

Degradation and Release Properties of Pellets Fabricated from Three Commercial Poly(D,L-lactide-co-glycolide) Biodegradable Polymers

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Abstract □ Poly(D,L-lactide-co-glycolide, 50:50) samples of similar molecular weight were obtained from three commercial sources and were characterized by gel permeation chromatography, differential scanning calorimetry, X-ray powder diffraction, viscometry, and proton nuclear magnetic resonance spectroscopy. Pellets were prepared by melt-pressing spray-dried polymer with a 4-mm standard concave punch and die set and a thermostated holder of original design. Amaranth (5% w/w) was incorporated in pellets used for release studies. Degradation and release studies were conducted at 37 °C in pH 7.2 phosphate buffered saline. The molecular weights of all polymers were found to decrease continuously after exposure to phosphate buffered saline. All polymers showed two distinct regions of molecular weight decrease. Mass loss experiments for all polymers resulted in sigmoidal curves typical of polymers undergoing bulk hydrolysis. The onset of mass loss (defined as 10% mass loss) was found to differ by as much as 6 days among the three polymers studied. The release studies showed an initial burst of release followed by a period of 15–25 days during which little or no dye was released. A second phase of release followed, lasting ~10 days, until all dye was released. The time at which release began slightly preceded the onset of mass loss.

Synthetic biodegradable polymers have been studied for various applications including the controlled release of drugs and biologicals.^{1–5} Biodegradable polymers often have low toxicity, are not tissue reactive, and do not require surgical removal from the host.¹ Copoly(esters) were chosen for comparison in this study because they are currently used in medical applications, they biodegrade to natural materials of very low toxicity, and they are currently available in large quantities from several commercial sources.^{6–11} Each manufacturer uses proprietary synthetic methods that may employ different catalysts, solvents, and synthetic routes. Different manufacturing conditions may lead to polymers with different processing, degradation, and/or release properties. The purpose of this study was to compare degradation and release characteristics of a water-soluble dye from matrices prepared from poly(D,L-lactide-co-glycolide, 50:50) obtained from three major manufacturers of biodegradable polymers [Dupont, Birmingham Polymers Inc. (BPI), and Henley Chemicals].

Experimental Section

Materials—Poly(D,L-lactide:glycolide, 50:50) copolymers were obtained from Dupont (Medisorb, lot no. S9093S031; Wilmington, DE), Birmingham Polymers (lot no. 051-68-1; Birmingham, AL), and Henley Chemicals, Inc. (RG505, lot no. 640663; Montvale, NJ). All three products were labeled by the manufacturer to have inherent viscosities between 0.5 and 0.8 dL/g. Amaranth (95%) was purchased from Aldrich Chemical Company (Milwaukee, WI). Polystyrene molecular weight (MW) standards (MW 600–104 000) were purchased from Polysciences, Inc. (Warrington, PA). D,L-Lactic acid (lithium salt), glycolic acid, and deuterium oxide (99.9 atom%) were purchased from Sigma Chemical Company (St. Louis, MO). All other chemicals and solvents were of reagent grade or better.

Preparation of Pellets—The polymers dissolved in methylene chloride and amaranth dissolved in water were separately spray dried to form particles of uniform sizes with a Yamato Pulvis Mini-spray GA-32 spray drier (Yamato Scientific Company, Chicago, IL). The details of the spray-drying procedure have been described previously.³ Polymer pellets were prepared by compressing ~35 mg of the spray-dried polymers at 56–57 °C for 1 min with a 4-mm diameter standard concave punch and die set and a thermostated holder. The resulting pellets were ~3.7 mm in diameter and 3.1 mm thick. Polymer pellets containing 5% (w/w) dispersed amaranth were prepared by compressing dry blends of the spray-dried materials. The Dupont and BPI formulations were compressed at 56–57 °C for 1 min, whereas the Henley formulation were compressed at 67 °C for 5 min. A higher temperature and a longer compression time was required to minimize initial rapid release (burst effect) from the Henley formulation.

