Drug Release From Irradiated PLGA and PLLA Multi-Layered Films

SAY CHYE JOACHIM LOO, ZHI YING SERLIN TAN, YI JUN CHOW, SIEW LING IVY LIN

School of Materials Science and Engineering, Nanyang Technological University, 50 Nanyang Avenue, Singapore 639798, Singapore

Received 24 August 2009; revised 2 December 2009; accepted 8 December 2009

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.22079

ABSTRACT: Poly(lactide-*co*-glycolic acid) (PLGA) and poly(L-lactide) (PLLA) films are widely studied for various biomedical applications. Because of their use for drug delivery, achieving controlled release from these biodegradable films has become an area of intense research. The objective of this study is therefore to investigate how PLGA and PLLA films fabricated through an irradiated-multi-layer approach can be a viable technique to achieve controlled drug delivery. In this study, lidocaine base (lido-base) and lidocaine salt (lido-salt) were used as model hydrophobic and hydrophilic drugs, respectively. Results show that multi-layer PLGA underwent pseudo surface degradation, while multi-layer PLLA degraded to a lesser extent over the same study period. Triphasic release was observed for lido-base, whereas lido-salt was released through a biphasic profile, from both polymer systems. The two dominating release phases for both drugs were diffusion and zero-order release, where the latter is characterized by the onset of mass loss. It was shown that PLGA had a shorter diffusion phase and a longer zero-order phase, while the contrary was true for PLLA. This difference was due to the faster degradation for PLGA. In conclusion, the hydrophilic gradient induced from an irradiated-multi-layer film system shows potential for controlled and sustained release of drugs. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:3060–3071, 2010

Keywords: controlled release; biodegradable polymers; materials science; polymeric drug delivery systems; water sorption

INTRODUCTION

Biodegradable polymers, such as poly(L-lactide) (PLLA) and poly(lactide-*co*-glycolic acid) (PLGA), are promising materials for biomedical and pharmaceutical applications. They are extensively investigated as nanoparticles,[1] microparticles,[2] injectable depots,[3] films,[4,5] scaffolds,[6] and as a bulk implant[7] for drug delivery, because they demonstrate good toxicological safety and tunable biodegradability.[8–10] These controlled drug delivery systems are gaining practical importance because they improve treatment and patient compliance, provide optimized drug concentration on site over prolong periods and reduce undesired side effects of the drug.

In the recent decades, there have also been strong interests in the use of PLGA and PLLA specifically for localized drug delivery. PLGA and PLLA films, in particular, have been studied for treating periodontal disease,[11–13] glaucoma,[14] cancer,[15,16] as a polymer coating on metallic stents,[17,18] and even as fully biodegradable stents.[19–21] So far, different strategies have been employed to optimize their hydrolysis, drug release profiles, and mechanical integrity to suit to various applications.

One of the key areas of intense research is therefore to achieve an optimal and desirable controlled and sustained drug release from these biodegradable films. Incorporating the use of nanoparticles for controlled drug release from films is one such strategy that has been employed. A study by Lim et al.[22] who used drug-loaded nanoparticles as a means to reduce burst release from vascular grafts showed an effective decrease in burst release, although sustained release of the drug was not observed. Multi-layer PLGA/PLLA polymeric systems, through a sandwich configuration, have also been developed to achieve controlled release of sirolimus, but sustained release beyond 30 days was not attained.[23] Blending of diblock copolymers with PLGA films was another strategy employed to optimize drug delivery. Jackson et al.[20] blended PDLLA–PEG into PLGA films to increase the initial drug release rate, which is required in perivascular applications. In this blended system, a slow sustained release was subsequently

Correspondence to: Say Chye Joachim Loo (Telephone: +65-6790-4603; Fax: +65-6790-9081; E-mail: joachimloo@ntu.edu.sg)

Journal of Pharmaceutical Sciences, Vol. 99, 3060–3071 (2010)

observed from the 30% w/w blended films, of which 20% of the loaded drugs were released. Other factors, such as drug concentration and type, glycolide content in PLGA, polymer molecular weight and device geometry,[24,25] have also been studied to optimize drug release rates and profiles. However, achieving a desirable drug release profile with optimal release kinetics still remains very much a challenge.

Previously, electron beam (e-beam) radiation has been shown to modify the physical properties of PLGA and PLLA and their copolymers,[26] upon which tunable hydrolysis rates from these polymers can be achieved.[27,28] Preliminary drug release results from these irradiated polymer films also show that radiation accelerates the onset (or reduces the lag phase) of drug release from these bulk degrading polymers (results not published). At the same time, e-beam irradiation had also been shown to elicit surface degradation characteristics from single layer[29] and multi-layer non-drug loaded PLGA films,[30] which incidentally may allow for a better control and predictability of drug release rates from PLGA.[31]

Controlling rate of hydrolytic degradation is desirable in order for drug delivery to be effectively applied. However, one factor working against a constant rate of drug release from PLGA and PLLA is that they undergo bulk degradation.[8] If these bulk-degrading polymers can be made to exhibit surface degradation or layer-by-layer degradation, they would provide a promising control of drug release.[32–34] The objective of this paper is therefore to report on the drug release rates and profiles of drug-loaded polymer films, through an irradiation-cum-multi-layer strategy, using a single starting polymer of either PLGA or PLLA. In this study, we are showing for the first time how multi-layer polymer films that undergoes surface degradation or layer-by-layer degradation can provide controlled and sustained release of drugs. Understanding how drugs are released through this strategy could provide an alternative approach to fine-tune and achieve a desirable drug release profile from polymeric films. Achieving of which would then broaden the bandwidth in the use of these polymers for a myriad of localized drug delivery applications.

MATERIALS AND METHODS

Preparation of Films for Irradiation

PLLA (intrinsic viscosity, IV: 2.38) and PLGA (80:20) (IV: 5.01) were purchased from Purac Far East (Singapore) and used as-received. The polymers were first individually dissolved in HPLC-grade dichloromethane (DCM), purchased from E. Merck (Darmstadt, Germany), at mass ratios of 1:10 and 1:15, respectively, and left to stir for a day to obtain a homogenous polymer solution. Films were then cast using a film applicator on a glass substrate, before leaving to dry in air at room temperature for 24 h. Subsequently, the films were placed in a vacuum oven at 55°C for a week to remove any remaining solvent. To reduce drying time, there may be a need to look into alternative drying methods to hasten the DCM removal process. The dry thicknesses of the films were measured to be $55 \pm 3\,\mu m$, allowing for full penetration of the e-beam.[35] Dried polymer films were then cut into rectangular strips of $2 \times 2\,cm^2$ for e-beam irradiation. E-beam irradiation was performed using the Energy Sciences, Inc. (ESI, Massachusetts) electron-beam accelerator at an accelerating voltage of 175 kV, at room temperature (25°C), humidity, and in the presence of oxygen. Films were irradiated at doses of 5 and 20 Mrad. These radiation doses were chosen because previous studies had shown that polymers irradiated at these doses exhibited a moderate (5 Mrad) to substantial (20 Mrad) increase in their degradation rates,[27,28] which would give rise to pseudo surface degradation from 20–5 to 0 Mrad multi-layer film constructs.[5]

Preparation of Drug-Loaded Multi-Layer Films

After irradiation, the polymer films were redissolved in DCM and 5 wt% of drugs were added together to form a homogeneous drug–polymer solution. The drugs used in this study were model hydrophilic lidocaine hydrochloride (lido-salt) and hydrophobic lidocaine base (lido-base) drugs, both purchased and used as received from Sigma–Aldrich (Singapore). The multi-layer films were then fabricated using the solvent evaporation technique by pouring successive layers onto a Petri dish.[5] The base layer (non-irradiated: 0 Mrad) was first poured onto the dish and left to dry for 24 h before the second layer (5 Mrad) was applied. After 24 h, the top and final layer (20 Mrad) was added and left to dry overnight, before this triple-layer film was placed in the vacuum oven at 45°C for a week. Both PLGA and PLLA multi-layer films were prepared in the same manner.

