In vitro degradation and erosion behavior of commercial PLGAs used for controlled drug delivery

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Abstract
Copolymers of lactic (or lactide) and glycolic (or glycolide) acids (PLGAs) are among the most commonly used materials in biomedical applications, such as parenteral controlled drug delivery, due to their biocompatibility, predictable degradation rate, and ease of processing. Besides manufacturing variables of drug delivery vehicles, changes in PLGA raw material properties can affect product behavior. Accordingly, an in-depth understanding of polymer-related “critical quality attributes” can improve selection and predictability of PLGA performance. Here, we selected 19 different PLGAs from five manufacturers to form drug-free films, submillimeter implants, and microspheres and evaluated differences in their water uptake, degradation, and erosion during in vitro incubation as a function of L/G ratio, polymerization method, molecular weight, end-capping, and geometry. Uncapped PLGA 50/50 films from different manufacturers with similar molecular weights and higher glycolic unit blockiness and/or block length values showed faster initial degradation rates. Geometrically, larger implants of 75/25, uncapped PLGA showed higher water uptake and faster degradation rates in the first week compared to microspheres of the same polymers, likely due to enhanced effects of acid-catalyzed degradation from PLGA acidic byproducts unable to escape as efficiently from larger geometries. Manufacturer differences such as increased residual monomer appeared to increase water uptake and degradation in uncapped 50/50 PLGA films and poly(lactide) implants. This dataset of different polymer manufacturers could be useful in selecting desired PLGAs for controlled release applications or comparing differences in behavior during product development, and these techniques to further compare differences in less reported properties such as sequence distribution may be useful for future analyses of PLGA performance in drug delivery.

Keywords PLGA · Controlled drug release · Long-term drug release · Polymer in vitro behavior

Introduction
Copolymers of lactic (or lactide) and glycolic (or glycolide) acids (PLGAs) are the most commonly investigated biodegradable polymers to achieve long-acting release for a variety of drugs, such as small molecules, peptides, and proteins due to their well-known biocompatibility and ease of processing into numerous distinct formulations such as micron-scale particulate systems and larger implantable devices [1]. There are currently 19 US FDA-approved drug products that use PLGA to achieve controlled release from weeks to months [1]. Despite patent expirations for many of these medications, there are no generics available due to the significant complexity of the formulation, such as a lack of understanding of the effects of raw material properties and manufacturing variables on product performance [2].

Drug encapsulated in PLGA is typically released from the formulation through a combination of mechanisms, including diffusion through the polymer matrix or water-filled pores, osmotically induced events (swelling and pore-formation), and/or erosion of the polymer itself [3]. Polymer pore closure and drug-polymer interactions have also
been shown to influence drug release in certain formulations [4–6]. The main events of drug release begin with an initial water uptake followed by polymer degradation, or a decline of the polymer molecular weight; eventually, the polymer molecular weight reduces enough (to ~1 kDa or lower) that the chains become water-soluble oligomers and monomers inducing mass loss and diffusion out of the polymer vehicle [7]. The rate and extent to which these events occur can be affected by changing various properties of the polymer, the main ones being the molecular weight, L/G ratio, and polymer end-capping (and polymer crystallinity if PLGA is semi-crystalline, although rare). Decreasing the polymer chain molecular weight results in increased hydration and chain mobility which can increase the rate of polymer degradation and subsequent mass loss [8]. Elevating the L/G ratio decreases the rate of degradation and erosion because lactic units are more hydrophobic and sterically hindered to hydrolysis. Polymers with uncapped end groups have a higher rate of hydrolysis compared to those with aliphatic ester capped end groups due to increased water uptake and auto-catalysis [9].

PLGA is most commonly synthesized by two methods, direct condensation of the acid monomers, or ring-opening polymerization (ROP) of the cyclic dimers, namely lactide and glycolide [10, 11]. Direct condensation, or polycondensation, of the two acid monomers, lactic and glycolic acid, is in competition with the depolymerization into the dimers due to the generation of water in the reaction which requires elevated temperatures with high vacuum to control resulting in a difficulty to obtain higher molecular weight polymers [12]. Herein, we predominantly investigated polymers synthesized by ROP, the most commonly used method for commercial PLA/PLGA synthesis, except for Wako® 7515 which uses polycondensation. ROP involves the reaction of lactide and glycolide dimers in the presence of a catalyst and initiator species from a couple of minutes to hours [10, 12]. The most commonly used and accepted catalyst is stannous octoate and co-initiators are typically OH-bearing molecules such as fatty alcohols, or even “free” lactic and glycolic acid [13]. During polymer synthesis, glycolide/glycolic acid is slightly more reactive than lactide/lactic acid, so it is not unusual that short “blocks” of glycolic and lactic linkages can form along the polymer chains rather than a purely alternating or “sequenced” distribution [14]. Knowledge of the monomer distribution along the polymer chain is important because the glycolide linkages tend to be more labile towards hydrolysis and, thus, larger lengths would lead to an accelerated degradation and erosion of the polymer, likely accompanied by a faster drug release [15–18]. For example, Vey et al. determined that the glycolic unit consistently hydrolyzes 1.3 times faster than the lactic unit across polymer films with varying L/G ratios, submerged in phosphate buffer [19], and Washington et al. demonstrated the relative reactivities of various linkages to be G-G > G-L and L-G > L-L [20].

Polymer selection and changes in source/batch of polymer are only one aspect of the more complex development of long-acting release drug product development along with drug properties, drug-PLGA interactions, included excipients, formulation geometry, and formulation parameters [1, 2, 21–24]. However, better knowledge and control of the relevant macro- (e.g., shape and porosity) and micro-structural (e.g., arrangement of L/G sequence and end-capping) properties of the polymer may help bridge the gap between the effects of raw materials or manufacturing variables and the product performance, allowing for better polymer selection and could potentially increase the number of approved PLGA drug products. Herein, we selected 19 different linear PLGAs from five manufacturers to form drug-free films, implants, and microspheres and investigated differences in the main events during drug release: water uptake, degradation, and erosion behaviors during incubation as a function of L/G ratio, molecular weight, end-capping, and formulation geometry. We also compared the diffusion of BODIPY fluorescent dye in PLA microspheres, an important marker of release of small molecules (e.g., water-soluble acids or steroids) to demonstrate potential differences in drug release due to faster degradation and erosion behavior as previously described by our lab [25–27]. Previously, we evaluated the sequence distribution of glycolide/glycolic acid and lactide/lactic acid for these polymers [28] and, here, we were able to connect these results with our analyses of in vitro performance.

