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FUNDAMENTAL STUDIES ON THE HYDRATION, EROSION AND RELEASE PROPERTIES OF BIODEGRADABLE POLY(ESTERS).

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Background

Synthetic biodegradable poly(esters), in particular the homopolymers and copolymers of lactic and glycolic acids have been used for a variety of medical applications including the controlled release of drugs and biologicals [1]. The mechanism by which drugs are released from these polymers is complex involving both the physico-chemical and morphological properties of the incorporated drug and the polymeric matrix. In view of the large number of publications dealing with the release of drugs from poly(lactide-co-glycolide) matrices surprisingly little is known about the fundamentals of degradation and release. Recent work from our laboratory [2,3] and from Li and Vert [4,5,6] have begun to address some of these important issues.

Materials and Methods

Poly(D,L-lactide-co-glycolide, 50:50) was obtained from Dupont or Birmingham Polymers Inc. (BPI). The Dupont polymer was spray dried and melt pressed into 4 mm diameter pellets weighing approximately 35 mg. The molecular weights of pellets exposed to 150 mM phosphate buffered saline (PBS) were determined by gel permeation chromatography (GPC) at 30°C in $CHCl_3$ using an Ultrasyragel® Linear column. Calibration curves were constructed using polystyrene molecular weight standards ranging from 600 to 104,000. The retention volumes corresponding to the peak maxima in the sample chromatograms were used to calculate the molecular weights of the poly(D,L-lactide-co-glycolide, 50:50) samples. Water loss from hydrated polymer pellets was measured gravimetricly using a Cahn C-31 microbalance.The BPI polymer was dissolved into HPLC grade CH_2Cl_2 (25% w/v) and cast into membranes. The permeability of membranes to tritium labelled water was measured using diffusion cells (Crown Glass) and analyzed by liquid scintillation counting. NMR studies were conducted on a wide-bore Bruker WM 300 NMR spectrometer using magic angle spinning. ^3H-labelled water (2.113 μCi/g H_2O) was obtained from Amersham.

Results and Discussion

Results previously obtained when measuring the effect of surface area/volume, $\Delta\eta$, ΔM_r and release characteristics as a function of time confirmed bulk erosion of poly(lactide-co-glycolide) was taking place. [2] Figure 1 shows the change in relative molecular weight of residual polymer as a function of hydrolysis time. The observation of an immediate and constant decrease in polymer molecular weight supports a bulk erosion degradation mechanism.

Melt-pressed tablets showed a mass increase of almost 20% after exposure to water at 37°C for 15 days. The loss of water from a hydrated tablet as a function of time is shown in Figure 2. The two slopes of this plot suggested the presence of both tightly and loosely bound water in the polymer. The results of a preliminary solid state NMR study on a melt-pressed polymer pellet (low water content), shown in Figure 3, gave additional evidence for the presence of two types of water in the polymer. The area under the broad peak is a measure of the tightly bound water while the area under the sharp peak corresponds to the weakly bound water. Integration of these areas indicates that 98.9% of the water is tightly bound and 1.1% of the water is loosely bound.

To examine water penetration of the polymer, membrane films were cast and placed in diffusion cells. Isotonic PBS was placed on both sides of the membrane. Tritium labelled water was also added to the donor side of the cell. The movement of radioactivity across the membrane and into the receptor chamber was determined as a function of time (Figure 4). These data suggest that either ^3H_2O or $^3H^+$ was able to move through the intact membrane. This movement of label was through the polymer itself and not through pores. These results suggest that the dissolution of water in the polymer plays an important role in poly(ester) biodegradation. The current mechanism of poly(ester) biodegradation does not take the role of dissolved water into account and may need to be revised.

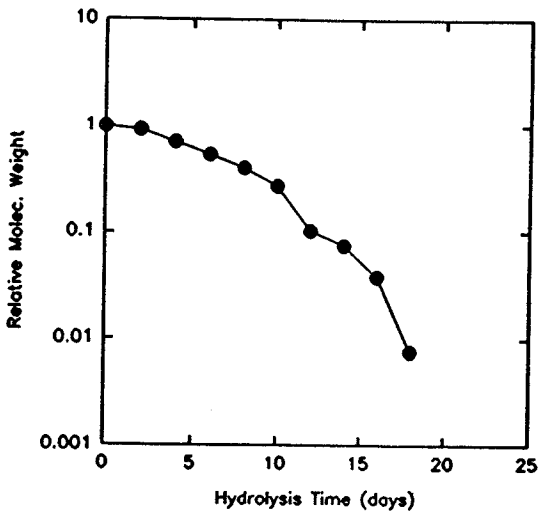

Figure 1. Relative molecular weight of melt-pressed polymer pellets as a function of hydrolysis time.

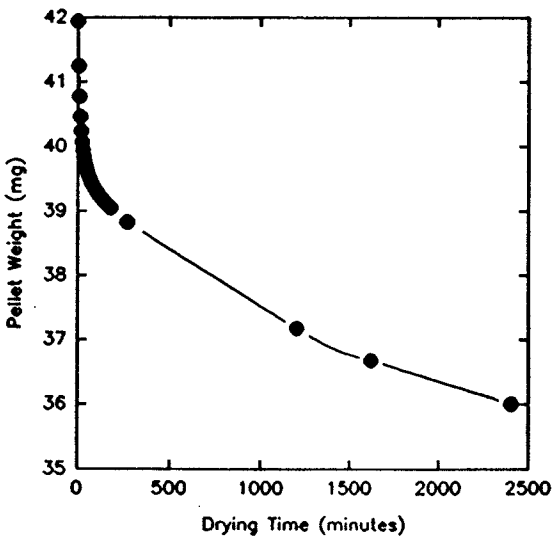

Figure 2. Weight-loss of a hydrated polymer pellet as a function of drying time.

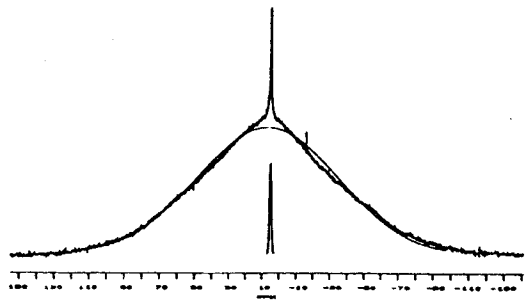

Figure 3. Solid-state NMR of melt-pressed polymer pellet.

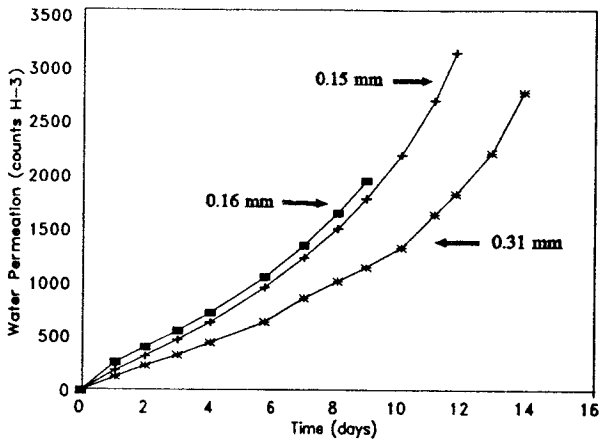

Figure 4. Permeation of tritium through poly(D,L-lactide-co-glycolide, 50:50) membranes at pH 7.2 and 37°C.

Acknowledgement

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References

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