Gamma Irradiation Effects on Molecular Weight and *in Vitro* Degradation of Poly(D,L-Lactide-*CO*-Glycolide) Microparticles

Angela G. Hausberger,[1] Richard A. Kenley,[2] and Patrick P. DeLuca[3,4]

Received July 18, 1994; accepted December 14, 1994

Purpose. The objective of the reported work was to quantitatively establish γ-irradiation dose effects on initial molecular weight distributions and *in vitro* degradation rates of a candidate erodible biopolymeric delivery system. ***Methods.*** Poly(D,L-lactide-co-glycolide) (PLGA) porous microparticles were prepared by a phase-separation technique using a 50:50 copolymer with 30,000 nominal molecular weight. The microparticles were subjected to 0, 1.5, 2.5, 3.5, 4.5, and 5.5 Mrad doses of γ-irradiation and examined by size exclusion chromatography (SEC) to determine molecular weight distributions. The samples were subsequently incubated *in vitro* at 37°C in pH 7.4 PBS and removed at timed intervals for gravimetric determinations of mass loss and SEC determinations of molecular weight reduction. ***Results.*** Irradiation reduced initial molecular weight distributions as follows (M_n values shown parenthetically for irradiation doses): 0 Mrad (M_n = 25200 Da), 1.5 Mrad (18700 Da), 2.5 Mrad (17800 Da), 3.5 Mrad (13800 Da), 4.5 Mrad (12900 Da), 5.5 Mrad (11300 Da). *In vitro* degradation showed a lag period prior to zero-order loss of polymer mass. Onset times for mass loss decreased with increasing irradiation dose: 0 Mrad (onset = 3.4 weeks), 1.5 Mrad (2.0 w), 2.5 Mrad (1.5 w), 3.5 Mrad (1.3 w), 4.5 Mrad (1.0 w), 5.5 Mrad (0.8 w). The zero-order mass loss rate was 12%/week, independent of irradiation dose. Onset of erosion corresponded to M_n = 5200 Da, the point where the copolymer becomes appreciably soluble. ***Conclusions.*** The data demonstrated a substantial effect of γ-irradiation on initial molecular weight distribution and onset of mass loss for PLGA, but no effect on rate of mass loss.

KEY WORDS: poly(D,L-lactide-co-glycolide); polyester degradation; gamma irradiation; polymer mass loss.

INTRODUCTION

Bioabsorbable polyesters, such as the lactide and glycolide homo- and copolymers, have been examined extensively as controlled release delivery systems for various drugs, including: contraceptives, chemotherapeutics, narcotic antagonists, antibiotics and proteins (1–7). Results have been promising in many instances. Any parenteral product must be free from harmful microorganisms, and terminal sterilization procedures are preferred over aseptic processing. Presently, the most expedient method for terminally sterilizing moisture- and heat-sensitive substances (including degradable polymers) is ^{60}Co gamma irradiation. Prior studies demonstrate that γ irradiation of bioabsorbable polyesters induces dose-dependent chain scission and concomitant molecular weight loss (8,9). Tice, et al., studied the effects of ^{60}Co irradiation on the average molecular weight (as determined by intrinsic viscosity) of 92:8 poly(D,L-lactide-*co*-glycolide), PLGA. These authors observed that increasing γ irradiation dose decreases the PLGA molecular weight average, and accelerates *in vivo* bioerosion rates in rats (10). However, γ-irradiation effects on PLGA molecular weight distributions and *in vitro* degradation rates have not been suitably established on a quantitative basis. Therefore, the objectives of this paper were twofold, namely, to determine dose-related γ-irradiation effects on: 1) polyester molecular weight distributions and *in vitro* degradation kinetic profiles, and 2) polyester mass loss onset times. The material chosen for study was a microparticulate 50:50 PLGA that has potential drug delivery applications (11).

MATERIALS AND METHODS

Preparation

The microparticles used in the study were prepared by a phase separation technique from PLGA 50:50 with a nominal 30,000 Da molecular weight (Resomer® RG503, Boehringer Ingelheim, Germany). The microparticle diameters ranged from 150 to 500 μm (mean = 300 μm), with surface area = 1.2 m^2/g, and a bulk density = 0.35 g/mL.