Materials and methods

Materials

All Expansorb® polymers were provided by Merck KGaA (Germany). Resomer® and Purasorb® polymers, Wako® 7515, and Lactel® DL-PLG B6007-2 were purchased from Sigma-Aldrich (USA), Corbion (The Netherlands), Wako Pure Chemical Industries, Ltd. (Japan), and Durect Corp. (USA), respectively. All polymers used in this investigation were the racemic (D,L) form of lactide or lactic acid and are further described in Table 1. Acid-terminated polymers are referred to as “uncapped” and polymers with an aliphatic ester end group are referred to as “end-capped.” Dichloromethane (DCM) was from Merck KGaA. Acetone (99.8%, extra dry, Acros Organics), tetrahydrofuran (THF, HPLC grade), and reusable PTFE Evaporating Dishes (product no. 02617148) were acquired from FisherSci (USA). Circular lever punches, 1.6 cm in diameter, were obtained from Michaels® Craft Store (USA). Platinum-cured silicone tubing (0.5 mm i.d., product no. 95802–00) was from Cole Parmer (USA). Poly(vinyl alcohol) (PVA, 88% hydrolyzed, molecular weight ~25 kDa)
Table 1  List of polymers used and their physical chemical properties. End-capping, inherent viscosity, and residual monomer as listed by the manufacturer. Molecular weight ($n=3$) and dry glass transition temperature ($T_g, n=2$) determined as described herein by gel permeation chromatography and differential scanning calorimetry, respectively. Similar polymers are shown grouped together.

| Polymer           | Lot No            | End Cap | Labeled L/G | Measured L/G^a | Avg MW (SE), kDa | Inherent Viscosity^b, dL/g | Average Block Length^c | Blockiness^d | Dry $T_g$ AVG (SE), °C | Residual Monomer^e |
|-------------------|-------------------|---------|-------------|----------------|------------------|-----------------------------|------------------------|--------------|----------------------|-------------------|
| Expansorb® DLG 50-2A | PP10056489        | uncapped | 50/50       | 50.7/49.3      | 10 (0.1)         | 0.19                        | 4.4                    | 4.2          | 1.9                  | 41.5 (0.2)        |
| Resomer® RG 502H  | BCBZ7916          | uncapped | 50/50       | 50.2/49.8      | 14 (0.2)         | 0.22                        | 3.0                    | 3.0          | 1.4                  | 45.3 (0.1)        |
| Expansorb® DLG 50-3A | PP10056559        | uncapped | 50/50       | ND             | 20 (1.5)         | 0.31                        | ND                     | ND           | ND                  | 44.3^c            |
| Resomer® RG 503H  | BCBZ1918          | uncapped | 50/50       | 49.2/50.8      | 26 (1.1)         | 0.37                        | 3.4                    | 3.2          | 1.5                  | 47.7 (0.1)        |
| Expansorb® DLG 50-5A | PP10059967        | uncapped | 50/50       | 49.3/50.7      | 33 (0.2)         | 0.47                        | 4.0                    | 4.0          | 0.7                  | 48.0 (0.2)        |
| Resomer® RG 504H  | BCBX4108          | uncapped | 50/50       | 48.6/51.4      | 41 (0.2)         | 0.57                        | 2.9                    | 2.9          | 1.3                  | 48.4 (0.1)        |
| Purasorb® PDLG 5004A | 1110001124       | uncapped | 50/50       | 51.2/48.8      | 24 (0.1)         | 0.37                        | 3.4                    | 3.2          | 1.6                  | 46.3 (0.4)        |
| Expansorb® DLG 50-2E | C100011425        | end-capped | 50/50       | 48.6/51.4      | 15 (0.1)         | 0.21                        | 2.5                    | 2.6          | 1.4                  | 38.0 (0.2)        |
| Resomer® RG 502   | BCCB0256          | end-capped | 50/50       | 50.5/49.5      | 13 (0.1)         | 0.20                        | 2.6                    | 2.5          | 1.5                  | 43.5 (0.3)        |
| Expansorb® DLG 75-2A | PP10056560        | uncapped | 75/25       | 73.4/26.6      | 7 (0.3)          | 0.12                        | 6.9                    | 2.5          | 0.5                  | 39.8 (0.3)        |
| Resomer® RG 752H  | BCBw4713          | uncapped | 75/25       | 75.3/24.7      | 11 (0.1)         | 0.22                        | 8.5                    | 2.6          | 0.7                  | 46.9 (0.1)        |
| Purasorb® PDLG 7502A | 1802030617       | uncapped | 75/25       | 74.0/26.0      | 10 (0.1)         | 0.19                        | 7.8                    | 2.7          | 0.5                  | 41.9 (0.8)        |
| Wako® 7515        | TWO.1257          | uncapped | 75/25       | 75.6/24.4      | 12 (0.1)         | 0.18                        | 10.6                   | 1.4          | 0.6                  | 41.3 (0.3)        |
| Expansorb® DLG 75-9E | C100011427        | end-capped | 75/25       | 73.3/26.7      | 90 (3.8)         | 0.95                        | 6.7                    | 2.4          | 0.5                  | 49.9 (0.1)        |
| Lactel® DL-PLG B6007-2 | A17-068           | end-capped | 75/25       | 72.5/27.5      | 86 (3.5)         | 0.81                        | 5.5                    | 2.1          | 0.6                  | 45.9 (0.1)        |
| Resomer® RG 756S  | BCBZ4240          | end-capped | 75/25       | 75.3/24.7      | 80 (2.7)         | 0.90                        | 5.8                    | 1.7          | 1.7                  | 51.2 (0.2)        |
| Expansorb® DLG 100-2A | PP10059963        | uncapped | 100.00      | 100.00         | 11 (0.1)         | 0.18                        | NA                     | NA           | NA                   | 45.2 (0.1)        |
| Resomer® R 202H  | BCBV6665          | uncapped | 100.00      | 100.00         | 16 (0.1)         | 0.24                        | NA                     | NA           | NA                   | 50.9 (0.1)        |
| Purasorb® PDL 02A | 1703003820        | uncapped | 100.00      | 98.6/1.4       | 14 (0.1)         | 0.22                        | NA                     | NA           | NA                   | 46.2 (0.1)        |

NR not reported, ND not determined

^a Measured L/G ratio, average block lengths, and blockiness were previously determined according to [28] and are reported here for completeness

^b Expansorb® inherent viscosity (i.v.): 0.5% chloroform, 25 °C. Resomer® i.v.: 0.1 % in chloroform at 25 °C. Purasorb® PDLG 5004A i.v.: 0.5 g/dL in chloroform at 25 °C. Purasorb® PDLG 7502A, and Purasorb® PDL 02A i.v.: 1 g/dL in chloroform at 25 °C. Lactel® i.v.: 0.5 g/dL in chloroform at 30 °C. Wako® i.v. method not reported.

^c Expansorb® 50-3A dry $T_g$ was analyzed at $n=1$

^d Residual monomer determined by the manufacturers: Expansorb® and Resomer® by NMR, Purasorb® by GC, and Lactel® not reported
was provided by PolySciences, Inc (USA) and Merck KGaA. PBS (Gibco) was from the University of Michigan Bioresearch store. 63 mm-diameter polypropylene jars (product no. 3UCP3 or 32V496) were purchased from Grainger, Inc. (USA). All other chemicals and solvents were of analytical grade and used as received.

**Methods**

**Film preparation by solvent casting**

Expansorb® DLG 50-2A, Resomer® RG 502H, Expansorb® DLG 50-3A, Resomer® RG 503H, Expansorb® DLG 50-5A, Resomer® RG 504H, Purasorb® PDLG 5004A, Expansorb® DLG 50-2E, Resomer® RG 502, Expansorb® DLG 75-9E, Resomer® RG 756S, and Lactel® DL-PLG B6007-2 were prepared as thin films. Polymers were dissolved in THF at 50 mg/mL except for Resomer® RG 502, Expansorb® DLG 75-9E, Resomer® RG 756S, and Lactel® DL-PLG B6007-2 dissolved at 75 mg/mL. Eight mL of the polymer solution was dispersed via a glass pipette into the center of circular, 10 cm diameter, PTFE low form evaporating dish on a leveled surface. Dishes were covered with a 2-L beakers to limit but not completely prevent airflow and allowed to dry for 24 h at room temperature under a ventilated chemical hood. Then, films were dried under vacuum (23 in. Hg) at 40 °C with desiccant for 48 h. Films were carefully removed from the PTFE dishes using forceps, cut into discs using a 1.6-cm-diameter circle lever punch, and stored at 4 °C until use. The average film thickness was ~53 μm, ranging from 30 to 78 μm. Residual solvent was not determined for films and additional matrices, implants, and microspheres, described below, but is expected to be similar among the different groups of polymer formulations.