Polymer Characterization—Polymer MWs were determined by gel permeation chromatography (GPC) at a flow rate of 1.0 mL/min in chloroform at 30 °C with a 7.8 mm (i.d.) × 30 cm Ultrastaygel linear column (Waters, Milford, MA) and a refractive index detector (Shimadzu RID-6A, Tokyo, Japan). Polystyrene MW standards at 0.25% (w/v) in chloroform were used to calibrate the column. Sample concentrations ranged from 0.20 to 0.35 (%w/v) in chloroform. The number-average (M_n) and weight-average (M_w) MWs were calculated from the GPC chromatograms of the native polymers by standard procedures.¹² The M_{GPC} is the MW corresponding to the peak of the GPC chromatogram. The M_{GPC} values were calculated for the native polymers and all samples with a MW of 600 or greater. The intrinsic and inherent viscosities of the polymers at 30 °C in chloroform were determined with a Cannon-Ubbelode viscometer (Cannon, State College, PA). Polymer solutions with concentrations of 0.25, 0.5, and 1.0 g/dL were used for determining viscosities. The 0.5-g/dL solutions were used for calculating inherent viscosities. The glass transition temperatures and melting behavior were determined by differential scanning calorimetry at a scan rate of 10 °C/min with a Perkin-Elmer calorimeter (DSC 7, Perkin Elmer, Wilton, CT) with aluminum sample pans. The glass transition temperature reported was taken at the midpoint of the transition. Crystallinity was determined by X-ray powder diffraction with a Phillips DW1710 diffractometer with PC-APD software operating on an IBM-compatible microcomputer. Copolymer composition was determined by hydrolyzing 100 mg of spray-dried polymer completely in distilled water at 85 °C. The resulting monomer solutions were then lyophilized, and the remaining solid dissolved in D₂O. The proton nuclear magnetic resonance (¹H NMR) spectra of the samples were obtained with a Bruker WM-360 NMR spectrophotometer (Bruker Instruments, Inc., The Woodlands, TX). The ratio of monomers was calculated from a standard curve obtained from the spectral analysis of mixtures of glycolic and D,L-lactic acids.

Degradation and Release Studies—Prewighed pellets were placed in individual screw-topped test tubes containing 10 mL of pH 7.2 phosphate buffered saline. The tubes were then agitated in an incubator shaker (Lab-Line Instruments, Inc., Melrose Park, IL) at 37 °C. At specific sampling times, tubes were removed, and the buffer solution was assayed for dye content by measuring absorbance at 518 nm with a Hewlett-Packard 8450A UV-visible spectrometer (Hewlett-Packard Company, Palo Alto, CA). The pellets were washed with distilled water, dried in a vacuum desiccator for several days, and then weighed to determine the residual polymer mass. The M_{GPC} of

the polymer residue was then determined by GPC with polystyrene standards. Each time point on the plots describing the degradation and release data represents a separate pellet.

Results

Characterization of Polymers—The results of the characterization studies conducted on the three polymers are shown in Table I. The Dupont and BPI polymers have very similar MWs and polydispersities. The Henley polymer had a somewhat higher MW than the other two polymers; however, the polydispersity was approximately the same. Differential scanning calorimetry showed the three polymers had glass transition temperatures between 46.4 and 49.2 °C and showed no melting endotherms, suggesting the amorphous nature of the polymers. The absence of crystallinity was confirmed by powder X-ray diffraction studies. The experimentally determined D,L-lactide:glycolide compositions of the Dupont, Henley, and BPI copolymers were 50:50, 51:49, and 55:45, respectively. Table II shows the polymer data supplied by the individual manufacturers.