^{60}Co Irradiation of the PLGA Microparticles

The microparticles were accurately weighted into 100-mg portions and transferred to individual 20-mL glass screw cap scintillation vials (Research Products International Corporation, Mt. Prospect, IL). The vials were labeled, packed into six cylindrical cardboard cartons (one carton for each radiation dose), and shipped to Nordion International Inc. (Montreal, Canada) for ^{60}Co irradiation. The irradiation doses were 0, 1.5, 2.5, 3.5, 4.5, and 5.5 Mrad, applied at a 2.4-Mrad/hr dose rate with dry ice packs surrounding the samples, since the hydrolytic degradation process is accelerated by heat. This ensured that the temperature did not approach the glass transition of the polymer. Upon return from the irradiation, molecular weight distributions were determined for representative samples at each irradiation dose by size exclusion chromatography (SEC). Remaining samples were then used for *in vitro* degradation analysis.

In Vitro Degradation

Individual vials of microparticles were filled with 10 mL of pH 7.4, 0.2 μm filtered 0.1 M phosphate buffered saline (PBS). The buffer was prepared with distilled water passed through a Milli-Q water system (Millipore, Bedford, MA), using sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, and sodium chloride (all from J. T. Baker Inc., Phillipsburg, NJ). To prevent microbial

[1] Pfizer, Inc., Groton, Connecticut.
[2] Amylin Pharmaceuticals, Inc., San Diego, California.
[3] College of Pharmacy, University of Kentucky, Lexington, Kentucky.
[4] To whom correspondence should be addressed at University of Kentucky, College of Pharmacy, Room 333, Lexington, Kentucky 40536-0082.

0724-8741/95/0600-0851$07.50/0

growth, the PBS contained 0.1% w/v sodium azide (Sigma Chemical Co., St. Louis, MO). The vials were placed in a thermostatted shaking water bath (Precision Scientific Inc., Chicago, IL) that was maintained at 37°C and 60 cycles/min. Duplicate samples were retrieved at timed intervals and the microparticles were filtered, rinsed with distilled water to remove any residual buffer salts, and dried in a vacuum oven for approximately 24 hours at room temperature. The dry microparticles were weighed and analyzed chromatographically for molecular weight distribution and gravimetrically for mass loss.

Molecular Weight Analysis

Average molecular weights and polydispersities of the PLGA microparticles were determined by size exclusion chromatography (SEC). The chromatography system included the following: an M-45 Solvent Delivery System, a 990 Photodiode Array UV Detector, and the Maxima 820 Software with GPC Option, tandem 500 Å and 10^4 Å, 30 × 0.4 cm Ultrastyragel THF columns (all by Waters, Milford, MA); and an SP8780XR Autosampler (Spectra-Physics, Fremont, CA). Detection was at 220 nm. Sample molecular weight averages were determined relative to polystyrene monodisperse standards with molecular weights ranging from 500 to 170,000 Da (Polysciences, Inc., Warrington, PA). HPLC grade THF (Aldrich Chemical Co., Milwaukee, WI), was prefiltered through a 0.5-μm filter, degassed 15 min, and used as mobile phase at 1.0 mL/min. PLGA samples were prepared in THF at 10 mg/mL, gently stirred overnight at room temperature, then filtered through a 0.2-μm polyvinylidene difluoride Gelman Sciences Acrodisc LC13 (Baxter Scientific Products, McGaw Park, IL) using a 13-mm glass syringe. The injection volume was 20 μL, and run times were 22 min. Peak slicing was used to calculate the weight-average and number-average molecular weights, M_w and M_n respectively, and the sample polydispersities, PD (12).

Mass Loss Analysis

Mass loss was determined gravimetrically. Individual sample weights initially and after *in vitro* degradation, m_i and m_t, respectively, were used to calculate %Mass, the percentage of polymer mass remaining after *in vitro* degradation, according to equation (1):

$$\%\text{Mass} = \frac{m_t}{m_i} * 100 \quad (1)$$

where m_i and m_t are, respectively sample weights determined initially and after degradation for time, t.