In Vitro Drug Release From Multi-Layer Films

Drug loading and release were determined using the Fourier-transformed infrared spectroscopy (FTIR) and UV–Vis spectrophotometer, respectively. After drug loading, the infrared spectra of the drug-loaded films were obtained from the Perkin-Elmer system 2000 FTIR. The FTIR spectra were obtained with 16 scans per sample over the range of 4,000–400 cm^{-1}.

For *in vitro* drug release, the multi-layer films ($2 \times 2\,cm^2$) were placed in 6-well cell culture plates filled with phosphate-buffered saline (PBS) solution (pH 7.4) and incubated at 37°C for various lengths of time. Non-drug loaded films were used as control samples. A piece of sterile gauze was placed on top of

each film to ensure full submergence of the film in PBS. At pre-determined time intervals, the PBS was drawn out for testing before replenishing with fresh PBS. UV–Vis spectrophotometer was performed using the Shimadzu UV-250 to detect for drug released, at wavelength 263 nm. Drug release studies were conducted in triplicates ($n = 3$).

Characterization of Physical Properties During Drug Release

The hydrolyzed drug-loaded films were also characterized during the period of drug release study. Films were removed, rinsed with distilled water and surface dried using water-absorbent paper. The samples were then dried in a vacuum oven at 40°C for a week, before the final dry mass (m_d) was recorded. Mass loss was taken as the difference in the dry mass (m_d) with respect to the initial mass (m_0) of sample. Results for mass loss were normalized by dividing over their initial masses (m_0) and reported in terms of percentage. The physical properties of the films were characterized using the gel permeation chromatography (GPC), modulated differential scanning calorimeter (MDSC), and scanning electron microscopy (SEM).

The molecular weight (i.e., through elution times) of each sample was determined using the Agilent 1100 series GPC, performed at 35°C with 100% chloroform as solvent, using the reflective index detector (RID). The calibration was done in accordance to polystyrene standards and the flow rate used was 1 mL min^{-1}. Changes to the thermal properties and polymer crystallinity were investigated with the use of a TA Instrument DSC 2920 Modulated DSC apparatus. To avoid oxidative degradation, the samples and reference pans were purged with nitrogen at a constant flow rate of 48 mL min^{-1}. Approximately 5 mg of the sample was heated from −20 to 250°C at a scan rate of 10°C min^{-1}. SEM, JEOL JSM-5310, and JSM-6360, were used to analyze both the cross-section and surface of the multi-layer films. An accelerating voltage of 15 and 3 kV was used for cross-section and surface analysis, respectively. Samples were first gold-coated for 40 s using the sputter coater model SPI-Module before SEM analysis.

RESULTS

Drug Loading of Multi-Layer Films

The FTIR spectra of drug-loaded multi-layer PLLA films are shown in Figure 1. The inset shows the spectra for lido-base and lido-salt drugs. From Figure 1, distinctive drug peaks at 3,250 cm^{-1} (N–H) for lido-base and 1,520 cm^{-1} (C(=O)–N) for lido-salt are observed from their respective drug-loaded polymer spectra, indicating that drugs were successfully loaded into these multi-layer PLLA films. Similarly, successful loading of drugs was observed from the FTIR spectra of drug-loaded multi-layer PLGA films (results not shown).

Mass Loss of Polymers

PLGA

Figure 2 plots the % mass loss of drug-loaded single layer and multi-layer PLGA films with increasing drug elution time. It was observed that the initiation of mass loss for single layer films commenced earlier for the irradiated samples (5 and 20 Mrad), indicating faster dissolution rates of these films. Rate of mass loss for drug-loaded multi-layer PLGA films were observed to be between that of the 0 and 5 Mrad single layer films. Lido-base multi-layer films were observed to undergo a faster mass loss as compared to lido-salt multi-layer films.

PLLA

Figure 3 plots the % mass loss of drug-loaded single layer and multi-layer PLLA films with increasing drug elution time. Similar to the mass loss of PLGA films, the rates of mass loss for both drug-loaded multi-layer PLLA films were observed to be between that of the 0 and 5 Mrad single layer films. Lido-base multi-layer films also underwent a faster mass loss as compared to the lido-salt films.

PLGA Versus PLLA

Comparing between PLGA and PLLA (Fig. 2 vs. Fig. 3), mass loss was more significant for PLGA than PLLA films, due to the steric hindrance provided by the methyl side group of the LA structure (Scheme 1) against hydrolytic attack of its ester bonds. Mass loss for both the drug-loaded multi-layer PLGA films occurred linearly (Fig. 2), whereas mass loss profiles for PLLA films (Fig. 3) showed a small initial mass loss (~2%), followed by a lag phase before significant mass loss was recorded after 60 days. This initial mass loss observed from PLLA was likely due to the dissolution of the top 20 Mrad layer, as verified from the mass loss of a 20 Mrad single layer film. Initial mass loss for both PLGA and PLLA multi-layer films can therefore be attributed to dissolution of the top 20 Mrad irradiated polymer layer.[27,28]

Water Uptake

Water uptake of the drug-loaded PLGA and PLLA multi-layer films are plotted in Figure 4. PLGA films were found to have a much higher water uptake in comparison to PLLA films, and water uptake also differs for non-drug loaded and drug-loaded films. Lido-base loaded films were found to have a higher

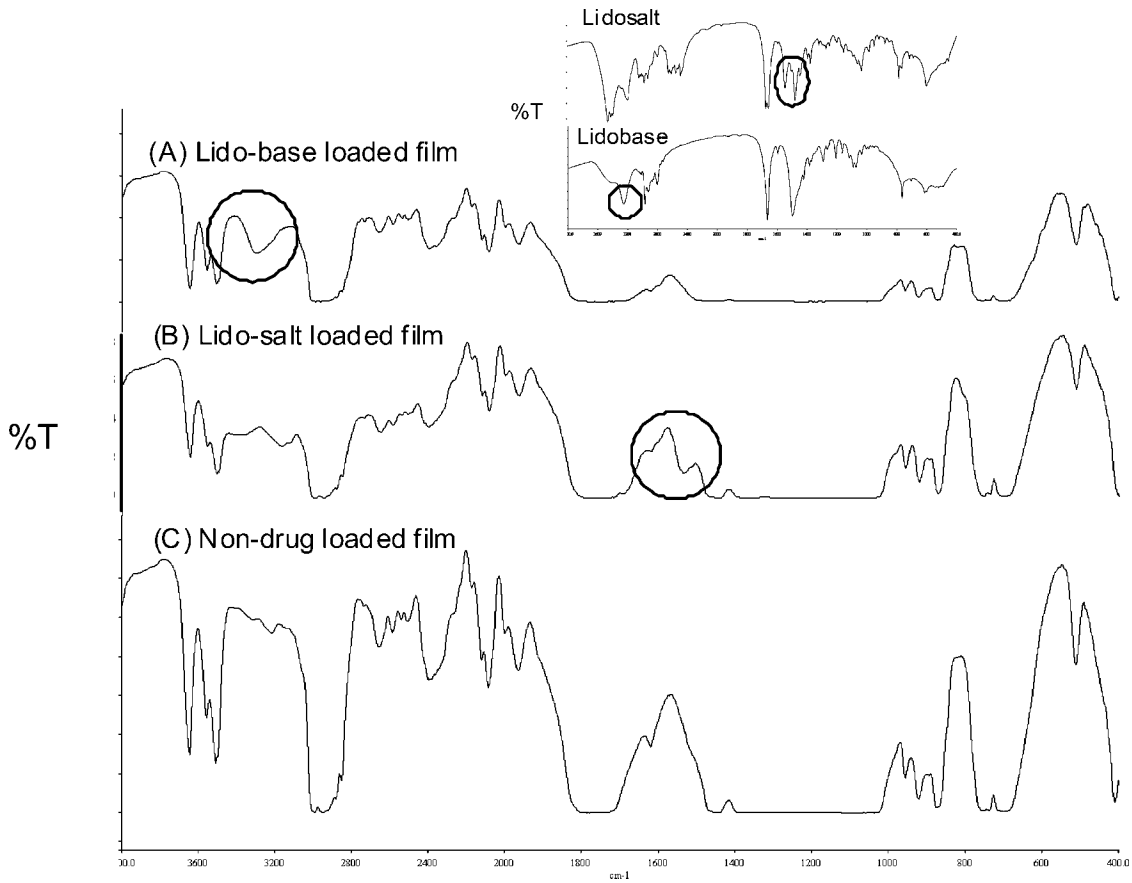


Figure 1. FTIR spectra of (A) lido-base loaded, (B) lido-salt loaded, and (C) non-drug loaded PLLA films showing distinctive drug peaks for lido-base and lido-salt loaded films. Inset: FTIR spectra of lido-base and lido-salt drugs.