**Implant formulation**

Expansorb® DLG 75-2A, Resomer® RG 752H, Purasorb® PDLG 7502A, Wako® 7515, Expansorb® DL 100-2A, Resomer® R 202H, and Purasorb® PDL 02A were prepared as implants similarly as previously described [29]. Polymers were dissolved with acetone at a ratio of 2/1 (w/w, polymer/acetone) and extruded via a 3-mL syringe and a blunt-tip needle into the silicone tubing. Paper clips were placed in the ends of the tubing to prevent the polymer solution from leaking and to compress the mixture to avoid air pockets in the extrudate. Extrusions were dried at room temperature for 48 h followed by drying under vacuum (23 in. Hg) at 40 °C with desiccant for 48 h. The silicone tubing was carefully removed from the polymer implants using a razor blade, and the implants were cut into 0.5-cm segments and stored at −20 °C until use.

**Microsphere formulation**

Expansorb® DLG 75-2A, Resomer® RG 752H, Purasorb® PDLG 7502A, and Wako® 7515 were prepared as microspheres similarly as previously described [27]. Polymers were dissolved in DCM at a concentration of 800 mg/mL in a 16 × 100 mm glass test tube for a total volume of 1 mL. An equal volume, 1 mL, of 0.5% PVA was added to the polymer solution and thoroughly vortexed for 1 min. The resulting O/W emulsion was immediately added to a 250-mL beaker containing 100 mL of 0.5% PVA and stirred with an overhead stirrer at 600 rpm for 3 h for microsphere hardening and solvent removal. Microspheres were then sieved and collected between 32 and 63 μm, rinsed with 1 L of distilled water to remove excess PVA, freeze-dried for 2 days, and stored at −20 °C until use.

For the BODIPY uptake experiments, Expansorb® DL 100-2A, Resomer® R 202H, and Purasorb® PDL 02A were formulated as microspheres. Polymers were dissolved at 600 mg/mL and microspheres were fabricated as described above.

**Incubation conditions**

Polymer films, implants, and microspheres were incubated in phosphate-buffered saline (PBS) pH 7.4 at 37 °C with low agitation (70 rpm, KS 125 basic shaker, IKA Laborotechnik, Germany); thin films (1.6 cm diameter) were incubated in 30-mL PBS in 63-mm-diameter polypropylene jars, and implants (0.5 cm length) and microspheres (10 mg) were incubated in 1-mL PBS in 2-mL Eppendorf tubes. At predetermined timepoints, the incubations were stopped by removing/separating the respective vehicle from the buffer and rinsing it with distilled water. Formulations were then dried at room temperature and under vacuum (23 in. Hg) with desiccant for 72 h.

**Determination of water content and mass loss**

Water content of films and implants (W(t)) at time, t, was determined during the incubation period by:

\[
W(t) = \frac{W_{wet}^t - W_{dry}^t}{W_{wet}^t}
\]

(1)

where \( W_{wet}^t \) and \( W_{dry}^t \) are the wet and dry formulation weights, respectively, after incubation and drying.

The percent mass loss was calculated according to:

\[
\text{% mass loss} = \frac{W_0 - W_{dry}^t}{W_0} \times 100
\]

(2)
where \( W_0 \) is the initial weight of the formulation before incubation.

For microsphere water uptake determination, particles were dried and the interparticle water was calculated as previously reported [21]. Briefly, incubated particles were collected on pre-weighed nylon membrane filters washed with distilled water and dried under vacuum for approximately 5 s to remove surface water and the wet weight was immediately determined. After drying at room temperature under vacuum for 72 h, the dry weight was recorded. To correct for the interparticle water, dry microspheres were dispersed in PBS at 4 °C (where water uptake into microspheres is assumed negligible) and the wet and dry weights were measured after filtering and drying, respectively, as described above. The weight difference between wet and dry particles was used to calculate the fraction of interparticle water \( (W_{\text{int}}) \), as defined as:

\[
W_{\text{int}} = \frac{(W^0_{\text{wet}} - W^0_{\text{dry}})}{W^0_{\text{dry}}}
\]

with \( W^0_{\text{wet}} \) and \( W^0_{\text{dry}} \) as the weights of wet microspheres and dry microspheres, respectively, after immediate collection at \( t = 0 \). The water uptake of microspheres at time, \( t \), \( W_{\text{ms}}(t) \) was then determined as defined as:

\[
W_{\text{ms}}(t) = \frac{(W^t_{\text{wet}} - W^t_{\text{dry}} - (W^t_{\text{dry}} W^t_{\text{int}}))}{W^t_{\text{dry}}}
\]

where \( W^t_{\text{wet}} \) and \( W^t_{\text{dry}} \) are the wet and dry microsphere weights after incubation and drying at time, \( t \). The percent mass loss was calculated as defined according to (2).

**Determination of relative molecular weight change**

Before formulation incubation (day 0) and at each timepoint during incubation, formulations were collected after drying and dissolved in THF. The obtained polymer solutions (\( \sim 4 \) mg/mL) were then subjected to gel permeation chromatography using two styrage columns in series (HR 1 and HR 0.5 columns, Waters, USA) with a Waters 1525 HPLC system and THF as the elution medium at a flow rate of 1 mL/min and detection by refractive index as previously described [21]. Poly(styrene) standards of known molecular masses were used for calibration. The weight average molecular weight of polymer samples is reported throughout this study.

**Determination of dry glass transition temperature (dry \( T_g \))**

Raw polymers (0.5–5 mg) were exactly weighed into aluminum pans with a lid and sealed. The dry \( T_g \) was determined by a modulated differential scanning calorimetry method as previously described [21] (Discovery, TA instruments, USA). A heat/cool/heat cycle was employed in which the temperature was ramped between –20 °C and 90 °C at 3 °C/min, with a modulated amplitude of 1 °C/min over 60 s. Results were analyzed by the TRIOS software.

**L/G ratio determination by nuclear magnetic resonance (NMR) spectroscopy**

Each PLGA sample (\( \sim 7 \) mg) was dissolved in deuterated chloroform (CDCl\(_3\)) (0.75 mL) and pipetted into a 5 mm × 7 mm NMR tube (Aldrich\(^{®}\) ColorSpec\(^{®}\) NMR tubes, parameter 800 MHz frequency). NMR scanning was performed using a Varian vnmr-500 MHz (11.7 Tesla) Premium Shielded NMR spectrometer running Vnmrj software for 1HNMR. Molar L/G ratios were determined by comparing proton intensities at chemical shifts 5.2 ppm (lactide, one proton) and 4.8 ppm (glycolide, two protons). The L/G molar ratio was converted to the L/G weight ratio. Significant differences were determined by comparing the changes in lactic content by subtracting the lactic content at day 0 from the lactic content determined at each timepoint.