RESULTS AND DISCUSSION

γ Irradiation Dose Effect on PLGA Initial Molecular Weight Distribution

As expected (8,9), SEC analysis revealed decreasing molecular weight averages and increasing polydispersities with increasing γ irradiation dose. Percentage of initial molecular weight values or each irradiation dose, plotted in Figure 1, indicate that the first 1.5 Mrad of radiation produced the largest drop in molecular weight, specifically a 14% drop in M_w and a 26% drop in M_n, compared with smaller percentage decreases for higher doses. The percentage values also reveal that irradiation decreases M_n more drastically than M_w. For instance, 2.5 Mrad reduced M_n to 70% of its initial value, whereas M_w only decreased to 85%. At 5.5 Mrad, M_n reduced to 45% of the initial value, while M_w maintained approximately 70%. Figure 1 illustrates the more rapid fall of M_n values compared with M_w values. This event is also demonstrated by the increasing polydispersity (PD = M_w/M_n) values with increasing γ irradiation dose (Figure 1), reflective of widening molecular weight distributions. As suggested by Gilding and Reed in their study of irradiation effects on poly(glycolide) sutures (8), this difference between M_n and M_w dependence on γ irradiation dose indicates that the PLGA backbone cleavage proceeds predominantly *via* unzipping the end groups rather than *via* random chain scission (13).

In Vitro Degradation

Mass loss and molecular weight data for the *in vitro* degradation studies are listed in Tables I and II for each γ irradiation dose. The data show that molecular weight averages immediately decreased with increasing incubation time, but that an induction period preceded the onset of mass loss. The observed relative rates of mass loss *versus* molecular weight reduction are consistent with a bulk erosion process rather than surface erosion for the PLGA microparticles. The following paragraphs separately address the γ irradiation effects on molecular weight changes and mass loss.

Mass Loss Results

Figure 2 shows representative % mass remaining *versus* incubation time for 0, 1.5, and 5.5 Mrad γ irradiation doses. In each case, a lag phase (characterized by constant mass) preceded a period of monotonic decrease in polymer mass. The time required to reach 50% of initial mass (t_{50}) decreased with increasing irradiation dose. Thus, t_{50} values were approximately 8 weeks (0 Mrad), 7 weeks (1.5 Mrad), 6 weeks (2.5 and 3.5 Mrad), and 5 weeks (4.5 and 5.5 Mrad).

The mass loss phase adheres to pseudo-zero-order kinetics according to the following equation (2):

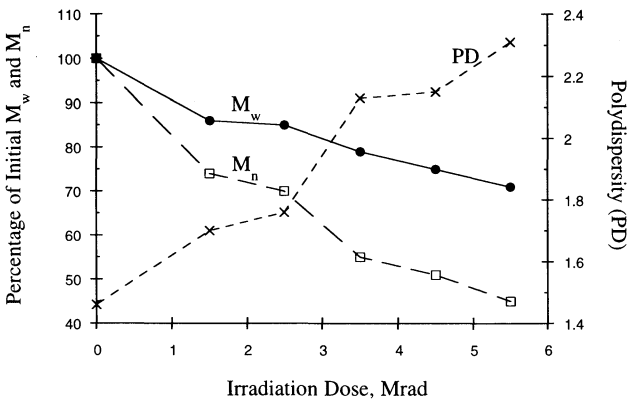

Fig. 1. Effect of Gamma Irradiation on PLGA Microparticle Molecular Weight Averages and Distributions.

