlone Institute of Technology research and development fund.

References

1. Borden M (2006) Wiley encyclopedia of biomedical engineering. Wiley, New York
2. Lanza R, Langer R, Vacanti J (2007) Principles of tissue engineering. Elsevier Academic Press, New York
3. Gunatillake PA, Adhikari R (2003) Eur Cells Mater 5:1
4. Geever L, Devine D, Nugent M, Kennedy J, Lyons J, Higginbotham C (2006) Eur Polym J 42:69
5. Edlund U, Albertsson AC (2002) Adv Polym Sci 157:67
6. Pitt CG (1990) Biodegradable polymers as drug delivery systems. Marcel Dekker, New York, pp 71–120
7. Benoit MA, Baras B, Gillard J (1999) Int J Pharm 184:73
8. Lewis DH (1990) Biodegradable polymers as drug delivery systems. Marcel Dekker, New York, pp 1–41
9. Vert M (1996) The complexity of PLAGA-based drug delivery systems. In: Proceedings of the international conference on advances in controlled delivery, Baltimore MD, pp 32–36
10. Utracki LA (2002) Polymer blends handbook. Kluwer Academic Publishers, London
11. Chen C, Chueh J, Tseng H, Huang H, Lee S (2003) Biomaterials 24:1167
12. Lyons JG, Holehonnur H, Devine DM, Kennedy JE, Geever LM, Blackie P, Higginbotham CL (2007) Mater Chem Sci 103:419
13. Hukins DWL, Mahomed A, Kukureka SN (2008) Med Eng Phys 30:1270
14. Scott G, Gilead D (1995) Degradable polymers: principles and applications. Chapman & Hall, London
15. Gowariker VR, Viswanathan NV, Sreedhar J (1986) Polymer science. New Age International (P) Ltd, India
16. Lim LT, Auras R, Rubino M (2008) Prog Polym Sci 33:820
17. Saha SK, Tsuji H (2006) React Funct Polym 66:1362
18. Gupta AP, Kumar V (2007) Eur Polym J 43:4053
19. Liu C, Xia Z, Czernuszka JT (2007) Chem Eng Res Des 85:1051
20. Mathiowitz E (1999) Encyclopedia of controlled drug delivery, vol 1–2. Wiley, New York
21. Bajpai AK, Shukla SF, Bhanu S, Kankane S (2008) Prog Polym Sci 33:1088
22. Södergård A, Stolt M (2002) Prog Polym Sci 27:1123
23. Coombes AGA, Rizzi SC, Williamson M, Barralet JE, Downes S, Wallace WA (2004) Biomaterials 25:315
24. Langer R (1995) Chem Eng Sci 50:4109
25. Eastmond GC (1999) Adv Polym Sci 149:59
26. Yu PQ, Xie XM, Wang Z, Li HS, Bates FS (2006) Polymer 47:1460
27. Chouzouri G, Xanthos M (2006) Degradation of aliphatic polyesters in the presence of inorganic fillers. In: Proceedings of ANTEC 2006 Plastics, Annual Technical Conference Society of Plastics Engineers
28. Little U, Buchanan F, Harkin-Jones E, McCaigue M, Farrar D, Dickson G (2009) Polym Degrad Stabil 94:213
29. Reed AM, Gilding DK (1981) Polymer 22:499
30. Domb AJ (1993) J Polym Sci A Polym Chem 31
31. Chen DR, Bei JZ, Wang SG (2000) Polym Degrad Stabil 67:455
32. Koleshe JV (1978) Polymer blends, vol 2. Academic Press, New York
33. Jali R, Nixon JR (1990) J Microencapsul 7:297
34. Cao X, Shoichet MS (1999) Biomaterials 20:329
35. Kweon H, Yoo MK, Park IK, Kim TH, Lee HC, Lee HS, Oh JS, Akaike T, Cho CS (2003) Biomaterials 24:801
36. Tsuji H, Ikada Y (1996) J Appl Polym Sci 60:2367
37. Wnek G, Bowlin G (eds) (2008) Encyclopedia of biomaterials and biomedical engineering. Informa Health Care, UK
38. Li S, McCarthy S (1999) Biomaterials 20:35
39. Alexis F (2004) Polym Int 54:36
40. Rutkowska M, Krasowska K, Heimowska A, Steink A, Janik H, Karlsson S, Haponiuk J (2002) Pol J Environ Stud 11:413
41. Kelen T (1983) Polymer degradation. Van Nostrand Reinhold Company, New York
42. Pitt CG, Gratzl MM, Jeffcoat AR, Zweidinger R, Schindler A (1979) J Pharm Sci 68:1534
43. Heya T, Okada H, Ogawa Y, Toguchi H (1991) Int J Pharmaceut 72:199
44. Shen Y, Sun W, Zhu KJ, Shen Z (2000) J Biomed Mater Res 50:528
45. Godinho J, Moore I, Donnelly L, Lew CY, Douglas P, Jones D, McNally GM, Murphy WR (2005) Antec 2:3125