**BODIPY uptake in microspheres**

About 10 mg of PLGA microspheres was incubated at 37 °C in 1 mL of PBS containing 0.02% (w/v) Tween-80 (PBST) under mild agitation for 21 days before monitoring the probe uptake. After incubation, 1 mg of the microparticles was separated from PBST solution by a brief centrifugation. Then, 1 mL of BODIPY in PBST (5 μg/mL), which was preincubated at 37 °C, was added, and the mixture was incubated at 37 °C for 1 day under mild agitation before laser scanning confocal microscopy. Briefly, microspheres were imaged using a Nikon A1 spectral confocal microscope (Japan) to observe dye distribution and microsphere morphology. The images were then analyzed using ImageJ software (National Institutes of Health, USA). Normalized dye intensity (\( I/I_0 \))–position (\( r/a \)) pairs were then fit to the solution of Fick’s second law of diffusion using Matlab and Simulink software (Oakdale Engineering, USA) to determine the effective solid-state diffusion coefficient of BODIPY (\( D_{\text{BODIPY}} \)), as described previously [27].

**Analysis of erosion rate and onset of erosion from mass loss data**

PLGA film erosion was analyzed by two parameters as previously reported [30]: the pseudo-first-order apparent rate of
erosion \( (k_{\text{ero}}) \) during the significant decay phase is calculated by:

\[
\ln(\% \text{ mass remaining}) = \text{intercept} - k_{\text{ero}} \cdot \text{time}
\]  

which was typically the last 3–4 timepoints, and the onset of erosion \( (t_{\text{on}}) \) was calculated by:

\[
t_{\text{on}} = \frac{\text{intercept} - \ln(100)}{k_{\text{ero}}}
\]

**Analysis of degradation rate and half-lives from molecular weight data**

The molecular weight (MW) pseudo-first-order apparent degradation rate constants, \( k_{\text{deg}} \), and half-lives, \( t_{1/2} \), were determined by the following:

\[
\ln(MW) = \text{intercept} - k_{\text{deg}} \cdot \text{time}
\]

\[
t_{1/2} = \frac{\ln(2)}{k_{\text{deg}}}
\]

**Statistical analyses**

Samples represented independent experiments and data represents mean ± standard error (SE). Statistical analyses and regressions were performed using Prism (Graphpad, USA). Comparisons were made using unpaired student \( t \) tests to determine two-tailed \( p \) values. Significance was established at the 95% confidence interval (\( \alpha < 0.05 \)) and all levels of significance are indicated with one asterisk (*). To compare the %lactic content remaining in each formulation during incubation, actual differences relative to their raw polymer starting %lactic content were used for statistical analyses.

**Results and discussion**

**Effect of polymer molecular weight**

The impact of the polymer molecular weight was investigated by comparing the following 50/50, “low” and “intermediate” molecular weight, uncapped PLGAs which were formulated into thin films: Expansorb\textsuperscript{®} DLG 50-2A, Expansorb\textsuperscript{®} DLG 50-3A, Expansorb\textsuperscript{®} DLG 50-5A, Resomer\textsuperscript{®} RG 502H, Resomer\textsuperscript{®} RG 503H, and Resomer\textsuperscript{®} RG 504H (Table 1). For each of these polymers, the water uptake was generally similar by 3 weeks of incubation, but the lower molecular weight films revealed an increased water uptake during the first 2 weeks (Fig. 1a, d). Expansorb\textsuperscript{®} DLG 50-5A, the highest molecular weight of the three, appeared to have two phases of molecular weight decline, a slower decline in the first 7 days followed by a relatively faster decline for the next 2 weeks. Comparing the apparent first-order rate of degradation of Expansorb\textsuperscript{®} DLG 50-5A with Expansorb\textsuperscript{®} DLG 50-3A and Expansorb\textsuperscript{®} DLG 50-2A films in the initial phase determined over the first 7 days of incubation using a least squared linear regression analysis (data not shown), as the starting molecular weight decreased, the initial apparent first-order rates of

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![Fig. 1](image-url)  
Fig. 1 Effect of molecular weight on erosion behavior in 50/50 uncapped PLGA films. Kinetics of water content \((n=6)\), molecular weight (MW) loss as determined by gel permeation chromatography \((n=3)\), and mass loss \((n=6)\) are represented for Expansorb\textsuperscript{®} (a–c) and Resomer\textsuperscript{®} (d–f) films, respectively. Data represents mean ± standard error (SE). Film starting molecular weights are indicated in the legends, reproduced from Table 2.
degradation increased, 0.072, 0.091, and 0.092 days\(^{-1}\), respectively. Over the entire incubation period, the overall rate of degradation for Expansorb\textsuperscript{®} DLG 50-5A films increased, 0.086 days\(^{-1}\), resulting in similar degradation half-lives for all three polymer films, \(\sim 8\) days (Fig. 1a–c, Table 2). The lower molecular weight of Expansorb\textsuperscript{®} DLG 50-2A had a significant effect on the onset of erosion \((t_{on})\), with \(t_{on} = 1.3\) days, compared to Expansorb\textsuperscript{®} DLG 50-5A, \(t_{on} = 11.8\) days (Table 3). Similar trends were observed with the three Resomer\textsuperscript{®} polymers (Fig. 1d–f). These results are expected, as the effect of molecular weight on polymer degradation and erosion is well-known [8]. We expect the degradation rate of PLGA to remain roughly constant (i.e., \(\log(Mw) \) linear with time) with a decline in molecular weight until the molecular weight falls below some critical value (e.g., in the vicinity of \(\sim 20\) kDa as previously reported [31]), and the polymer chains become far more mobile and the time to reach a soluble polymer oligomer shortens. Hussman et al. previously observed that regardless of the initial molecular weight, polymer microspheres or implants reach a critical molecular weight, around 10–20 kDa, at which point the formulations collapse and undergo significant constant erosion [32–34]. The starting molecular weight does not appear to influence this critical molecular weight, but the time that it takes to reach the critical molecular weight increases with increasing molecular weight. We observed similar behaviors with our polymer formulations, the critical molecular weight ranged from 5 to 20 kDa (data not shown), and polymers with similar properties behaved similarly. The time to reach this critical molecular weight for our formulations ranged from 7 to 28 days with low molecular weight, uncapped, 50/50 films and 75/25 implants having a shorter time, and higher molecular weight, 75/25 end-capped films as well as PLA, uncapped implants taking longer to reach this critical molecular weight. Certainly, almost any desired polymer molecular weight can be achieved with “fine-tuning” the synthesis process. Here, when investigating the effects of other variables, we are only comparing formulations that have similar starting molecular weights.