Table I. *In Vitro* Degradation Results for PLGA Microparticles γ-Irradiated at Doses from 0 Mrad to 2.5 Mrad

Storage Interval Weeks	0 Mrad				1.5 Mrad				2.5 Mrad			
	Mass Left[a] % Initial	Mw Da	Mn Da	# Bonds Cleaved[b] X	Mass Left[a] % Initial	Mw Da	Mn Da	# Bonds Cleaved[b] X	Mass Left[a] % Initial	Mw Da	Mn Da	# Bonds Cleaved[b] X
0	100	36900	25300	0	100	31800	18600	0	100	31300	17800	0
0.43	99	36600	21600	0.21	99	31600	14700	0.26	99	27300	15600	0.21
1.0	99	30400	16500	0.53	98	25000	13100	0.42	98	21200	10200	0.74
2.3	99	21900	9200	1.8	98	13700	6300	2.0	97	10000	4700	2.8
3.0	98	16200	7100	2.6	93	8800	4200	3.4	86	7500	3800	3.7
4.0	93	9300	4600	4.5	73	7900	4600	3.1	67	7400	3900	3.6
5.0	80	7900	4200	5.0	67	6700	3900	3.8	60	6300	3700	3.8
6.0	65	6900	4000	5.3	52	6200	3700	4.0	42	5700	3500	4.1
7.0	57	6100	3100	7.2	42	5600	3600	4.2	37	5000	3400	4.2
8.0	46	5900	3600	6.0	30	4400	3000	5.3	25	3600	2600	5.9
10	19	2700	2000	12	11	2400	2000	8.3	10	2300	2000	8.0
12	8.7	1900	1400	17	4.2	1700	1200	14	3.1	1600	1000	17

[a] At 37°C, pH 7.4 phosphate buffer.
[b] Represents number of macromolecular bonds cleaved calculated according to equation 4.

$$\% \text{ Mass Remaining} = \text{intercept} - k_{obs} * t \quad (2)$$

where k_{obs} is the pseudo-zero-order rate constant for copolymer mas erosion (in %/week), and t is the incubation interval (in weeks) at pH 7.4 and 37°C.

Table III summarizes k_{obs} values, and shows that k_{obs} remained essentially invariant of γ irradiation dose (mean k_{obs} = 11.9 %/week).

Specific onset times, t_{on}, for mass loss for each sample were calculated from equation (3):

$$t_{on} = (-100 + \text{Intercept})/k_{obs} \quad (3)$$

where k_{obs} and intercept values are from equation (2) and substituting 100% for the mass remaining at erosion onset. Computed t_{on} values, shown in Table III, decrease with increasing γ irradiation dose. A semilogarithmic plot of the t_{on} values as a function of γ irradiation dose is linear (R^2 = 0.978) and therefore could assist in predicting t_{on} for similar polyesters exposed to γ irradiation doses less than 5.5 Mrad. As noted below, PLGA microparticles become soluble (and erosion ensues) when the average copolymer molecular weight of the measured insoluble portion of copolymer reduces to approximately 5200 Da. Note that the soluble fractions of copolymer, expected to have appreciably lower molecular weights than 5200 Da, were not averaged into this value. The inverse dependence of onset times on γ irradiation dose thus correlates with the reduced initial molecular weight values observed (Table I) for higher γ doses. Lower starting molecular weight averages correspond necessarily to shorter *in vitro* incubation intervals required to reach soluble molecular weights.

Molecular Weight Average Results

Both number-average and weight-average molecular weights decreased monotonically with increasing *in vitro* in-

Table II. *In Vitro* Degradation Results for PLGA Microparticles γ-Irradiated at Doses from 3.5 Mrad to 5.5 Mrad

