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Hydrolytic degradation characteristics of irradiated multi-layered PLGA films

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ABSTRACT

Poly(lactide-*co*-glycolide) (PLGA) has been extensively investigated for controlled drug release. Because they undergo bulk degradation, they do not allow for a good controlled-release of drugs. The objective of this study is therefore to understand if a multi-layer-cum-irradiation technique would elicit surface erosion from PLGA polymers. A linear loss of mass and film thinning from PLGA films were observed. Also, the erosion of the top layer, of this multi-layered structure, accelerates degradation of the underlying layers. It is this effect that results in the observed pseudo-surface erosion for irradiated multi-layered PLGA.

The recent focus in local controlled drug release as a non-invasive therapeutic approach has led to strong interests in the use of biodegradable polymers as drug carriers for cardiovascular and ureteric stenting (Zidar et al., 1994; Tamai et al., 2000). Biodegradable polymers, such as poly(lactide-*co*-glycolide) (PLGA), have been extensively investigated because they demonstrate good toxicological safety, tunable biodegradability and desirable mechanical properties (Vert et al., 1992; Athanasiou et al., 1996). Earlier reports have also shown that controlled dosage of electron beam (e-beam) radiation is able to predictably modify the polymer degradation rate by altering the physical properties of polymers through main-chain scission and cross-linking (Loo et al., 2004, 2005a, 2006). 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 is that it undergoes bulk degradation (Wu, 1995). If bulk-degrading PLGA polymers can be made to exhibit surface erosion or layer-by-layer degradation, they would provide a promising control of drug release (Conte et al., 1993; Abdul and Poddar, 2004; Chae et al., 2004; Chen et al., 2005). The objective of this paper is therefore to investigate the degradation characteristics of multi-layered e-beam irradiated PLGA films.

PLGA (Purac Far East, Singapore) was dissolved in dichloromethane (DCM) solvent (E Merck, Germany) at a weight ratio of 1:15. The polymer solution was then cast onto a clean glass substrate using a film applicator and left to dry in a 55 °C vacuum oven for a week. These films (50 ± 5 μm) were irradiated at 5 and 20 Mrad, using the Energy Sciences Inc. Electron Beam Accelerator at an accelerating voltage of 170 kV in atmospheric conditions. The irradiated single layer films were then re-dissolved in DCM. Multi-layered films were prepared by casting three layers; first the bottom layer (0 Mrad), followed by the centre layer (5 Mrad) and finally, the top 20 Mrad layer (Fig. 1), with each layer having the same thickness. The layers were cast by pouring the polymer solution into a clean Petri-dish used as mould. During casting, the underlying layer had to be semi-dried before casting the next layer. The final dry film thickness was approximately 105 ± 5 μm. The bottom layer (0 Mrad) film was then marked with a minute black dot using a water-insoluble marker pen. Films were cut into 2 cm × 2 cm samples for hydrolytic degradation at 37 °C in phosphate-buffered saline solution (PBS). At appropriate time intervals, water uptake and mass loss measurements were conducted.

The Agilent 1100 series Gel Permeation Chromatography (GPC) was used to determine elution times with Reflective Index Detector (RID) as the detector. The calibration was done in accordance to polystyrene standards with a flow rate of 1 ml min^{-1}. Scanning Electron Microscopy (SEM JEOL model JSM 6360) was used to examine the cross-section of the samples. Film thickness measurements were done using the SPOT Basic software v3.4 from the SEM micrographs.

The water uptake, mass loss and molecular weight results from the hydrolytic degradation of the single layer irradiated PLGA films, as part of the experimental control, were consistent with our previous findings (Loo et al., 2005b). Fig. 2 plots the water uptake and mass loss for the PLGA multi-layer film systems, and both

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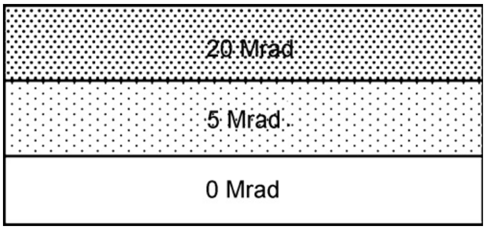

Fig. 1. Schematic diagram of multi-layer PLGA.