**Effect of polymer end-capping**

The impact of the polymer chain termination was investigated by comparing 50/50, uncapped with end-capped PLGA films of similar molecular weights within the same manufacturer, either Expansorb\textsuperscript{®} or Resomer\textsuperscript{®}. End-capped Expansorb\textsuperscript{®} DLG 50-2E and Resomer\textsuperscript{®} RG 502

| Table 2 Formulation vehicle starting molecular weights, apparent first-order degradation rate constants, and molecular weight half-lives for polymer formulations |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Polymer         | Formulation Vehicle | Formulation Starting MW, kDa | \(k_{\text{deg}}, \) days\(^{-1}\) | MW half life, days |
| Expansorb\textsuperscript{®} DLG 50-2A Film | 10.9 (0.1) | 0.092 (0.012) | 7.6 (1.4) |
| Resomer\textsuperscript{®} RG 502H Film | 12.6 (1.1) | 0.127 (0.005) | 5.5 (0.3) |
| Expansorb\textsuperscript{®} DLG 50-3A Film | 19.9 (1.3) | 0.091 (0.007) | 7.6 (0.8) |
| Resomer\textsuperscript{®} RG 503H Film | 25.9 (0.1) | 0.084 (0.002) | 8.2 (0.3) |
| Expansorb\textsuperscript{®} DLG 50-5A Film | 35.3 (0.6) | 0.086 (0.004) | 8.0 (0.6) |
| Resomer\textsuperscript{®} RG 504H Film | 36.9 (0.1) | 0.093 (0.004) | 7.5 (0.4) |
| Purasorb\textsuperscript{®} PDLG 5004A Film | 29.1 (0.2) | 0.086 (0.004) | 8.1 (0.5) |
| Expansorb\textsuperscript{®} DLG 50-2E Film | 15.4 (0.1) | 0.049 (0.006) | 14.3 (2.6) |
| Resomer\textsuperscript{®} RG 502 Film | 13.2 (0.1) | 0.032 (0.004) | 21.4 (3.7) |
| Expansorb\textsuperscript{®} DLG 75-2A Implant | 6.1 (0.1) | 0.047 (0.009) | 14.8 (3.9) |
| Resomer\textsuperscript{®} RG 752H Implant | 10.5 (0.1) | 0.067 (0.005) | 10.4 (1.2) |
| Purasorb\textsuperscript{®} PDLG 7502A Implant | 9.4 (0.2) | 0.049 (0.009) | 14.1 (3.6) |
| Wako\textsuperscript{®} 7515 Implant | 12.6 (0.2) | 0.078 (0.008) | 8.9 (1.2) |
| Expansorb\textsuperscript{®} DLG 75-2A Microsphere | 6.0 (0.2) | 0.054 (0.001) | 12.8 (0.5) |
| Resomer\textsuperscript{®} RG 752H Microsphere | 11.7 (0.1) | 0.057 (0.002) | 12.1 (0.7) |
| Purasorb\textsuperscript{®} PDLG 7502A Microsphere | 9.6 (0.1) | 0.050 (0.001) | 13.9 (0.4) |
| Wako\textsuperscript{®} 7515 Microsphere | 13.1 (0.7) | 0.076 (0.002) | 9.1 (0.4) |
| Expansorb\textsuperscript{®} DLG 75-9E Film | 71.0 (10.5) | 0.038 (0.002) | 18.5 (1.5) |
| Lactel\textsuperscript{®} DL-PLG B6007-2 Film | 79.8 (2.5) | 0.035 (0.003) | 20.0 (2.8) |
| Resomer\textsuperscript{®} RG 756S Film | 80.4 (2.2) | 0.022 (0.001) | 31.1 (3.1) |
| Expansorb\textsuperscript{®} DL 100-2A Implant | 10.5 (0.1) | 0.038 (0.003) | 18.3 (2.3) |
| Resomer\textsuperscript{®} R 202H Implant | 15.5 (0.2) | 0.035 (0.002) | 20.0 (1.8) |
| Purasorb\textsuperscript{®} PDL 02A Implant | 13.7 (0.1) | 0.049 (0.002) | 14.0 (0.8) |

Data represents the mean (standard error), \(n = 3\). Statistics represent unpaired \(t\) test, *\(p < 0.05\)
Table 3: Apparent erosion rates and onsets for polymer formulations

| Polymer | Formulation Vehicle | $t_{on}$, days | $k_{on}$, $days^{-1}$ |
|---------|---------------------|----------------|---------------------|
| Expansorb® DLG 50-2A Film | 1.3 (0.2) | 0.048 (0.006) |
| Resomer® RG 502H Film | 5.5 (0.4) | 0.080 (0.004) |
| Expansorb® DLG 50-3A Film | 16.4 (1.4) | 0.080 (0.007) |
| Resomer® RG 503H Film | 13.1 (0.1) | 0.067 (0.001) |
| Expansorb® DLG 50-5A Film | 11.8 (0.5) | 0.047 (0.002) |
| Resomer® RG 504H Film | 16.4 (1.3) | 0.060 (0.003) |
| Purasorb® PDLG 5004A Film | 15.9 (2.8) | 0.076 (0.01) |
| Expansorb® DLG 50-2E Film | 13.5 (3.2) | 0.047 (0.008) |
| Resomer® RG 502 Implant | 3.0 (0.1) | 0.044 (0.001) |
| Expansorb® DLG 75-2A Implant | 9.7 (0.8) | 0.030 (0.002) |
| Resomer® RG 752H Microsphere | 4.5 (0.1) | 0.025 (0.001) |
| Wako® 7515 Implant | 6.6 (0.8) | 0.042 (0.004) |
| Expansorb® DLG 75-2A Microsphere | 14.7 (2.2) | 0.100 (0.011) |
| Resomer® RG 752H Microsphere | 23.1 (1.8) | 0.084 (0.005) |
| Purasorb® PDLG 7502A Microsphere | 21.0 (0.6) | 0.086 (0.002) |
| Wako® 7515 Microsphere | 20.9 (5.8) | 0.154 (0.03) |
| Expansorb® DLG 75-9E Film | 20.8 (6.1) | 0.010 (0.002) |
| Lactel® DL-PLG B6007-2 Film | 21.8 (10.0) | 0.011 (0.003) |
| Resomer® RG 756S Implant | NA |
| Expansorb® DL 100-2A Implant | 19.4 (0.8) | 0.014 (0.003) |
| Resomer® R 202H Implant | NA |
| Purasorb® PDL 02A Implant | 22.9 (6.2) | 0.014 (0.003) |

Data represents mean (standard error), $n = 6$ for implants and films, $n = 5$ for microspheres. Statistics represent unpaired $t$ test, *$p<0.05$