Storage Interval Weeks	3.5 Mrad				4.5 Mrad				5.5 Mrad			
	Mass Left[a] % Initial	Mw Da	Mn Da	# Bonds Cleaved[b] X	Mass Left[a] % Initial	Mw Da	Mn Da	# Bonds Cleaved[b] X	Mass Left[a] % Initial	Mw Da	Mn Da	# Bonds Cleaved[b] X
0	100	29300	13800	0	100	27900	13000	0	100	26100	11300	0
0.43	99	24800	12900	0.06	99	24200	11200	0.16	98	21600	10100	0.12
1.0	98	18200	7500	0.83	99	17600	9800	0.32	99	16400	8500	0.34
2.0	—	—	—	—	96	9100	4900	1.7	96	8700	4700	1.4
2.3	93	8600	4200	2.3	—	—	—	—	—	—	—	—
3.0	79	7100	3600	2.8	78	6400	3300	3.0	78	6200	3100	2.7
4.0	62	7000	3800	2.6	63	6100	3000	3.4	60	5800	2900	2.9
5.0	55	6100	3500	3.0	49	4100	2400	4.4	46	4300	2600	3.4
6.0	39	5200	3300	3.2	40	3900	2300	4.5	39	3000	1900	4.9
7.0	32	4200	2500	4.6	—	—	—	—	—	—	—	—
8.0	23	3200	2400	4.7	16	2100	1700	6.6	16	2200	1700	5.6
10	7.4	2100	1800	6.5	7.4	1500	1200	9.9	5.2	1400	1100	8.9
12	2.2	1300	800	16	2.6	NA[c]	NA[c]	NA[c]	1.7	NA[c]	NA[c]	NA[c]

[a] At 37°C, pH 7.4 phosphate buffer.
[b] Represents number of macromolecular bonds cleaved calculated according to equation 4.
[c] Insufficient material remained for analysis.

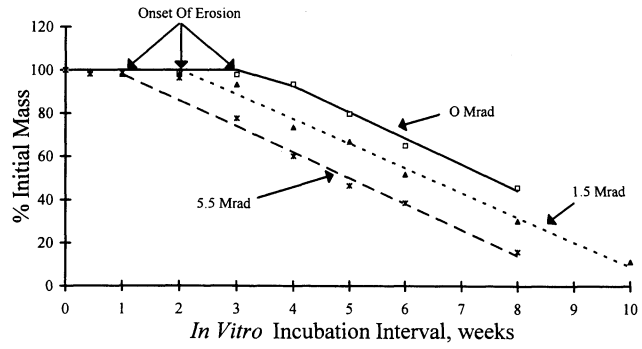

Fig. 2. The Effect of Gamma Irradiation Dose on *In Vitro* Mass Loss of PLGA Microparticles.

cubation intervals. Figure 3 shows representative M_n and M_w data for the PLGA microparticles receiving a 0 Mrad γ irradiation dose. The molecular weight decreases changed rapidly initially, but molecular weight reduction slowed at longer incubation intervals. The break in molecular weight reduction rates occurred approximately at the onset time for PLGA mass erosion. Presumably, after erosion onset, low molecular weight fragments become soluble, diffuse into the reaction medium and become unavailable for SEC analysis of molecular weight on retrieved samples (see Methods and Materials section).

The proposed mechanism for PLGA degradation in aqueous buffer is random chain scission due to hydrolytic cleavage of ester bonds in the polymer backbone (14–17). Note that M_w decreased faster than M_n, supporting the random chain scission as the mechanism for hydrolytic copolymer degradation. Here (in contrast to proposed unzipping mechanism for γ-induced molecular weight reduction), a faster rate of M_w decrease compared to M_n decrease signifies breaking of the large chains at random points creating smaller chains which are on the average larger than oligomers and monomers.

Bond Cleavage Results

The number of bond cleavages (X) per initial number-average molecule was calculated by a model developed by

Table III. Effect of γ Irradiation on Kinetic Constants of PLGA Microparticles Incubated at 37°C and pH 7.4

γ Irradiation Dose (Mrad)	Intercept (%)	k_{obs}[a] %/week	±95% CI	R^2	t_{on}[b] weeks
0	141	12.1	1.2	0.995	3.36
1.5	123	11.4	1.4	0.989	2.00
2.5	118	11.8	2.6	0.976	1.52
3.5	115	12.1	2.2	0.976	1.27
4.5	113	12.2	1.8	0.993	1.04
5.5	110	12.0	2.7	0.985	0.83
Mean (%RSD)		11.9 (2.5%)			

[a] Calculated according to equation (2).
[b] Calculated according to equation (3).