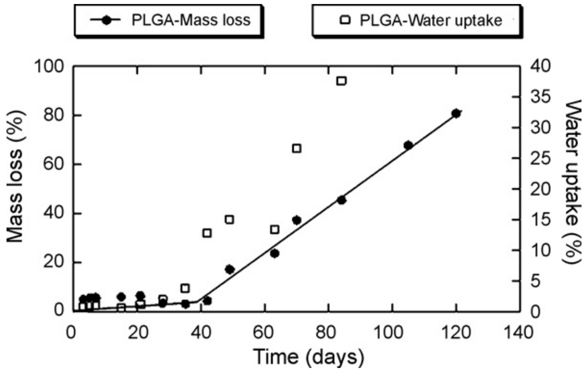

Fig. 2. Plot of water uptake and mass loss for PLGA samples.

parameters increased with time. Rapid mass loss for PLGA occurred after 49 days and subsequently only 20% of polymer mass remained. This onset of rapid mass loss coincides with the onset of mass loss from a 20 Mrad single layer film. Mass loss from multi-layer PLGA can therefore be partly attributed to the dissolution of the 20 Mrad layer. Subsequently, mass loss continues to increase somewhat in a linear fashion, characteristic of degradation by surface erosion.

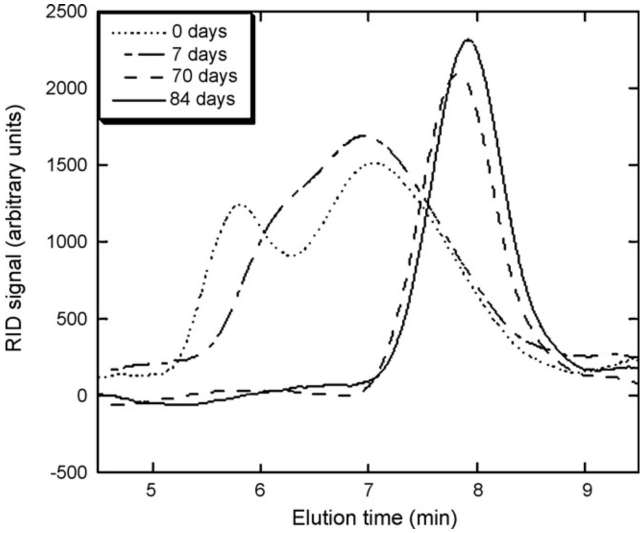

Fig. 3. GPC traces of PLGA at different degradation times.

Fig. 2 shows that approximately 50% mass of multi-layered PLGA was lost after 90 days, although 0 and 5 Mrad single layer films exhibited almost negligible mass loss. Mass loss from 0 and 5 Mrad layers could have contributed to the higher than expected mass loss. As the 20 Mrad layer degrades, hydrophilic oligomers are formed, which increases film hydrophilicity and water uptake (Schliecker et al., 2003). It is postulated that as the 20 Mrad surface begins to degrade, some of these soluble oligomers are leached out, while the remaining fraction of the oligomers diffuses towards the 5 Mrad