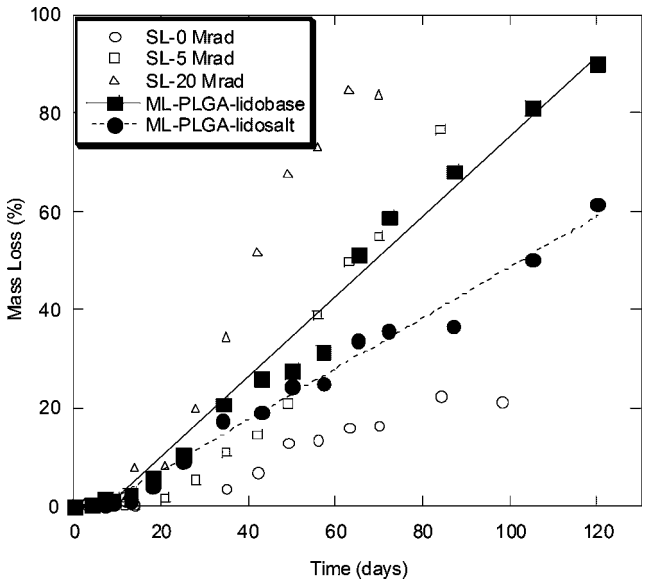


Figure 2. Mass loss (%) from single layer (SL) PLGA films (white symbols) loaded with lido-base drug and multi-layer (ML) PLGA films (black symbols) loaded with lido-base drug (■) and lido-salt drug (●).

water uptake as compared to lido-salt loaded films, with the control (non-drug loaded) having the lowest percentage values, consistently across both PLGA and PLLA samples. The water uptake results therefore explain for the mass loss observed in Figures 2 and 3, where films with higher water uptake (i.e., PLGA) were found to undergo a more rapid dissolution. Also, the higher water uptake, which would accelerate hydrolysis, of the lido-base loaded films resulted in faster mass loss as compared to lido-salt loaded films, as similarly observed and explained by Frank et al.[36]

GPC Traces at Different Drug Elution Times

Polymer degradation, through hydrolysis, could be further verified from the GPC traces of the polymers. Figure 5 shows the GPC traces of lido-base loaded PLGA at different drug elution times. Here, GPC traces were plotted because the molecular weights of each individual polymer layer could not be resolved due to the overlap of elution peaks. From these traces, it was observed that the elution time of the multi-layer PLGA film increased with drug elution time,

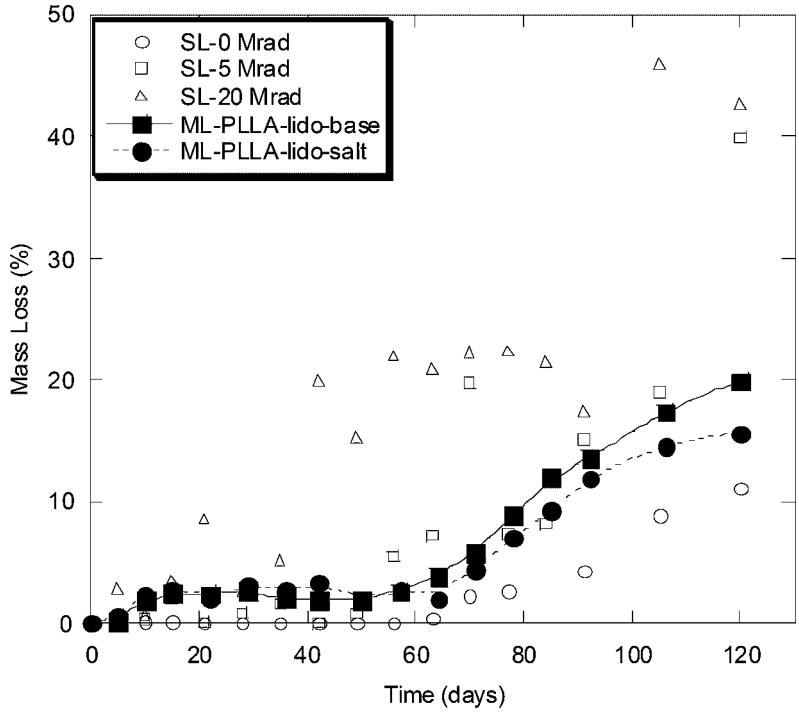
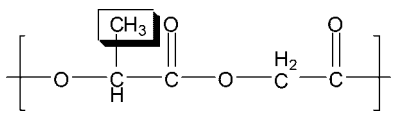


Figure 3. Mass loss (%) from single layer (SL) PLLA films (white symbols) loaded with lido-base drug and multi-layer (ML) PLLA films (black symbols) loaded with lido-base drug (■) and lido-salt drug (●).

indicating a decrease in molecular weight. There were two peaks from the GPC trace at day 0; a major peak at ~7 min and a smaller peak at ~6 min, representing the elution times of both the irradiated layers and the 0 Mrad layer, respectively. The peaks for each irradiated layer were indistinguishable from the major peak because their individual elution times were very close; 6.9 min for 5 Mrad and 7.1 min for 20 Mrad single layer films. The two peaks observed at day 0 merged at 34 days, possibly implying that the 0 Mrad layer was degrading rapidly. This is deduced from the disappearance of the 0 Mrad peak, suggesting the sudden increase in elution time for the 0 Mrad layer. At 87 days, two peaks were again resolved, with the larger peak (7.9 min) possibly arising from the combination of the 0 and 5 Mrad layer, while the smaller peak (9.2 min) was from the 20 Mrad layer. By this time, it is hypothesized that most of the 20 Mrad layer would have undergone dissolution (small GPC peak), as similarly suggested from the mass loss results (~60%) (Fig. 2).



Scheme 1. Chemical structure of PLGA showing the methyl side group of the LA structure.

GPC traces for lido-base loaded PLLA films at different drug elution times were plotted in Figure 6. The GPC trace at 0 day similarly showed two peaks, each again representing the elution time of both the irradiated layers and the 0 Mrad layer. At 57 and 85 days, the peaks have shifted right and a peak shoulder can be observed at ~8.2 min. It is believed that the larger peak was from the 0 and 5 Mrad layers, while the peak shoulder represented polymer from the 20 Mrad layer. Subsequently, with increasing drug elution time, only one peak was observed at 120 days, possibly implying that the peaks from the 0 and 5 Mrad layers had merged.