Degradation and Release Studies—The MWs of all polymers decreased continuously after being exposed to the phosphate buffered saline solution. Figure 1 shows the decrease in relative MW with time for melt-pressed polymer pellets without incorporated amaranth. Two distinct rates of chain scission were observed. During the first 15 to 20 days (region 1), the BPI and Henley polymers showed approximately the same rate, whereas the Dupont polymer degraded at a slightly faster rate. The second region began after ~10, 14, and 20 days of hydrolysis for Dupont, BPI, and Henley polymers, respectively. The M_{GPC} of the polymers at these times was 17 500, 15 500, and 11 000 for Dupont, BPI, and Henley polymers, respectively. The higher rate in the second region may result from the increased water uptake of the polymers and catalysis by the increased number of carboxylate groups in the polymers. The presence of amaranth dispersed in each polymer formulation did not markedly affect the rate of relative MW decrease (Figure 2). The results of the mass loss experiments for pellets formulated without the incorporation of amaranth show that all polymers give a sigmoidal curve characteristic of bulk hydrolysis (Figure 3). The times at which 10% of the polymer mass was lost were ~19, 23–24, and 24–25 days for Dupont, BPI, and Henley polymers, respectively. The percents of the original polymer mass remaining at the conclusion of the study (47 days) were 20, 26, and 43% for Dupont, BPI, and Henley polymers, respectively.

The release of amaranth and residual polymer matrix mass was determined as a function of time for the Dupont, BPI, and Henley formulations (Figures 4, 5, and 6, respectively). The

Table I—Experimentally Determined Polymer Properties

Property ^a	Source		
	Dupont	BPI	Henley Chemicals
M_{GPC}	68 000	67 000	91 000
M_n	45 000	52 000	77 000
M_w	78 000	89 000	140 000
M_w/M_n	1.76	1.70	1.81
$[\eta]$	0.44	0.43	0.55
$(\ln \eta_r)/c$, dL/g	0.44	0.42	0.54
T_g , °C	46.4	47.3	49.2
Crystallinity	amorphous	amorphous	amorphous
Composition (LA:GA)	50:50	55:45	51:49

^a M_{GPC} , peak MW; M_n , number-average MW; M_w , weight-average MW; M_w/M_n , polydispersity; $[\eta]$, intrinsic viscosity; $(\ln \eta_r)/c$, inherent viscosity at 0.5 g/dL; T_g , glass transition temperature; LA, lactic acid; GA, glycolic acid.

Table II—Polymer Properties Provided by Manufacturers

Property	Source		
	Dupont	BPI	Henley Chemicals
M_n	31 400 ^a	38 900 ^b	44 000 ^c
M_w	69 600 ^a	64 000 ^b	91 000 ^c
M_w/M_n	2.22	1.65	2.06
$(\ln \eta_r)/c$, dL/g	0.8 ^d	0.76 ^e	0.7 ^f
Composition (LA:GA)	49:51	54:46 ^g	51:49 ^g

^a Determined by GPC in CH_2Cl_2 . ^b Determined by GPC in $CHCl_3$ with Waters μ Styragel 500, 10 000, and 100 000 Å columns in series and polystyrene standards. ^c Determined by GPC in $CHCl_3$ with polystyrene standards. ^d Determined in $CHCl_3$ at 30 °C with a Cannon-Fenske viscometer. ^e Determined in hexafluoroisopropanol at 30 °C with a Cannon-Fenske viscometer. ^f Determined in $CHCl_3$ at 25 °C. ^g Determined by ¹H NMR.

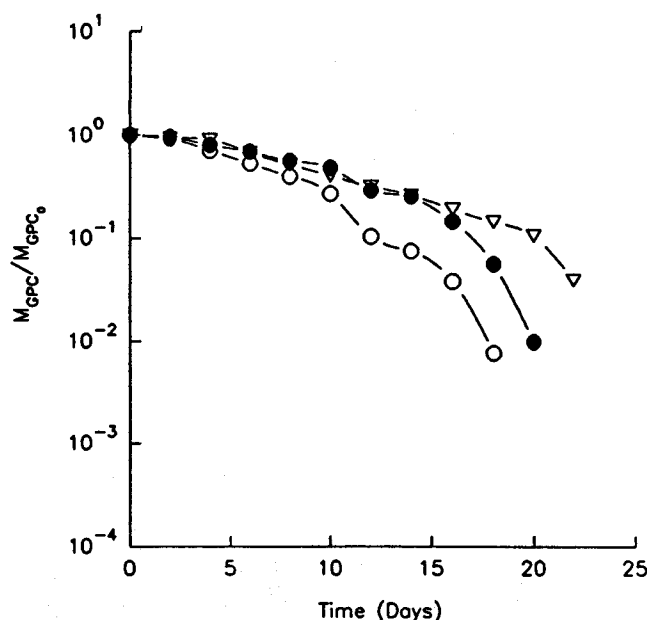


Figure 1— M_{GPC}/M_{GPC0} as a function of time for (○) Dupont, (●) BPI, and (▽) Henley poly(D,L-lactide-co-glycolide, 50:50) formulated as melt-pressed pellets without incorporation of amaranth.

