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

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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 erodable 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 (Mw values shown parenthetically for irradiation doses): 0 Mrad (Mw = 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 Mw = 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 polymers, 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 60Co gamma irradiation. Prior studies demonstrate that γ-irradiation of bioabsorbable polymers induces dose-dependent chain scission and concomitant molecular weight loss (8,9). Tice, et al., studied the effects of 60Co 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 m²/g, and a bulk density = 0.35 g/mL.

60Co 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 60Co 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 hydrolitic 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...
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 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, Mw and Mn, respectively, and the sample polydispersities, PD (12).

**Mass Loss Analysis**

Mass loss was determined gravimetrically. Individual sample weights initially and after in vitro degradation, m0 and m, respectively, were used to calculate %Mass, the percentage of polymer mass remaining after in vitro degradation, according to equation (1):

\[
\text{%Mass} = \frac{m_0}{m_i} \times 100
\]  

where m0 and mi 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 Mw and a 26% drop in Mn, compared with smaller percentage decreases for higher doses. The percentage values also reveal that irradiation decreases Mn more drastically than Mw. For instance, 2.5 Mrad reduced Mn to 70% of its initial value, whereas Mw only decreased to 85%. At 5.5 Mrad, Mn reduced to 45% of the initial value, while Mw maintained approximately 70%. Figure 1 illustrates the more rapid fall of Mw values compared with Mn values. This event is also demonstrated by the increasing polydispersity (PD = Mw/Mn) 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 Mn and Mw 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 (t50) decreased with increasing irradiation dose. Thus, t50 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):
Gamma Irradiation Effects

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

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<th>Storage Interval Weeks</th>
<th>Mass Left% Initial</th>
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<th>Mn Da</th>
<th>% Cleaved Bonds</th>
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<th>Mass Left% Initial</th>
<th>Mw Da</th>
<th>Mn Da</th>
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* At 37°C, pH 7.4 phosphate buffer.

% Mass Remaining = intercept - kobs * t (2)

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

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

Specific onset times, ton, for mass loss for each sample were calculated from equation (3):

\[ t_{on} = \frac{(-100 + \text{Intercept})}{k_{obs}} \] (3)

where kobs and intercept values are from equation (2) and substituting 100% for the mass remaining at erosion onset. Computed ton values, shown in Table III, decrease with increasing γ irradiation dose. A semilogarithmic plot of the ton values as a function of γ irradiation dose is linear (R² = 0.978) and therefore could assist in predicting ton 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

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* At 37°C, pH 7.4 phosphate buffer.

b Represents number of macromolecular bonds cleaved calculated according to equation 4.

Insufficient material remained for analysis.
cubation intervals. Figure 3 shows representative $M_n$ and $M_w$ data for the PLGA microparticles receiving a 0 Mrad $\gamma$ 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 $\gamma$-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 Inokuti (17, 18) for polymers undergoing random chain scission, represented by equation (4):

$$\frac{[M_n(t)]}{[M_{n0}]} = \frac{1}{1 + X}$$  \hspace{1cm} (4)

where: $[M_n(t)]$ indicates the number-average molecular weight at incubation time $t$, and $[M_{n0}]$ 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):

$$\ln(X) = k_1 \cdot t - \text{Int}_1$$ \hspace{1cm} (5)

$$\ln(X) = k_2 \cdot t - \text{Int}_2$$ \hspace{1cm} (6)

**Table III. Effect of $\gamma$ Irradiation on Kinetic Constants of PLGA Microparticles Incubated at 37°C and pH 7.4**

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<tr>
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<tr>
<td>Mean</td>
<td>11.9</td>
<td></td>
<td>(2.5%)</td>
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</tr>
</tbody>
</table>

$^a$ Calculated according to equation (2).

$^b$ Calculated according to equation (3).
Similarly, the $k_2$ values were essentially invariant with $k_1$ and $k_2$ values shown in Table IV. Values for $k_1$ were essentially invariant with irradiation dose and averaged 1.1 weeks$^{-1}$. Similarly, $k_2$ values were essentially invariant with 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):

$$M_n \text{ at Erosion Onset} = \frac{[M_n]_0}{\left(1 + \exp[\ln(t_2) + k_2 * (t_0 - \ln(t_2))/(k_2 - k_1)]\right)}$$  \hspace{1cm} (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 $3 \times 7$ mm cylindrical rod. For this sample, erosion occurred at 3.0 w (compared with $t_{on} = 3.36$ w in the current work). Also, the cylindrical sample showed $k_1 = 1.32$ w$^{-1}$ (versus $k_1 = 0.97$ w$^{-1}$ 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 $\gamma$ 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 $t_{on}$.

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