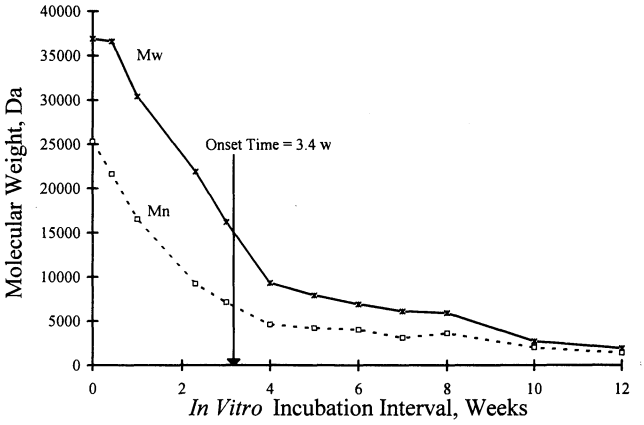

Fig. 3. *In Vitro* Molecular Weight Breakdown for PLGA Microparticles Receiving 0 Mrad Gamma Irradiation.

Inokuti (17,18) for polymers undergoing random chain scission, represented by equation (4):

$$\frac{[M_n]_t}{[M_n]_0} = \frac{1}{1 + X} \tag{4}$$

where: $[M_n]_t$ indicates the number-average molecular weight at incubation time t, and $[M_n]_0$ is the number-average molecular weight prior to *in vitro* incubation.

Values for X are listed in Tables I and II. Figure 4 is a representative plot of ln(X) *versus in vitro* incubation interval for PLGA microparticles receiving a 0 Mrad irradiation dose. The plot shows biphasic kinetics with one linear region prior to, and one linear region after erosion onset. As noted above, coincident with erosion onset, low molecular weight copolymer fractions dissolve into the buffer and therefore are not accounted for in the SEC analysis. This results in a reduced apparent detectable bond cleavage rate.

We treated the bond cleavage data according to pseudo-first-order kinetics for the pre- and post-onset regimes according to equations (5) and (6):

$$\ln(X) = k_1 * t - Int_1 \tag{5}$$
$$\ln(X) = k_2 * t - Int_2 \tag{6}$$

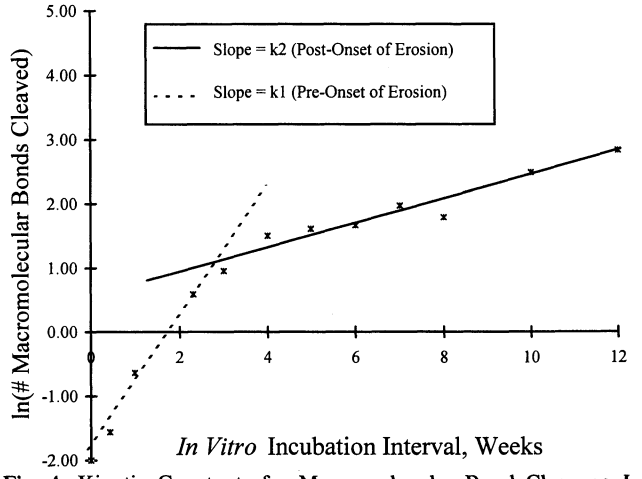

Fig. 4. Kinetic Constants for Macromolecular Bond Cleavage *In Vitro* of PLGA Microparticles Receiving 0 Mrad Gamma Irradiation. x = observed values.

Table IV. Effect of γ Irradiation on Kinetic Constants for Macromolecular Bond Cleavage of PLGA Microparticles Incubated at 37°C and pH 7.4