times required for 10% mass loss were 24, 30, and 27 days for the Dupont, BPI, and Henley polymers, respectively. The Dupont and Henley polymers had a M_{GPC} of ~600 at the onset of mass loss. The M_{GPC} of the BPI polymer at the onset of mass loss could not be accurately determined. The time for 10% mass loss from the Henley polymer containing amaranth (requiring a higher formulation temperature and a longer exposure time for melt pressing) was somewhat longer (2–3 days) than the polymer in the absence of amaranth. The Dupont and BPI formulations showed a burst effect of 5–10%, whereas the Henley formulation showed a 15–20% burst effect. The burst effect is due to the dissolution of amaranth particles that were not completely surrounded by polymer. The times at which the second phase of release began (defined as a 10% increase above the burst effect) were ~20, 28 and 24 days for the Dupont, BPI, and Henley formulations, respectively. These times precede the time for 10% matrix mass loss by 2–4 days. The duration of continuous release was ~10 days for each of the formulations.

Discussion

Amaranth is a water-soluble and organic solvent insoluble dye. Studies of polymer films conducted with diffusion cells in

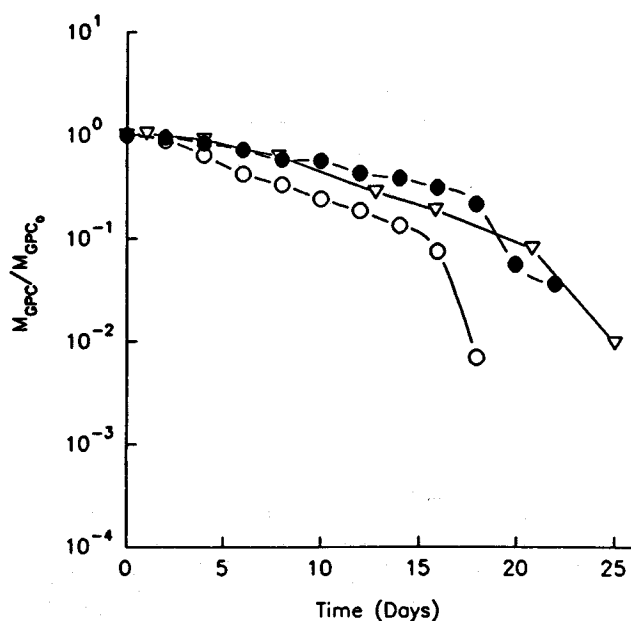


Figure 2— M_{GPC}/M_{GPC0} as a function of time for (○) Dupont, (●) BPI, and (▽) Henley poly(D,L-lactide-co-glycolide, 50:50) formulated as melt-pressed pellets with incorporation of 5% (w/w) amaranth.

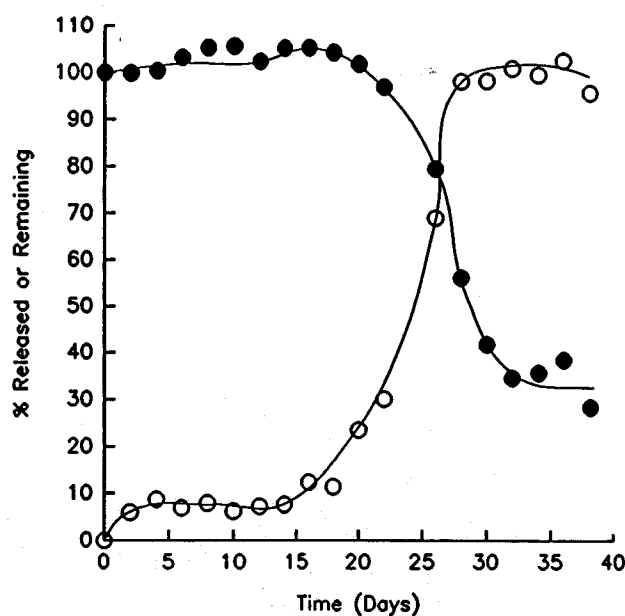


Figure 4—Percent amaranth released (○) and percent polymer remaining (●) as a function of time for melt-pressed pellets employing poly(D,L-lactide-co-glycolide, 50:50) obtained from Dupont.