NA not applicable; erosion not significant enough to analyze kinetics

compared to their uncapped analogs of similar molecular weights, Expansorb® DLG 50-2A and Resomer® RG 502H, respectively, all showed reduced overall water uptake and slower overall polymer degradation and erosion (Fig. 2). The onset of erosion and rate of erosion analyses captured the tail-end of the erosion vs. time curves, where significant erosion occurred and the linear fit was not optimal for the end-capped polymers, which did start eroding significantly until after 21 days and did not have enough erosion to analyze. Expansorb® DLG 50-2E films degraded slower than Expansorb® DLG 50-2A, the molecular weight degradation rate constants ($k_{deg}$) were 0.049 and 0.092 days$^{-1}$, respectively (Table 2). Expansorb® DLG 50-2A films displayed similar erosion rates compared with Expansorb® DLG 50-2A, $k_{ero}$ = 0.047 and 0.048 days$^{-1}$, respectively, but Expansorb® DLG 50-2A exhibited a much faster onset of erosion than Expansorb® DLG 50-2E: $t_{on}$ values were 1.3 and 13.5 days, respectively. Resomer® RG 502 films had a $k_{deg}$ of 0.032 days$^{-1}$ and a $t_{1/2}$ of 21.4 days (Table 2). Resomer® RG 502 films did not start to erode significantly until after 21 days (Fig. 2); thus, analysis of their erosion kinetics was not possible here. By contrast, Resomer® RG 502H films had faster degradation and erosion kinetics than their end-capped counterparts with $k_{deg}$ = 0.127 days$^{-1}$, $t_{1/2}$ = 5.5 days, $k_{ero}$ = 0.080 days$^{-1}$, and $t_{on}$ = 5.5 days (Tables 2 and 3). In both cases, the lactic content increased significantly faster for the uncapped films by either day 7 or day 21 compared to the end-capped films (Supplementary Fig. 1), further confirming the faster erosion apparent in uncapped polymers. The polymer chains equipped with an alkyl ester end are more hydrophobic and can reduce the polymer hydrolysis rate and onset due to decreased water uptake and lack of acid end groups available to engage in auto-catalyzed hydrolysis [3, 35, 36]. Huang et al. showed increasing PLGA carboxylic acid end groups positively correlated with an increased hydrophobic drug release, and by combining uncapped and end-capped PLGAs, they were able to tailor an intermediate drug release from PLGA films [36]. The type of ester end-capping is not typically reported by polymer manufacturers but has been shown to affect polymer hydrolysis. As an example, Tracy et al. observed a case where differences in the ester end-cap type can overcome differences in molecular weight between PLGA microspheres [9]. The end-cap type can be determined by NMR and would be an interesting future investigation to compare between manufacturers [35].

Effect of formulation geometry

To investigate the influence of formulation geometry, we compared 75/25, uncapped, “low” molecular weight (6–12 kDa) PLGAs, Expansorb® DLG 75-2A, Resomer® RG 752H, Purasorb® DLG 7502A, and Wako® 7515, as
implants and microspheres. Geometrically, larger implants had increased water uptake (Fig. 3a–d) and faster initial degradation (Fig. 3e–h) in the first week compared to microspheres of the same polymers, likely due to enhanced effects of auto-catalysis from PLGA acidic byproducts unable to escape as efficiently from larger geometries [3, 37, 38]. Implants had faster onsets of erosion (Table 3), 3–10 days, compared to their microsphere counterparts, 15–23 days, but eventually, implant erosion slowed down resulting in slower overall apparent rate constants than microspheres (Table 2). Despite the fact that implants had a faster initial degradation, implants and microspheres had similar erosion profiles over the first month (Fig. 3i–l), possibly because the degradation products may not have been able to escape as efficiently from larger geometries [3, 37, 38].

Fig. 2 Effect of end-capping on erosion behavior in 50/50 PLGA films. Kinetics of water content (n=6), molecular weight (MW) loss as determined by gel permeation chromatography (n=3), and mass loss (n=6) are represented for Expansorb® (a–c) and Resomer® (d–f) PLGA films, respectively. Data for Expansorb® DLG 50-2A and Resomer® RG 502H were reproduced from Fig. 1. Data represents mean ± standard error (SE). Film starting molecular weights are indicated in the legends, reproduced from Table 2.

Fig. 3 Effect of formulation size and geometry on erosion behavior in uncapped 75/25 PLGA implants and microspheres. Kinetics of water content (a–d, implants n=6, microspheres n=5), molecular weight (MW) loss as determined by gel permeation chromatography (e–h, n=3), and mass loss (i–l, implants n=6, microspheres n=5) were determined for Expansorb® (a, e, i), Resomer® (b, f, j), Purasorb® (c, g, k), and Wako® (d, h, l) PLGA formulations, respectively. Data represents mean ± standard error (SE). Implant and microsphere starting molecular weights are indicated in the legends, reproduced from Table 2.
efficiently due to the larger geometry of implants (0.5 mm diameter × 0.5 cm length) vs. microspheres (32–63 μm diameter). Microspheres also have a higher surface area to volume ratio influencing their eventual faster erosion. Typically, the thicker the PLGA device, the faster the degradation [38]. Our results showed that the larger geometry implants resulted in faster initial degradation than microspheres, but an overall slower degradation. Similar results were reported by Witt et al., where PLGA rods initially degraded faster than PLGA microspheres, but eventually slowed down [30]. They also observed that the erosion of the rods was delayed and did not coincide with the faster initial degradation.

**Effect of polymer manufacturer**

To compare the effects of different manufacturers, we focused on formulations that had the same L/G ratio, end-capping, and similar starting molecular weights to keep all variables as constant as possible. Therefore, (1) Expansorb® DLG 50-5A, Resomer® RG 504H, and Purasorb® PDLG 5004A films and (2) Expansorb® DLG 50-2A and Resomer® RG 502H films were compared. The water uptake between these films was generally very similar (Fig. 4a, e), shown by the fact that the water content remained constant over the first 3 days of incubation but they diverged in their initial first-order degradation constants, determined over the first 3 days of incubation using a least squared linear regression analysis (data not shown). Expansorb® DLG 50-5A and Purasorb® PDLG 5004A films both had faster initial degradation rate constants, \( k_{deg} = 0.108\) days\(^{-1}\) and 0.105 days\(^{-1}\), respectively, than Resomer® RG 504H, \( k_{deg} = 0.078\) days\(^{-1}\). Expansorb® DLG 50-2A films initial degradation rate constant, \( k_{deg} = 0.13\) days\(^{-1}\), was only slightly faster than Resomer® RG 502H films, \( k_{deg} = 0.108\) days\(^{-1}\). Our lab previously analyzed the monomer sequence distribution of these same polymers using high-resolution \(^{13}\)C-NMR spectroscopy and determined their blockiness values, \( R_c \), which describe the presence of glycolic linkages [39] and their block lengths, \( L_G \), which describe the length of the glycolide sequences [40] by determining relative intensities of the glycolyl and lactyl carbonyls. The PLGAs discussed here are polymers with random monomer distribution along the polymer chain with block lengths > 2, thus, cannot be considered having a “truly alternating” sequence with block lengths of 1, such as L-G-L-G, or even L-L-G-G-L-G-G, which would result from a perfect ring opening of lactide and glycolide and have block lengths of 2. In the case of Expansorb® DLG 50-5A, Resomer® RG 504H, and Purasorb® PDLG 5004A films, both an increased glycolic blockiness and glycolic block length value appeared to be influential leading to the increased degradation of Expansorb® DLG 50-5A and Purasorb® PDLG 5004A films [28]. Expansorb® DLG 50-5A polymer had a higher glycolic block length, \( L_G = 4.0\), than both Purasorb® PDLG 5004A, \( L_G = 3.2\), and Resomer® RG 504H, \( L_G = 2.9\), polymers [28]. While Purasorb® PDLG 5004A had a slightly lower block length, it had a higher glycolic blockiness value, \( R_c = 1.6\), than Expansorb® DLG 50-5A, \( R_c = 0.7\), and Resomer® RG 504H, \( R_c = 1.3\) [28]. Expansorb® DLG 50-2A polymer had higher glycolic block length and blockiness values, \( L_G = 4.2\) and \( R_c = 1.9\), than Resomer® RG 502H, \( L_G = 3.0\) and \( R_c = 1.4\) [28]. Both the presence of glycolic linkages and the longer length of these glycolic sequences can influence the faster initial rate of degradation. Expansorb® DLG 50-5A films showed an accelerated onset of erosion compared to the remaining lactic content was determined by \(^{1}H\)NMR and actual differences relative to their raw polymer starting %lactic content were compared for statistical analyses. Data represents mean±standard error (SE). Statistics represent unpaired t test; *p < 0.05. Data represents mean±standard error (SE). Film starting molecular weights are indicated in the legends, reproduced from Table 2.
other two polymer formulations, Resomer® RG 504H and Purasorb® PDLG 5004A, but a significantly slower overall erosion rate compared to Resomer® RG 504H (Table 3), so the faster degradation may have led to a faster initial onset of erosion within the polymer film. Similarly, Expansorb® DLG 50-2A had a faster onset of erosion but a slower overall rate of erosion compared to Resomer® RG 502H (Table 3). Although the erosion profiles (Fig. 4c, g) do not clearly show these differences due to inherent variability in weighing the degraded films, we have more definitive evidence from 1H NMR determining the lactic content remaining in the samples after incubation. Figure 4d, h show the lactic content remaining in the films after incubation for 7, and 21 or 28 days. Expansorb® DLG 50-5A films revealed a higher increase in lactic content (or loss in glycolic content) relative to their starting contents, ~ 10%, than Resomer® RG 504H, ~ 7%, and Purasorb® PDLG 5004A, ~ 8%, after 28 days. Expansorb® DLG 50-2A films also had a higher increase in lactic content, ~ 12%, than Resomer® RG 502H films, ~ 10%, after 21 days. In both cases, the Expansorb® films lost glycolic units faster than the Resomer® films, as expected with their higher glycolic block lengths and faster initial degradation rates. This can also explain why both erosion and degradation rates eventually slow down because these polymers had slightly higher lactic content after the initial glycolic unit loss, which is expected to erode slower.