γ Irradiation Dose (Mrad)	Kinetic constants for pre-onset bond cleavage[a] Int$_1$	k_1 (weeks^{-1})	k_1 ± 95% CI	R^2	Kinetic constants for post-onset bond cleavage[a] Int$_2$	k_2 (weeks^{-1})	k_2 ± 95% CI	R^2	Mn Initial (Da)	Mn at t_{on}[c] (Da)
0.00	−1.79	0.97	0.51	0.970	0.610	0.18	0.074	0.920	25300	6020
1.50	−1.82	1.0	0.25	0.994	0.200	0.20	0.061	0.951	18600	6300
2.50	−1.71	1.1	0.85	0.939	0.129	0.21	0.076	0.937	17800	6440
3.50	−2.52	1.3	2.1	0.783	0.126	0.22	0.085	0.930	13800	5680
4.50	−2.25	1.2	0.74	0.961	0.560	0.17	0.090	0.970	13000	3430
5.50	−2.42	1.2	0.74	0.962	0.420	0.17	0.13	0.939	11300	3280
Mean		1.1				0.19				5200
(%RSD)		(11%)				(11%)				(28%)

[a] Calculated from equation (5) using data points prior to onset of mass erosion (see Table III for onset times).
[b] Calculated from equation (6) using data points prior to onset of mass erosion (see Table III for onset times).
[c] Calculated from equation (7).

where the subscripts 1 and 2, respectively refer to kinetic regimes occurring before and after mass loss erosion onset. In equation (5) k_1 represents the pseudo-first-order rate constant for copolymer hydrolytic bond cleavage and k_2 is a composite value reflecting competing hydrolysis and erosion pathways for apparent molecular weight average changes.

Least-squares linear regression of ln(X) *versus in vitro* incubation interval according to equations (5) and (6) gave the k_1 and k_2 values shown in Table IV. Values for k_1 were essentially invariant with γ irradiation dose and averaged 1.1 weeks^{-1}. Similarly, k_2 values were essentially invariant with γ irradiation dose and averaged 0.19 weeks^{-1}.

Equations (4), (5) and (6) can be combined to estimate the molecular weight at which the PLGA copolymer becomes soluble. Thus, assuming that t_{on} corresponds to the intersection of equations (5) and (6), subtracting the two equations, combining with equation (4) and rearranging gives equation (7):

$$M_n \text{ at Erosion Onset} = [M_n]_0/\{+ \exp[\text{Int}_2 + k_2 * (\text{Int}_1 - \text{Int}_2)/(k_2 - k_1)]\} \quad (7)$$

Table IV shows M_n values calculated for erosion onset from equation (7) and indicates that, on average, the PLGA copolymer studies becomes soluble when M_n of the insoluble copolymer portion reaches approximately 5200 Da.

Finally, it is useful to compare the current results with those of Kenley (17). These authors studied *in vitro* erosion and molecular weight breakdown from a non-irradiated 50:50 PLGA (M_n = 17.8 kDa and M_w = 28.8 kDa) sample pressed into a 3 × 7 mm cylindrical rod. For this sample, erosion onset occurred at 3.0 w (compared with t_{on} = 3.36 w in the current work). Also, the cylindrical sample showed k_1 = 1.32w^{-1} (versus k_1 = 0.97w^{-1} in the current work). The same authors reported an M_n for erosion onset erosion of 2.3 kDa versus 5.3 kDa in the current work. The agreement between the two studies seems acceptable and small differences in M_n at onset and k_1 values are probably due to differences in the polymer samples used. Although both studies used 50:50 PLGA samples, the initial molecular weight distributions were slightly different and there may also have been differences in comonomer randomness between the two studies.

CONCLUSIONS

The knowledge of the effect that γ irradiation has on the long-term degradation behavior of PLGA polymers is of utmost importance in development of a terminally sterilized and reliable PLGA drug delivery system. If the irradiation dose may be varied without sacrificing sterility, use of the relationship between t_{on} and irradiation dose will eliminate guess work and lower costs and time required in selection of an appropriate dose to achieve a desired t_{on}.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dr. B. C. Thanoo for his helpful suggestions concerning this research.