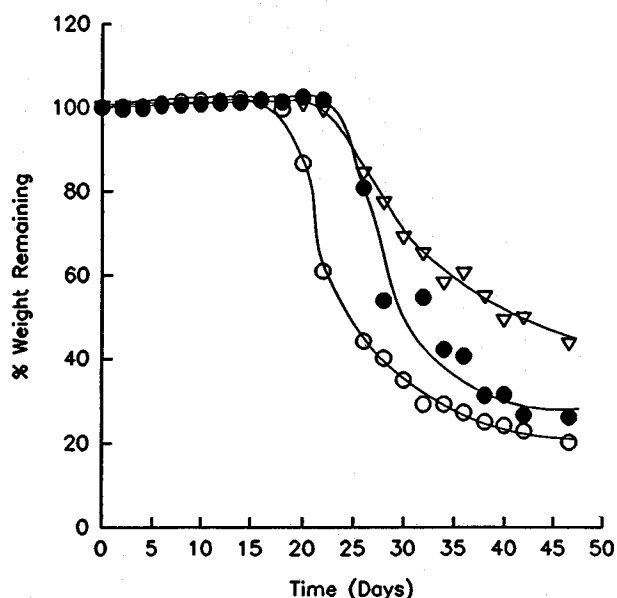


Figure 3—Weight percent of polymer remaining as a function of time for (○) Dupont, (●) BPI, and (▽) Henley poly(D,L-lactide-co-glycolide, 50:50) formulated as compressed pellets without incorporated amaranth.

our laboratory demonstrate that amaranth will not diffuse through poly(D,L-lactide-co-glycolide, 50:50) having a M_{GPC} of $>30\,000$. Thus, the initial release of amaranth from poly(D,L-lactide-co-glycolide) matrices employed in this study will only occur by dissolving in water and diffusing from the surface or through a porous network within the pellet. The second phase of release is probably due to a combination of increased water uptake of the polymer, decreased MW, and the formation of a porous network caused by hydrolysis of the polymer. The onset of the second phase of release appears to slightly precede the onset of polymer matrix mass-loss, suggesting that the dye can diffuse through low MW polymer or that low MW polymers have poor film-forming properties, thus exposing the dispersed dye particles to release medium.

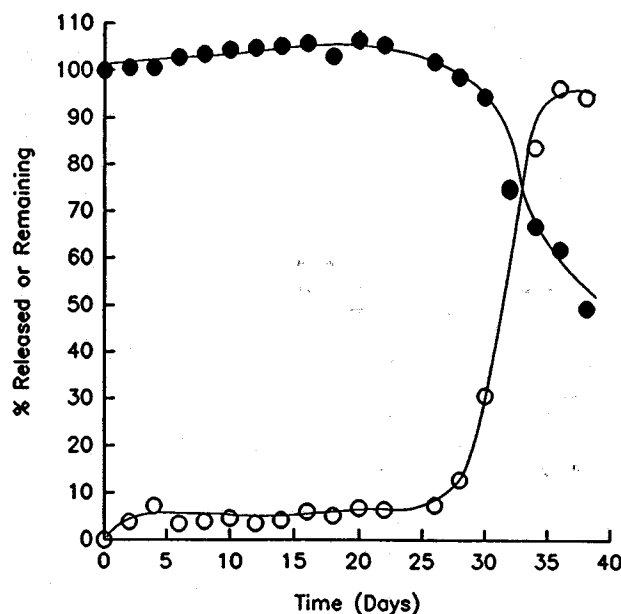


Figure 5—Percent amaranth released (○) and percent polymer remaining (●) as a function of time for melt-pressed pellets employing poly(D,L-lactide-co-glycolide, 50:50) obtained from Birmingham Polymers Inc.