The GPC traces of non-drug lido-base and lido-salt loaded PLLA at 120 days are shown in Figure 7. At 120 days, it is evident that the molecular weights of lido-base loaded PLLA films had decreased considerably in comparison to the lido-salt and non-drug loaded films. This is in agreement with the mass loss and water uptake results which showed a more significant mass loss and water uptake for the lido-base loaded films. A more rapid degradation for lido-base loaded films is therefore attributed to the base catalyst effect of the lido-base drug during hydrolysis.[36]

Glass Transition Temperature and Polymer Degradation

The degradation of the polymers can also be inferred from the changes to the thermal properties of the

 DOI 10.1002/jps

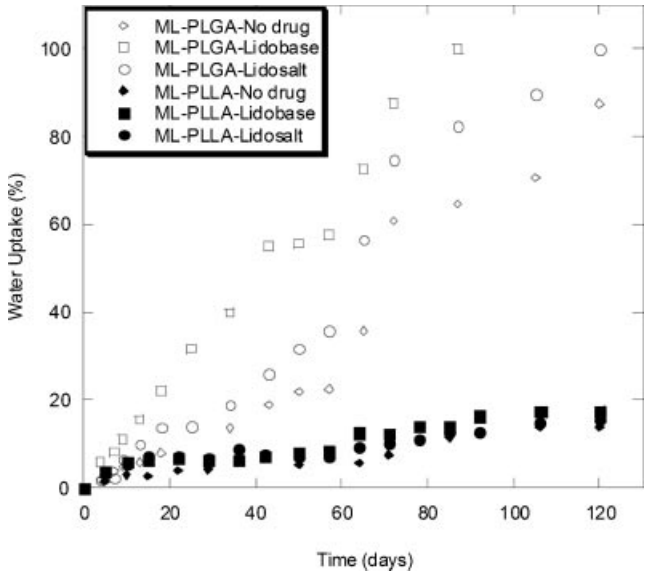


Figure 4. Water uptake (%) of drug loaded (lido-base and lido-salt) and non-drug loaded PLGA (white symbols) and PLLA (black symbols) films with drug elution time.

polymers. From their DSC traces, both PLGA and PLLA films were found to be semi-crystalline. Figure 8 plots the change in T_g of both multi-layered PLGA and PLLA with drug elution time. T_g decreased with drug elution time for both polymers, with PLGA having a more drastic decrease from 71 to 53°C within 13 days. It is also evident that lido-base loaded samples, for both PLGA and PLLA, had lower T_g values as compared to the non-drug and lido-salt loaded films, implying a faster degradation for lido-base loaded films. This decrease in T_g therefore implied a similar decreasing trend in molecular weight,[37] and an increased free volume in the polymer.

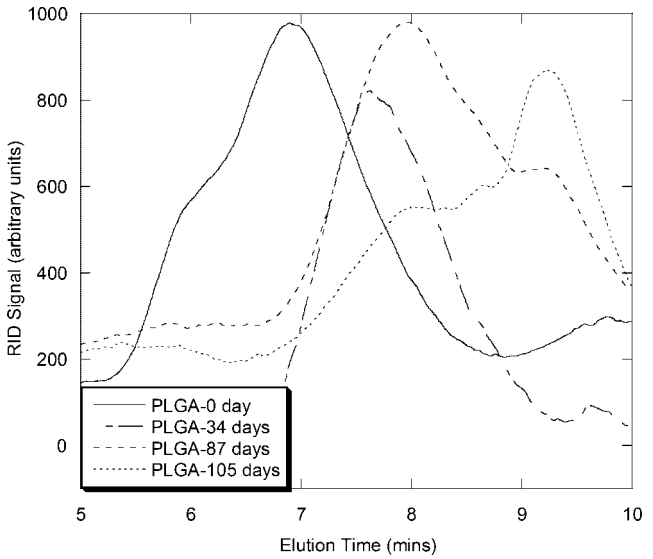


Figure 5. GPC traces of lido-base loaded multi-layer PLGA films at different drug elution times.

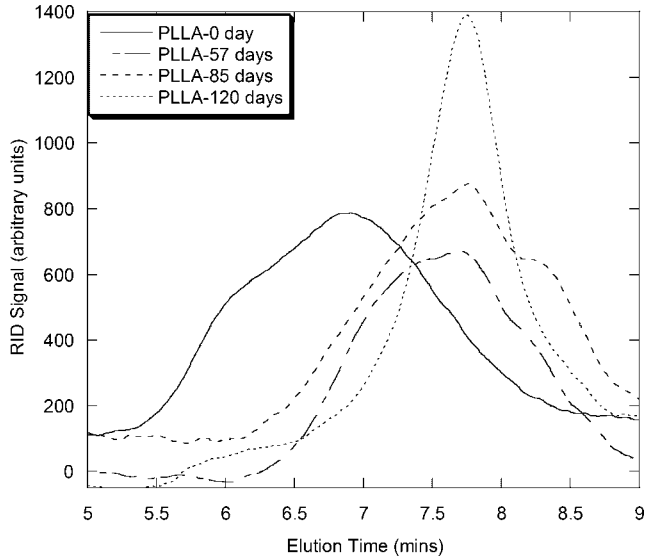


Figure 6. GPC traces of lido-base loaded multi-layer PLLA films at different drug elution times.

Scanning Electron Microscope (SEM)

The surface and cross-section SEM micrographs for lido-base loaded PLGA are shown in Figure 9. From the surface, the formation of pores is evident on the surface of PLGA films at 105 days, arising from both the release of drugs and the dissolution of degrading polymer. Cross-sectional views show the thinning of multi-layer PLGA with time, which was similarly observed and reported for non-drug loaded multi-layer PLGA films.[5,30] This thinning effect is likened to a pseudo surface degradation effect where the polymer film with a faster degradation rate (i.e., 20 Mrad) will be removed first, arising from a more

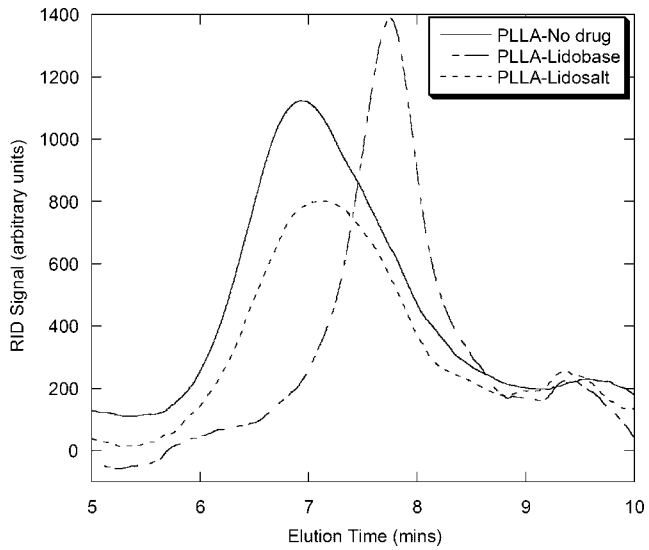


Figure 7. GPC traces of non-drug and drugs-loaded multi-layer PLLA films at 120 days.

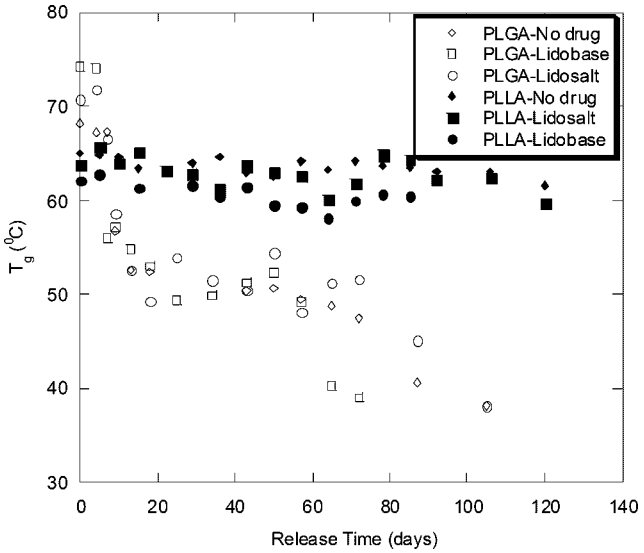


Figure 8. Glass transition temperature (T_g) of multi-layer PLGA and PLLA films with drug elution time.

rapid dissolution rate. This confirms the mass loss results where substantial mass loss was similarly observed at 105 days. On the contrary, this thinning effect (i.e., pseudo surface degradation) was not so significant for lido-base loaded PLLA films, as observed from Figure 10. PLLA films were also found to undergo thinning, but to a lesser extent, that is, ~20%.