In both cases, the Expansorb® and Purasorb® polymers had higher residual monomers, as reported from their certificates of analysis, than the Resomer® polymers. Expansorb® DLG 50-2A and DLG 50-5A both had 0.5% total residual monomer and Purasorb® PDLG 5004A had 1.3%, while Resomer® RG 502H and 504H had 0.2% and 0.3% total residual monomer, respectively. The presence of residual monomer has been shown to contribute to faster degradation due to the increased water uptake, presence of carboxylic acids, and plasticization, resulting in enhanced acid-catalyzed hydrolysis [41–44], and has been shown to lead to an acidic microclimate pH within the first week, even with thin films such as the ones here [45], indicating the possibility that they are still present and capable of leading to chain scission. The residual monomers may still be escaping relatively quickly within these uncapped thin films, explaining why their impact is seen during the initial increased water uptake within the first day of incubation (specifically in Expansorb® 50-2A) and faster initial degradation but overall similar water uptake and degradation within the groups over time. Therefore, the differences in residual monomer and monomer sequence could both lead to faster initial degradation and erosion and further careful experimentation would be needed to decouple these two effects.

Microspheres and implants of Wako® 7515, a PLGA synthesized by polycondensation [2], consistently degraded faster than the comparable formulations from Expansorb® DLG 75-2A, Resomer® RG 752H, and Purasorb® PDLG 7502A, PLGAs synthesized by ring-opening polymerization (ROP) (Fig. 3, Table 2). The initial apparent first-order degradation rate constant, determined from the first 7 days of incubation, of Wako® 7515 microspheres was 0.068 days⁻¹ compared to 0.061, 0.060, and 0.052 days⁻¹ of Expansorb® DLG 75-2A, Resomer® RG 752H, and Purasorb® PDLG 7502A microspheres, respectively. The initial apparent first-order degradation rate constant of Wako® 7515 implants was 0.106 days⁻¹ compared to 0.075, 0.086, and 0.082 days⁻¹ of Expansorb® DLG 75-2A, Resomer® RG 752H, and Purasorb® PDLG 7502A implants, respectively. Wako® 7515 microspheres also had a significantly faster apparent rate of erosion compared to the other three manufacturers, and Wako® 7515 implants showed significantly faster $k_{eq}$ values than Resomer® RG 752H and Purasorb® PDLG 7502A, which is consistent with previous data from our group studying leuprolide-loaded microspheres, where Wako® 7515 microspheres showed faster drug release compared to Resomer® RG 752H microspheres [2]. The glycolic blockiness and block length values previously determined [28] from these four polymers alone do not completely explain the patterns observed since Wako® 7515 had a drastically lower glycolic block length but only a slightly higher blockiness value compared to the others. There may be multiple variables in their manufacturing processes, polycondensation vs. ROP, consistently causing differences in performance such as the different types and levels of catalysts and initiators, the reaction temperature and timing conditions, or the purification process, which would require more information and further investigation, ideally with more batches to clearly compare the two manufacturing processes.

High molecular weight, 75/25 end-capped PLGA films across three brands, Expansorb® DLG 75-9E, Lactel® DL-PLG B6007-2, and Resomer® RG 756S, were compared (Fig. 5). Resomer® RG 756S films had a lower overall water uptake, while Expansorb® DLG 75-9E and Lactel® DL-PLG B6007-2 had similar water uptake profiles (Fig. 5a). Subsequently, Resomer® RG 756S films had a slower and steadier overall degradation and minimal mass loss after 56 days compared to Expansorb® DLG 75-9E and Lactel® DL-PLG B6007-2 (Fig. 5b, c). These trends were apparent in overall degradation rates and half-lives. Resomer® RG 756S degradation rate constant was 0.022 days⁻¹ and $t_{1/2}$ was 31.1 days compared to Expansorb® DLG 75-9E and Lactel® DL-PLG B6007-2 which both had higher degradation rates, 0.038 and 0.035 days⁻¹, respectively, and shorter half-lives, 18.5 and 20 days, respectively (Table 2). All three polymer films eroded slowly for the first 42 days (Fig. 5c), Resomer® RG 756S films maintained this minimal erosion by the end of the 60 days of incubation, while Expansorb® DLG 75-9E and Lactel® DL-PLG B6007-2 films started to show erosion after 42 days and had similar $t_{1/2}$ values, 20.8 and 21.8 days,
respectively, and similar $k_{ew}$ values, 0.010 days$^{-1}$ (Table 3). Based on our previous analyses, Resomer® RG 756S polymer had a higher blockiness value, $R_c = 1.7$, but a lower glycolic block length, $L_G = 1.7$, compared to both Expansorb® DLG 75-9E polymer, $R_c = 0.5$ and $L_G = 2.4$, and Lactel® DL-PLG B6007-2 polymer $R_c = 0.6$ and $L_G = 2.1$ [28]. This lower glycolic block length in Resomer® RG 756S may have more influential than its higher blockiness value leading to the lower water uptake and slower degradation and erosion. Resomer® RG 756S also had a lower total residual monomer (0.2%) compared to Expansorb® DLG 75-9E polymer (1.1%) and Lactel® DL-PLG B6007-2 (1.8%) and as discussed, this would be expected to lead to faster degradation kinetics [41–45]. Overall, the higher molecular weight, higher L/G ratio, and end-capping demonstrate how a combination of PLGA properties can be used to dramatically reduce degradation and erosion and would be expected to lead to a slower drug release.