The differences in the release and mass-loss profiles for the three polymer formulations containing dispersed amaranth might be caused by one or more of the following factors: different initial MWs of the polymers, different rates of polymer chain scission, different monomeric compositions, and/or different degrees of randomness (or blockiness) among the copolymers. All of these properties except degree of randomness were measured and compared with the time for 10% mass loss (Figures 4, 5, and 6). The initial M_{GPC} values of the three polymers in the amaranth formulations were 68 000, 67 000, and 64 000 for Dupont, BPI, and Henley polymers, respectively. It is interesting to note that the Henley formulation containing amaranth, requiring a higher

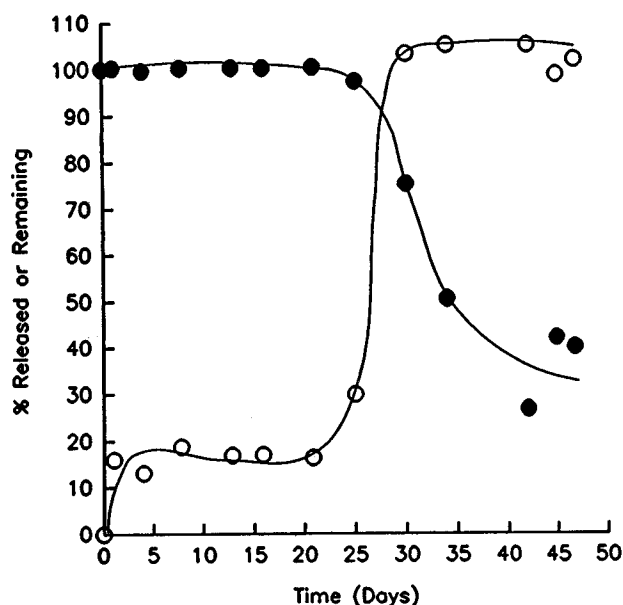


Figure 6—Percent amaranth released (○) and percent polymer remaining (●) as a function of time for melt-pressed pellets employing poly(D,L-lactide-co-glycolide, 50:50) obtained from Henley Chemicals.

temperature and a longer exposure time for effective melt pressing, resulted in a decrease in M_{GPC} from 91 000 to 64 000. Similar reductions in MW during melt processing have been previously reported.¹³ The relative initial rates of chain scission (Figure 2) were Dupont > Henley \approx BPI. The compositions of the polymers as percent lactic acid are 50, 55, and 51% for Dupont, BPI, and Henley polymers, respectively. The times required for 10% mass loss (Figures 4, 5, and 6) were 24 (Dupont), 30 (BPI) and 27 (Henley) days. By comparing the measured polymer properties with the mass loss data we see that the time for mass loss increases with increasing lactic acid content of the copolymer. An increase in the initial rate of chain scission (Figure 2, region 1) results in a decrease in the time required for the onset of mass loss. The randomness of the copolymers, a quantity which is very difficult to measure, may also play a role in the differences observed between the polymers. Another possible cause for the differences observed is the response of the polymers to the processing procedures. Evidence for this is shown by comparing the times for 10% mass loss between the two Henley formulations. The Henley formulation containing amaranth,

which had an initial M_{GPC} of 64 000, had an onset of mass loss 2–3 days later than the formulation without incorporated amaranth, which had an initial M_{GPC} of 91 000. This result is opposite to that expected based on the initial MWs. This is evidence that processing variables may be more important than commonly used chemical properties, such as MW, in determining the hydrolysis and release properties of some biodegradable polymers. In conclusion, this study has shown that the three poly(D,L-lactide-co-glycolide, 50:50) polymers studied, while similar, are not equivalent in hydrolysis or release properties. The time required for 10% mass loss varied by as much as 6 days and the onset of the second phase of release varied by as much as 8 days between polymers of similar MW. This may be the result of small differences in monomeric composition and/or degree of randomness in the copolymer structure. These properties may also affect the processing characteristics of the polymers, which ultimately affects their observed hydrolysis and release properties.

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