Drug Release From Multi-Layer PLGA and PLLA Films

Drug release from lido-base and lido-salt loaded multi-layer PLGA films are plotted in Figure 11a. Drug release profiles and kinetics are shown to be different for both drugs. This difference may be attributed to the extent of water uptake of these drugs (Fig. 4). Lido-base loaded films showed a three phase (triphasic) release profile—a short (3 days) initial slow release, followed by a substantial release (~50%), before a linear zero-order release was observed after 21 days. The mid-phase release could indicate that lido-base is diffusing rapidly through the irradiated polymer layers, facilitated by the high water uptake of these samples. On the other hand, lido-salt loaded films showed a biphasic release profile, where a slow initial release (~10%) was observed, followed by a zero-order release after 21 days. The release of lido-base (50%) and lido-salt (~10%), before 21 days, is therefore through diffusion; since diffusion is the mechanism of drug release if drug release is faster than matrix erosion.[38,39] The initial release results also fitted well ($r^2 > 0.98$) to Higuchi's model (Fig. 11b) further confirming diffusional release, as summarized in Table 1. At the latter phase (after 21 days), drugs are released as the polymers undergo pseudo surface degradation giving a zero-order release.

Figure 12a plots the cumulative % drug release from multi-layer PLLA films. The initial loss of lido-salt (~20%) could be attributed to some drugs adsorbed on the surface of the films. Similarly, for lido-salt PLLA, its release was observed to be biphasic. From the Higuchi plot (Fig. 12b), a diffusional release was observed up to 63 days for these samples, followed by a zero-order release (Fig. 12a). This onset of zero-order release coincides with the time period of rising mass loss for PLLA. For lido-base loaded films, the drugs are again released through a triphasic profile—a slower initial release (up to 18 days), a diffusional release (up to 63 days), and a final zero-order release as the polymer starts to exhibit significant mass loss.

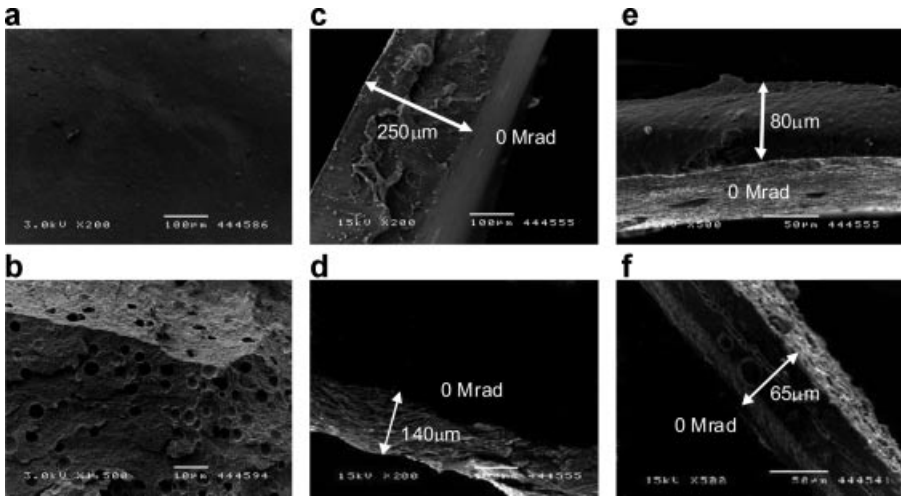


Figure 9. SEM micrographs of lido-base loaded PLGA multi-layer films at (a) surface 0 day, (b) surface 105 days, (c) cross-section 0 day, (d) cross-section 34 days, (e) cross-section 87 days, and (f) cross-section 105 days.

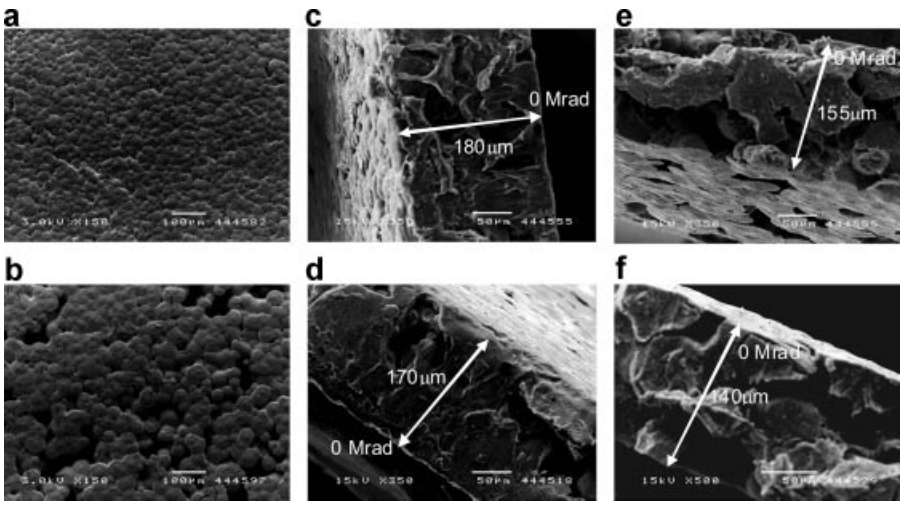


Figure 10. SEM micrographs of lido-base loaded PLLA multi-layer films at (a) surface 0 day, (b) surface 120 days, (c) cross-section 0 day, (d) cross-section 57 days, (e) cross-section 92 days, and (f) cross-section 120 days.

DISCUSSION

Degradation of Multi-Layer PLGA and PLLA Films

Drug-loaded multi-layer PLGA and PLLA films underwent hydrolysis and drugs (lido-base or lido-salt) were simultaneously released from these films. The results showed that both lido-base and lido-salt loaded PLGA films were observed (i.e., mass loss, GPC, and SEM) to degrade faster than their corresponding PLLA films. This is attributed to the relatively higher water uptake of PLGA films in comparison to PLLA films. The degradation of multi-layer PLGA resulted in film thinning as observed from the SEM, indicative of the film undergoing pseudo surface degradation. This thinning effect can be explained from the hydrophilic gradient effect attributed from an irradiated-multi-layer film system. Irradiated films were shown to be more hydrophilic with increasing radiation dose.[27,28] The more hydrophilic 20 Mrad layer therefore allows for a greater influx of water through this layer, which will accelerate water penetration into the film. Subsequently, this hydrophilic layer will undergo a faster dissolution rate and hydrolyze into smaller soluble oligomers. Oligomers that are formed could either leach out to the release medium resulting in mass loss, or partition into the other layers further increasing their hydrophilicity.[5] This would further accelerate hydrolysis of the other layers (0 and 5 Mrad), as observed from the GPC results (Fig. 5).

PLLA films, on the other hand, experienced degradation to a lesser extent for the same study period, as deduced from the low mass loss and small changes to the GPC elution time. Film thinning of PLLA was less extensive (~20%) as observed from the SEM micrographs. The chemical structure of the PLLA polymer provides steric hindrance against water penetration, thus explaining for a lower water uptake and therefore less significant polymer degradation.

Drug-loaded films were found to degrade faster than the non-drug loaded films, for both PLGA and PLLA. The presence of drugs increased water uptake (Fig. 4) and accelerated hydrolysis (Figs. 7 and 8). It was further noted that water uptake was higher for the lido-base loaded films as compared to the lido-salt samples. Lido-base loaded samples also degraded faster than the lido-salt samples due to base catalyst effect.[36]

Biphasic Release of Lido-Salt From PLGA and PLLA Films

For the same drug, the release profiles were found to be similar in both polymer systems. Lido-salt samples were observed to release through a biphasic profile from both PLGA and PLLA. From Table 1, two observations were made: (1) the diffusion release rate from PLLA was found to be faster than PLGA; and (2) the diffusion phase for PLGA (21 days) was shorter than PLLA (63 days). The faster diffusion rate of lido-salt from PLLA can be attributed to its lower T_g (~64°C) in comparison to that of PLGA (~71°C) during the initial release period. A lower T_g indicated a larger polymer free volume that would facilitate the diffusion of lido-salt from PLLA.