Compared to 75/25, uncapped PLGA implants of similar molecular weight, PLA implants typically showed slower degradation and significantly reduced erosion over 56 days, as expected with the 100% racemic lactide polymers. PLA implants, Expansorb® DL 100-2A, Resomer® R 202H, and Purasorb® PDL 02A eroded very slowly, with a small initial erosion phase in the first few weeks followed by a small increase in erosion that resulted in 25–35% mass loss after 56 days of incubation (Fig. 6c). Between the manufacturers, Resomer® R 202H had the slowest water uptake, and slowest degradation and erosion (Fig. 6a–b, Tables 2 and 3). Resomer® R 202H also had the highest dry $T_g$, $\sim 51$ °C, indicative of its lower reported residual monomer (0.2%), while Expansorb® DL 100-2A and Purasorb® PDL 02A

![Fig. 5](image-url) Effect of manufacturer on the erosion behavior and lactic content of 75/25 end-capped PLGA films. Kinetics of water content (a, $n=6$), molecular weight (MW) loss as determined by gel permeation chromatography (b, $n=3$), and mass loss (c, $n=6$) are shown. Data represents mean ± standard error (SE). Film starting molecular weights are indicated in the legends, reproduced from Table 2.

![Fig. 6](image-url) Effect of manufacturer on the erosion behavior of acid-terminated PLA implants. Kinetics of water content (a, $n=6$), molecular weight (MW) loss as determined by gel permeation chromatography (b, $n=3$), and mass loss (c, $n=6$) were determined for Expansorb®, Resomer®, and Purasorb® implants; data represents mean ± standard error (SE). Representative confocal images of microspheres after 21 days of incubation (d–f) and effective BODIPY diffusion coefficients and are shown (g); data represents mean ± standard error (SE), $n=4$. Statistics represent unpaired $t$ test; *$p<0.05$. Implant starting molecular weights are indicated in the legends, reproduced from Table 2.
revealed $T_g$ values of ~45 °C and ~46 °C, respectively (Table 1), and both had 10× higher reported residual monomers (2%). As discussed above, the residual monomers can lead to more pronounced auto-catalysis and this effect would be expected to be enhanced with the larger geometry of the implants. To further characterize these differences, we evaluated the molecular diffusion as a function of incubation time with spherical microspheres of these same PLA polymers incubated with BODIPY fluorescent dye, which is known to diffuse through solid PLGA over reasonable time scales and can be monitored by laser fluorescence confocal microscopy and diffusion coefficients can be calculated using the spherical geometry [27]. Increases in the diffusion coefficient of BODIPY may be indicative of higher polymer chain mobility and polymer hydrolysis rate. Figure 6d–g show the BODIPY diffusion coefficients and representative confocal images of a single microsphere of each of the three polymers. Purasorb® PDL 02A, the fastest degrading polymer, had a significantly greater diffusion coefficient on day 21 of incubation, compared to the other two polymers, and the confocal imaging further showed how degraded these microspheres became, while Resomer® R 202H, the slowest degrading, was still “intact” by day 21.

We observed differences in sequence distribution, glass transition temperatures, and reported residual monomer between polymer manufacturers that manifested in differences between their water uptake, degradation, and erosion behaviors when formulated into films, implants, and microspheres. These differences may arise from the polymer synthesis process and manufacturing parameters. For example, the ROP method has several variables involved such as the reaction temperature, time, amount of catalyst present, amount of co-initiator present, timing of monomer addition, and the extent of purification. Differences in optimized conditions between manufacturers, or inherent variations between batches within the same manufacturer, can lead to deviations in polymer properties that may not be monitored or reported. The amount of catalyst present can help to increase the molecular weight quickly, but can also result in residual monomer, or higher chain dispersity. The addition of monomer to the growing chain can be affected by the catalyst used and by the reactivity of each monomer and can be reflected in the polymer block length/blockiness values. Glycolide/glycolic acid has a slightly higher reactivity of addition to the growing polymer chain end, both when adding to a lactic or glycolic unit, which can result in “blockiness” of lactic or glycolic units [11, 46]. The residual tin content, likely from the catalyst, was reported for each polymer except for Wako® 7515 and was below 200 ppm for all polymers and would likely have less of an effect on performance compared to other properties as it is reasonable to expect that residual catalyst levels and their impact on osmotic pressure would be masked by residual solvents also in the polymer. Over time, side reactions including chain back-biting and chain rearrangement can lead to the formation of cyclic dimers and more chain dispersity or residual monomers [12]. In general, ROP can offer better control over the sequence distribution and molecular weight than polycondensation, especially when no catalyst is used in polycondensation [47]. The effects of the monomer sequence have been extensively studied by Li et al. and it is clear that the heterogeneity of the sequence, the increased number or lengths of the glycolic linkages, leads to significantly faster swelling and hydrolysis and, thus, polymer erosion [18, 20, 48]. These studies were done comparing a typical polymer synthesized by ROP to a sequence-controlled polymer, so the differences were very evident. Here, we compared random (co-)polymers, synthesized by ROP (except for Wako® 7515), and their differences in glycolic blockiness values and block lengths are less evident. The differences in glycolic sequence that we observed between manufacturers appeared to result in increased initial degradation and generally resulted in heterogeneous degradation of the glycolic and lactic monomers. This faster initial hydrolysis could potentially lead to a faster initial release of drug which could result in a non-ideal release profile, or dose dumping. We also observed apparent effects of increased residual monomer and lower glass transition temperature on water uptake, hydrolysis, and erosion. The residual solvent due to processing was not determined and would be expected to influence the $T_g$ values and subsequent performance, although within the groups of polymers compared here, we expect residual solvent to be similar. To gain more insight into the effects of manufacturing variables, it would be interesting to investigate the differences between multiple product batches within the same manufacturer. The data here is a limited example but begins to establish the effects of variations between manufacturers or polymer synthesis methods on PLGA degradation and erosion behavior.

**Conclusion**

This work presents data for 19 commercially available PLGA polymers from five different manufacturers. We investigated differences between manufacturers by comparing drug-free films, implants, and microspheres with similar L/G ratios, end-capping, and molecular weights. Increased glycolic block lengths and higher residual monomer in 50/50, uncapped PLGA films appeared to increase the initial degradation rate constants. A lower residual monomer and increased $T_g$ value in PLA uncapped implants appeared to result in lower water uptake and slower overall degradation and erosion. In 75/25, uncapped PLGA implants, the larger geometry had enhanced acid-catalyzed hydrolysis and, thus, increased initial degradation rate constants compared to microspheres. Any change in the formulation water uptake, hydrolysis and degradation, or erosion would be expected to also affect drug release since these events are all involved
in the mechanism of release. Overall, this work provides a sizeable comparison of commercially available polymers and has investigated differences in less-studied variables, such as the glycolic monomer distribution, that can provide a better understanding of selection of polymers for a desired polymer behavior, such as lower glycolic linkages to have a more controlled and consistent polymer degradation, and a better understanding when deciphering between differences in behaviors when changing polymer suppliers or even polymer batches during development or manufacturing.

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Author contribution Material preparation, data collection, and analysis were performed by Jennifer Walker. Data collection and analysis were also performed by Jason Albert, Desheng Liang, Jing Sun, Richard Schutzman, Cameron White, and Raj Kumar. Steven P Schwendeman, Moritz Beck-Broichsitter, Jennifer Walker, and Jason Albert contributed to study conception and design. All authors whose names appear on the submission approved the version to be published.

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Declarations

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