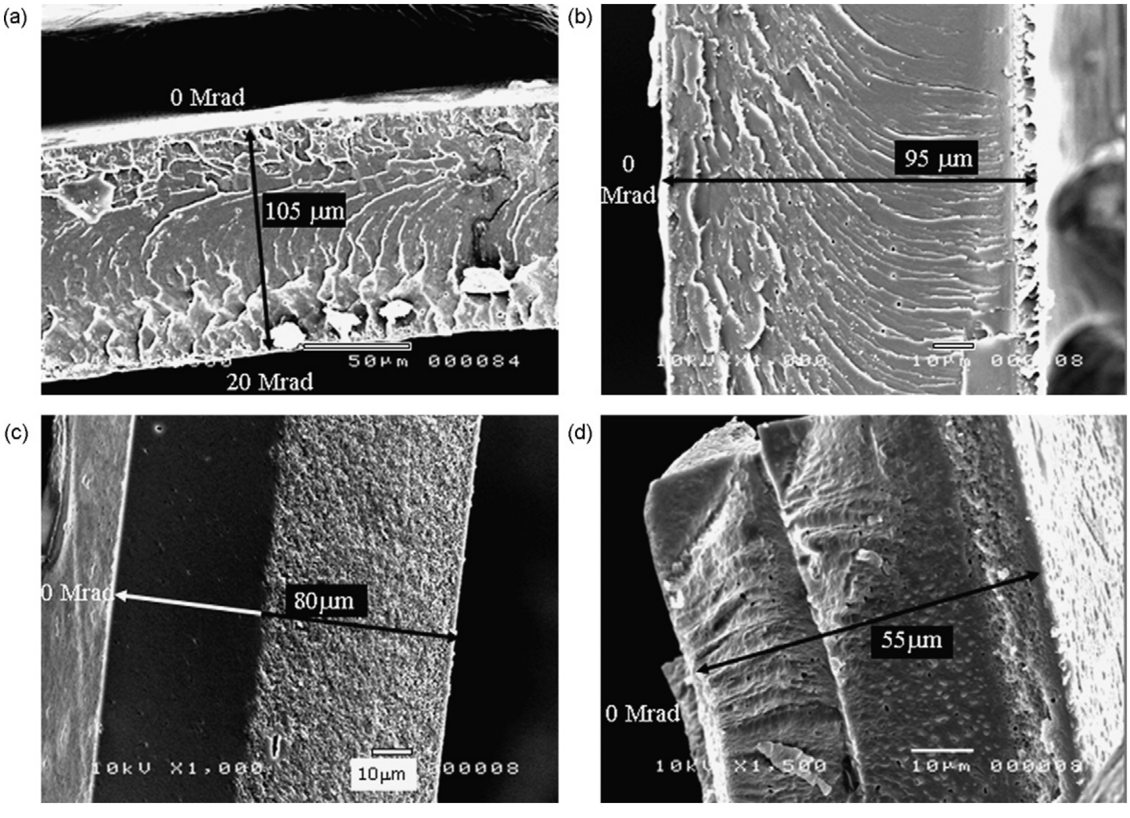

Fig. 4. SEM micrographs of multi-layer PLGA at (a) 0 days, (b) 28 days, (c) 70 days, and (d) 105 days.

layer. These inward migrating oligomers would therefore accelerate hydrolysis in both the 0 and 5 Mrad layers.

The faster degradation of the 0 and 5 Mrad layers can be observed from the GPC (Fig. 3). Before hydrolytic degradation, two main peaks were observed; a broader peak from the irradiated layers (∼7 min) and a narrower peak (5.8 min) from the 0 Mrad layer. After 7 days, a broad peak with a left shoulder was observed, in which this shoulder came from the higher molecular weight layer (0 Mrad). The sudden increase in elution time of the 0 Mrad layer would imply that its molecular weight was decreasing rapidly, resulting in a higher than expected mass loss.

The loss in polymer material can be observed from the SEM micrographs (Fig. 4). The micrographs show that the PLGA matrix did not degrade homogeneously. Rather, from film porosity, polymer degradation was shown to be more severe on the 20 Mrad side of the film. From Fig. 4(b), a thin layer (∼5 mm) of polymer on the 20 Mrad side shows signs of severe degradation. Polymer degradation, resulting in pore formation, was also observed at the centre of the film at 70 days, as shown from Fig. 4(c). Film thickness decreased steadily from 105 to 55 mm.

In conclusion, the multi-layered irradiated PLGA films were observed to degrade by surface erosion. However, unlike the case of a truly surface-eroding polymer where the molecular weight remains constant, molecular weight of these multilayer films decreases with time. These results therefore conclude that a multi-layer-cum-irradiation technique can elicit degradation characteristics reminiscent of surface erosion from PLGA polymers.

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