The shorter diffusion phase for PLGA was due to its earlier onset of degradation (characterized by mass loss), resulting in a faster transition into the zero-order phase. In the zero-order phase, drugs are released through a dual release mechanism—diffusion and polymer degradation. A zero-order release was observed when the polymer started to undergo

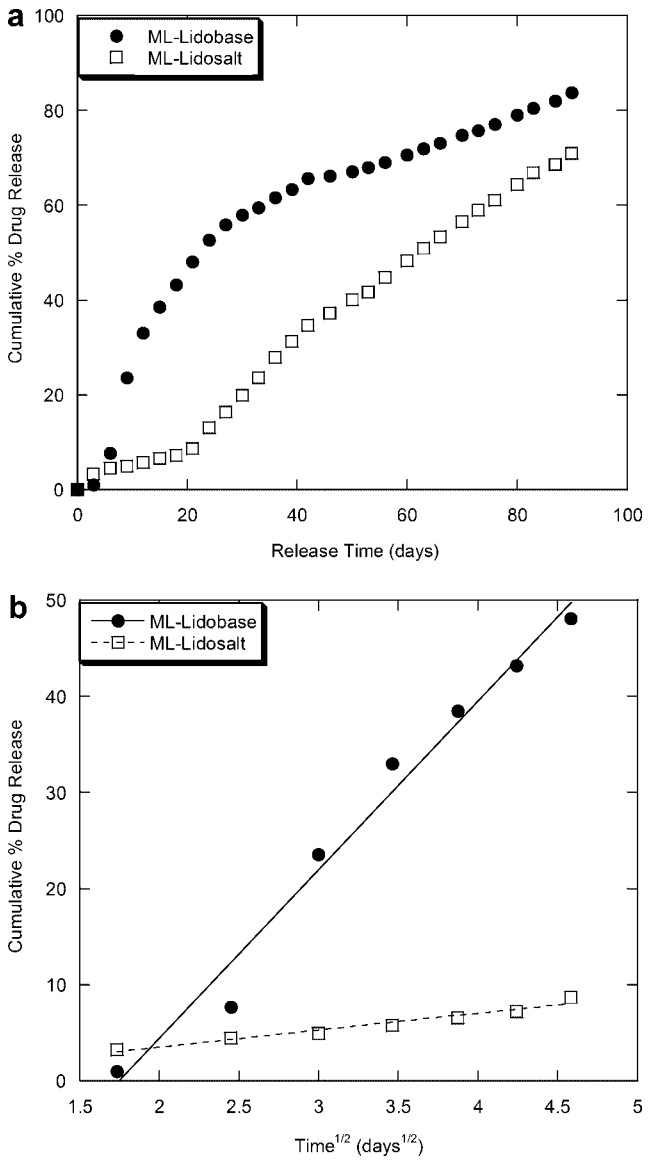


Figure 11. a: Cumulative % drug release from multi-layer PLGA films. b: Higuchi plots during diffusion phase for multi-layer PLGA films.

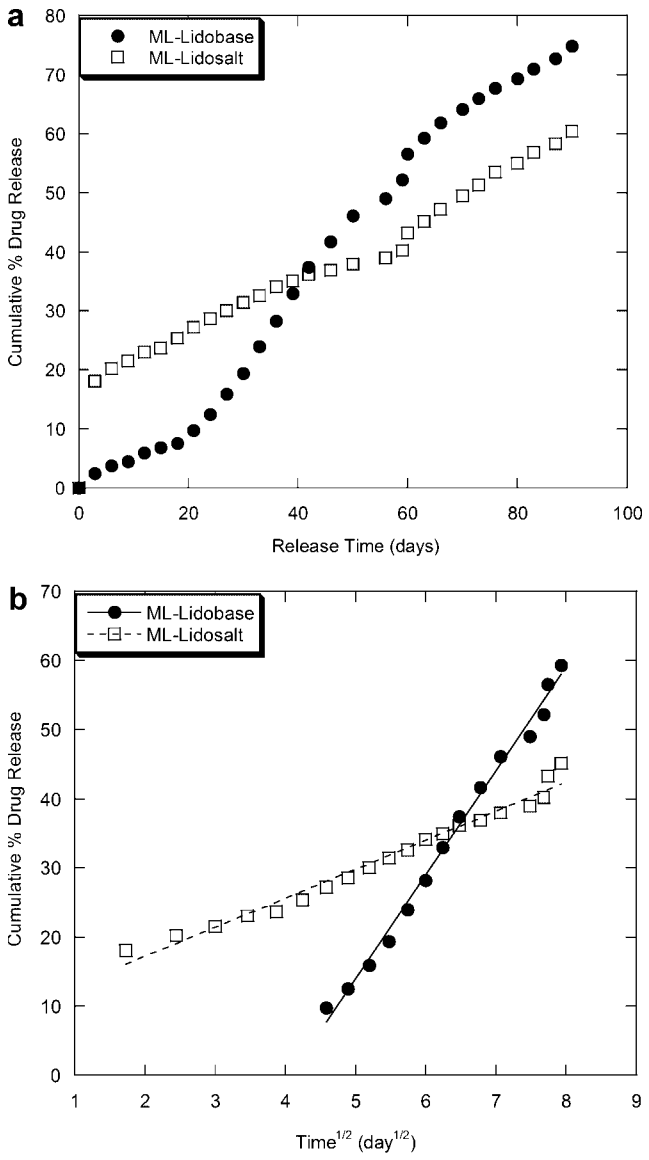


Figure 12. a: Cumulative % drug release from multi-layer PLLA films. b: Higuchi plots during diffusion phase for multi-layer PLLA films.

surface degradation. Previous reports had also shown that polymers undergoing surface degradation characteristics will exhibit zero-order release kinetics.[40,41] The pseudo surface degradation profiles of these multi-layer films therefore resulted in the observed linear drug release profile. A faster degradation rate of PLGA would subsequently promote a faster release rate of lido-salt from PLGA as compared to PLLA. Here, a sustained release of lido-salt beyond 90 days was shown to be achievable through this multi-layer

Table 1. Drug Release Rates for Lido-Base and Lido-Salt Loaded PLGA and PLLA Films at Different Release Phases

	Lido-Base			Lido-Salt	
	Initial Lag Phase	Diffusion Phase (% day$^{-1/2}$)	Zero-Order Phase (% day^{-1})	Diffusion Phase (% day$^{-1/2}$)	Zero-Order Phase (% day^{-1})
PLGA	First 3 days	17.55 ($r^2 = 0.980$)	0.42 ($r^2 = 0.986$)	1.75 ($r^2 = 0.979$)	0.88 ($r^2 = 0.992$)
PLLA	First 18 days	15.01 ($r^2 = 0.993$)	0.52 ($r^2 = 0.997$)	4.39 ($r^2 = 0.968$)	0.55 ($r^2 = 0.995$)

 DOI 10.1002/jps

configuration from both PLGA and PLLA multi-layer systems.