REFERENCES

1. D. H. Lewis. Controlled Release of Bioactive Agents From Lactide/Glycolide Polymers. In M. Chasin and R. Langer (eds.). *Biodegradable Polymers as Drug Delivery Systems,* Marcel Dekker Inc., New York. 1990, pp 1–41.
2. R. G. Sinclair. Glycolide and Lactide Copolymers for Slow Release of Chemotherapeutic Agents. *5th International Symposium on Controlled Release of Bioactive Materials,* Gaithersburg, MD. Aug. 14–16, 1978.
3. G. Spenlehauer, M. Vert, J. P. Benoit, F. Chabot, and M. Veillard. Biodegradable Cisplatin Microspheres Prepared by the Solvent Evaporation Method: Morphology and Characteristics. *J. Control. Rel.* 7:217–229 (1988).
4. C. G. Pitt, M. M. Gratzl, A. R. Jeffcoat, R. Zweidinger, and A. Schindler. Sustained Drug Delivery Systems II: Factors Affecting Release Rates From Poly(E-caprolactone) and Related Biodegradable Polyesters. *J. Pharm. Sci.* 68:1534–1538 (1979).
5. Y. Cha, and C. G. Pitt. The Acceleration of Degradation-Controlled Drug Delivery from Polyester Microspheres. *J. Control. Rel.* 8:259–265 (1989).
6. S. Yolles, and M. F. Sartori. Degradable Polymers for Sustained Drug Release. In R. L. Juliano (ed.). *Drug Delivery Systems,* University Press, London. 1980, p. 84.
7. R. Bodmeier, K. H. Oh, and H. Chen. The Effect of the Addition of Low Molecular Weight Poly(D,L-lactide) on Drug Re-

lease from Biodegradable Poly(D,L-lactide) Drug Delivery Systems. *Int. J. Pharm.* **51**:1–8 (1989).

8. D. K. Gilding, A. M. Reed. Biodegradable Polymers for Use in Surgery-Poly(glycolic)/Poly(lactic acid) Homo- and Copolymers: 1. *Polymer.* **20**:1459–1464 (1979).
9. M. C. Gupta, and V. G. Deshmukh. Radiation Effects on Poly-(lactic acid). *Polymer.* **24**:827–830 (1983).
10. T. R. Tice, D. H. Lewis, R. L. Dunn, W. E. Meyers, R. A. Casper, and D. R. Cowsar. Biodegradation of Microcapsules and Biomedical Devices Prepared with Resorbable Polyesters. *Proc. Int. Symp. Control. Rel. Bioact. Mater.* **9**:21 (1982).
11. R. C. Mehta, R. Jeyanthi, S. Calis, B. C. Thanoo, K. W. Burton, and P. P. DeLuca. Biodegradable Microspheres as Depot System for Parenteral Delivery of Peptide Drugs. *J. Control. Rel.* **29**:375–384 (1994).
12. W. W. You, J. J. Kirkland, and D. D. Bly. *Modern Size Exclusion Chromatography,* Wiley-Interscience, New York, 1978.
13. J. E. Wilson. *Radiation Chemistry of Monomers, Polymers, and Plastics,* Marcel Dekker Inc., New York, 1974, p. 374.
14. R. W. Baker. *Controlled Release of Biolocally Active Agents,* Wiley Interscience, New York, 1987, pp. 84–131.
15. H. Fukuzaki, M. Yoshida, M. Asano, M. Kumakura, T. Mashimo, H. Yuasa, K. Imai, and H. Yamanaka. *In Vivo* Characteristics of High Molecular Weight Copoly(L-lactide/glycolide) with S-Type Degradation Pattern for Application in Drug Delivery Systems. *Biomaterials.* **12**:433–437 (1991).
16. A. M. Reed, and D. K. Gilding. Biodegradable Polymers for use in Surgery–Poly(glycolic)/Poly(lactic acid) Homo- and Copolymers: 2. *In Vitro* Degradation. *Polymer.* **22**:494–498 (1981).
17. R. A. Kenley, M. O. Lee, T. R. Mahoney II, L. M. Sanders. Poly(lactide-co-glycolide) Decomposition Kinetics *In Vivo* and *In Vitro*. *Macromolecules.* **20**:2398–2403 (1987).
18. M. Inokuti. Weight-Average and Z-Average Degree of Polymerization for Polymers Undergoing Random Scission. *J. Chem. Phys.* **38**:1174–1178 (1963).