Triphasic Release of Lido-Base From PLGA and PLLA Films

Lido-base drugs are observed, for both PLGA and PLLA, to undergo a triphasic release—an initial lag phase, followed by a diffusion phase, then a zero-order phase. The initial lag phase, observed only for lido-base samples, may be explained from the hydrophobic nature of this drug. Higuchi[42,43] derived an equation previously to describe the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion (Eq. 1):

$$Q_t = 2DS\varepsilon(A - 0.5S\varepsilon)]^{0.5} \times t^{0.5} = k_H\sqrt{t} \qquad (1)$$

where Q_t is the amount of drug released in time t, D is the diffusion coefficient, S is the solubility of drug in the dissolution medium, ε is the porosity, A is the drug content per cubic centimeter of matrix tablet, and k_H is the release rate constant for the Higuchi model. Since k_H is dependent on S, it is highly probable that with increasing water influx, beyond a certain water uptake value (>5% from Fig. 3), the solubility of lido-base increased (k_H therefore increase). It had been previously reported by Tatai et al.[44] that the solubility of lido-base is enhanced in stoichiometric quantities of weak organic acids, of which acidic oligomers were formed as by-products of hydrolysis. The degradation of irradiated PLGA and PLLA resulted in the formation of acidic organic products,[27,45] which may therefore enhance the solubility of lido-base with increasing PBS uptake.[44] Once sufficient drug solubility is attained, the lag phase subsequently transits to the diffusion phase.

During the diffusion phase, lido-base PLGA had a higher diffusion release rate than PLLA, which can be attributed to its lower T_g during this phase. Also, Frank et al.[36] reported a higher D value for lido-base PLGA as compared to lido-base PLLA, thus further substantiating the difference in diffusion release rates. Similar to lido-salt samples, the diffusion phase of PLGA is shorter than PLLA due to its earlier onset of degradation.

A linear release of drug was subsequently observed in the zero-order phase. However, the rate zero-order release is slower for PLGA than PLLA, even though PLGA is degrading at a faster pace. One possible explanation could be due to the morphology of the PLLA films during degradation. From Figure 10d–f, it can be seen that lido-base PLLA films became more porous (57 days), while no obvious signs of increased porosity were observed for PLGA films (Fig. 9c–f). The lack of porosity observed for PLGA could be due to the fast dissolution and erosion of the PLGA films. For PLLA, pore formation would have accelerated the release of lido-base, since drugs could be released much easily through these water channels.[46] Another possible explanation could be the exhaustion of drugs from the edge of the film due to a rapid diffusional release (Fig. 11a). The fast diffusion of lido-base from PLGA could have depleted drugs at the edge of the polymer film. As PLGA surface degrades, less drugs is therefore available to be released from surface, resulting in a decrease in the release rate. Subsequently, as is the case for lido-salt, both multi-layer systems continue to provide sustained release of lido-base beyond 90 days.

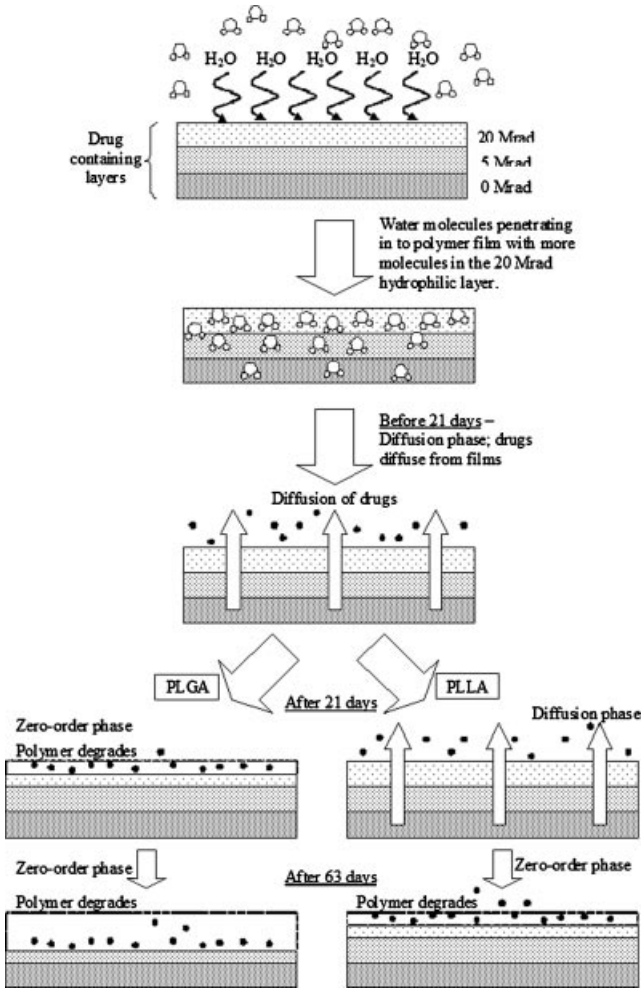


Figure 13. Schematic diagram of polymer hydrolysis and drug release from multi-layer PLGA and PLLA films.[5]

Summary of Drug Release From Multi-Layer Film Systems

In summary, triphasic release profile was observed for lido-base, while lido-salt underwent a biphasic release. Drug release occurs dominantly in the diffusion phase and the zero-order phase. Polymers with a faster degradation rate (i.e., PLGA) will undergo an earlier transition into the zero-order

release phase. In the zero-order phase, the polymer films are likened to undergo pseudo surface degradation because of the hydrophilic gradient effect attributed from an irradiated-multi-layer film system. Figure 13 shows a schematic diagram of polymer hydrolysis and the subsequent release of drugs from these multi-layer films.[5] An earlier onset of zero-order release can therefore be achieved by having a highly hydrophilic soluble layer, in a multi-layer system, to increase water influx and initiate early polymer dissolution.

CONCLUSIONS

Drug-loaded multi-layer irradiated PLGA and PLLA were fabricated and their drug release studied. It was observed that PLGA degraded through pseudo surface degradation, while PLLA degraded to a lesser extent for the same study period. Lido-base was found to be released through a triphasic profile, while lido-salt was released through a biphasic profile for both polymer systems. The two main phases of release are therefore diffusion phase, followed by a zero-order phase which is characterized as the onset of significant mass loss. Overall, lido-base was observed to be released at a faster rate than lido-salt due to its higher water uptake. The difference between PLGA and PLLA, however, lies in the time period of transition from diffusion to zero-order phase. PLGA, with a faster onset of degradation due to its hydrophilicity, underwent a faster transition. These results therefore show that an irradiated multi-layer film system has the potential for achieving controlled and sustained drug release through manipulation of polymer type, and layer hydrophilicity and solubility.

REFERENCES

1. Parveen S, Sahoo SK. 2008. Polymeric nanoparticles for cancer therapy. J Drug Target 16:108–123.
2. Mohamed F, van der Walle CF. 2008. Engineering biodegradable polyester particles with specific drug targeting and drug release properties. J Pharm Sci 97:71–87.
3. Raman C, McHugh AJ. 2005. A model for drug release from fast phase inverting injectable solutions. J Control Release 102:145–157.
4. Xie JW, Tan JC, Wang CH. 2008. Biodegradable films developed by electrospray deposition for sustained drug delivery. J Pharm Sci 97:3109–3122.
5. Loo SCJ, Tan WLJ, Khoa SM, Chia NK, Venkatraman S, Boey F. 2008. Hydrolytic degradation characteristics of irradiated multi-layered PLGA films. Int J Pharm 360:228–230.
6. Thakur RA, Florek CA, Kohn J, Michniak BB. 2008. Electrospun nanofibrous polymeric scaffold with targeted drug release profiles for potential application as wound dressing. Int J Pharm 364:87–93.
7. Ramchandani M, Pankaskie M, Robinson D. 1997. The influence of manufacturing procedure on the degradation of poly (lactide-co-glycolide) 85:15 and 50:50 implants. J Control Release 43:161–173.
8. Wu XS. 1995. Synthesis and properties of biodegradable lactic/glycolic acid polymers. In: Wise DL, Trantolo DJ, Altobelli DE, Yaszemski MJ, Gresser JD, Schwartz ER, editors. Encyclopedic handbook of biomaterials and bioengineering. New York: Marcel Dekker. pp 1015–1054.
9. Athanasiou KA, Niederauer GG, Agrawal CM. 1996. Sterilization, toxicity, biocompatibility and clinical applications of polylactic acid copolymers. Biomaterials 17:93–102.
10. Vert M, Li SM, Spenlehauer G, Guerin P. 1992. Bioresorbability and biocompatibility of aliphatic polyesters. J Mater Sci Mater Med 3:432–446.
11. Perugini P, Genta I, Conti B, Modena T, Pavanetto F. 2003. Periodontal delivery of ipriflavone: New chitosan/PLGA film delivery system for a lipophilic drug. Int J Pharm 252:1–9.
12. Agarwal RK, Robinson DH, Maze GI, Reinhardt RA. 1993. Development and characterization of tetracycline-poly(lactide glycolide) films for the treatment of periodontitis. J Control Release 23:137–146.
13. Webber WL, Lago F, Thanos C, Mathiowitz E. 1998. Characterization of soluble, salt-loaded, degradable PLGA films and their release of tetracycline. J Biomed Mater Res 41:18–29.
14. Huang SF, Chen JL, Yeh MK, Chiang CH. 2005. Physicochemical properties and in vivo assessment of timolol-loaded poly(D,L-lactide-co-glycolide) films for long-term intraocular pressure lowering effects. J Ocul Pharmacol Ther 21:445–453.
15. Dorta MJ, Oliva A, Munguia O, Llabres M, Farina JB. 2002. In vitro release of fluoropyrimidines from PLGA film implants. J Pharm Pharmacol 54:757–763.
16. Dong Y, Zhang Z, Feng SS. 2008. D-alpha-Tocopheryl polyethylene glycol 1000 succinate (TPGS) modified poly(L-lactide) (PLLA) films for localized delivery of paclitaxel. Int J Pharm 350:166–171.
17. Sternberg K, Kramer S, Nischan C, Grabow N, Langer T, Hennighausen G, Schmitz KP. 2007. In vitro study of drug-eluting stent coatings based on poly(L-lactide) incorporating cyclosporine A-drug release, polymer degradation and mechanical integrity. J Mater Sci Mater Med 18:1423–1432.
18. Westedt U, Wittmar M, Hellwig M, Hanefeld P, Greiner A, Schaper AK, Kissel T. 2006. Paclitaxel releasing films consisting of poly(vinyl alcohol)-graft-poly(lactide-co-glycolide) and their potential as biodegradable stent coatings. J Control Release 111:235–246.
19. Tamai H, Igaki K, Kyo E, Kosuga K, Kawashima A, Matsui S, Komori H, Tsuji T, Motohara S, Uehata H. 2000. Initial and 6-month results of biodegradable poly L-lactic acid coronary stents in humans. Circulation 102:399–404.
20. Jackson JK, Smith J, Letchford K, Babiuk KA, Lindsay M, Signore P, Hunter WL, Wang KY, Burt HM. 2004. Characterization of perivascular poly (lactic-co-glycolic acid) films containing paclitaxel. Int J Pharm 283:97–109.
21. Wang XT, Venkatraman S, Boey F, Loo JSC, Tan LP. 2007. Effects of controlled-released sirolimus from polymer matrices on human artery smooth muscle cells. J Biomater Sci Polym Ed 18:1401–1414.
22. Lim HJ, Nam HY, Lee BH, Kim DJ, Ko JY, Park JS. 2007. A novel technique for loading of paclitaxel-PLGA nanoparticles onto ePTFE vascular grafts. Biotechnol Prog 23:693–697.
23. Wang XT, Venkatraman SS, Boey FYC, Loo JSC, Tan LP. 2006. Controlled release of sirolimus from a multilayered PLGA stent matrix. Biomaterials 27:5588–5595.
24. Gumusderelioglu M, Deniz G. 2000. Sustained release of mitomycin-C from poly(DL-lactide)/poly(DL-lactide-co-glycolide) films. J Biomater Sci Polym Ed 11:1039–1050.
25. Klose D, Siepmann F, Elkhamz K, Siepmann J. 2008. PLGA-based drug delivery systems: Importance of the type of drug and device geometry. Int J Pharm 354:95–103.

26. Miao PK, Zhao CN, Xu GL, Fu Q, Tang WR, Zeng K, Wang YP, Zhou HF, Yang G. 2009. Degradation of Poly(D,L-lactic acid)-b-poly(ethylene glycol)-b-poly(D,L-lactic acid) Copolymer by Electron Beam Radiation. J Appl Polym Sci 112:2981–2987.
27. Loo SCJ, Tan HT, Ooi CP, Boey YCF. 2006. Hydrolytic degradation of irradiated and non-irradiated PLLA. Acta Biomater 2:287–296.
28. Loo SCJ, Ooi CP, Boey YCF. 2005. Influence of electron beam radiation on the hydrolytic degradation behaviour of poly(lactide-co-glycolide) (PLGA). Biomaterials 26:3809–3817.
29. Leonard DJ, Pick LT, Farrar DF, Dickson GR, Orr JF, Buchanan FJ. 2009. The modification of PLA and PLGA using electron-beam radiation. J Biomed Mater Res A 89A:567–574.
30. Chia NK, Venkatraman SS, Boey FYC, Cadart S, Loo JSC. 2008. Controlled degradation of multi-layered PLGA films using electron beam irradiation. J Biomed Mater Res A 84A:980–987.
31. Alexis F. 2004. Factors affecting the degradation and drug-release mechanism of poly(lactic acid) and poly[(lactic acid) -co-(glycolic acid)]. Polym Int 54:36–46.
32. Abdul S, Poddar SS. 2004. A flexible technology for modified release of drugs: Multi layered tablets. J Control Release 97:393–405.
33. Chen MC, Liang HF, Chiu YL, Chang Y, Wei HJ, Sung HW. 2005. A novel drug eluting stent spray-coated with multi-layers of collagen and sirolimus. J Control Release 108:178–189.
34. Conte U, Maggi L, Colombo P, Lamanna A. 1993. Multilayered hydrophilic matrices as constant release devices (Geomatrix™ systems). J Control Release 26:39–47.
35. Loo SCJ, Ooi CP, Tan ML, Boey YCF. 2005. Isothermal annealing of PLGA and its effect on radiation degradation. Polym Int 54:636–643.
36. Frank A, Rath SK, Venkatraman SS. 2005. Controlled release from bioerodible polymers: Effect of drug type and polymer composition. J Control Release 102:333–344.
37. Loo SCJ, Ooi CP, Boey YCF. 2004. Radiation effects on poly(-lactide-co-glycolide) (PLGA) and poly(L-lactide) (PLLA). Polym Deg Stab 83:259–265.
38. Niwa T, Takeuchi T, Hino T, Kunou N, Kawashima Y. 1993. Preparations of biodegradable nanospheres of water-soluble and insoluble drugs with D,L lactide/glycolide copolymer by a novel spontaneous emulsification solvent diffusion method, and the drug release behavior. J Control Release 25:89–98.
39. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. 2001. Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release 70:1–20.
40. Göpferich A, Tessmar J. 2002. Polyanhydride degradation and erosion. Adv Drug Deliv Rev 54:911–931.
41. Chasin M, Domb A, Ron E, Mathiowitz E, Langer R, Leong K, Laurencin C, Brem H, Grossman S. 1990. Polyanhydrides as drug delivery systems. Drug Pharm Sci 45:43–70.
42. Higuchi T. 1963. Mechanism of sustained action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 52:1145–1149.
43. Higuchi T. 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. J Pharm Sci 50:874–875.
44. Tatai A, Aigner Z, Eros I, Kata M. 2007. Preparation and investigation of mixtures containing lidocaine base and beta-cyclodextrin. J Inclusion Phenom Macrocyclic Chem 59:105–113.
45. Loo SCJ, Ooi CP, Boey FYC. 2005. Degradation of poly(lactide-co-glycolide) (PLGA) and poly(L-lactide) (PLLA) by electron beam radiation. Biomaterials 26:1359–1367.
46. Klose D, Siepmann F, Elkharraz K, Krenzlin S, Siepmann J. 2006. How porosity and size affect the drug release mechanisms from PLIGA-based microparticles. Int J Pharm 314:198–206.