In Vitro Degradation of Polylactide and Poly(lactide-*co*-glycolide) Microspheres

JIA-HUEI ZHU*[1], ZHENG-RONG SHEN[1], LAN-TING WU[2], and SHI-LIN YANG[2]

[1]Institute of Materia Medica, Zhejiang Academy of Medicine, Hangzhou, People's Republic of China and
[2]Department of Chemistry, Zhejiang University, Hangzhou, People's Republic of China

SYNOPSIS

Polylactide (PLA) and poly(lactide-*co*-glycolide) (PLGA) were prepared by bulk ring-opening polymerization of lactide or lactide/glycolide using stannous octoate as initiator. PLA and PLGA microspheres with an average diameter of 65–100 μm were prepared by a solvent evaporation process. An *in vitro* degradation test of different molecular weight PLA and of different composition PLGA were carried out in pH 7.4 buffer solution at 37°C in the form of microspheres. Quantitatively, the degree of degradation was monitored by gel permeation chromatography (GPC), by measurement of mass loss and determination of lactic/glycolic acid in degradation medium, and qualitatively, by observing the morphological changes of microspheres with a scanning electron microscope (SEM). The decrease in weight average molecular weight ($\bar{M}_w$) for PLA with higher molecular weight is faster at the first degradation stage; afterward, the tendency of $\bar{M}_w$ to decrease for PLA with different molecular weight is almost the same. PLGA degrades much faster than does PLA, and the degradation rate is significantly enhanced with the increase of glycolic acid (GA) content in copolymers.

INTRODUCTION

Polylactide (PLA) and poly(lactide-*co*-glycolide) (PLGA) are known to undergo degradation in the physiological environment and to yield normal metabolites of low toxicity. Such polymers have been investigated for prosthetic implants and drug delivery systems in recent years because of their biodegradability. The use of PLA and PLGA as a drug-loaded matrix has been examined in the hope that the matrix will decompose after releasing the drug in a sustained manner over a long period of time in the human body. *In vitro* investigation provides a convenient method to study the degradable characteristics of these polymers.[1,2]

This paper describes a study on the degradation of PLA and PLGA in the form of microspheres that is often used for drug-controlled release. In the present work, the polymer microspheres under investigation were incubated for predetermined periods (1–149 days) in pH 7.4 buffer solution at 37°C. On removal of the microspheres from the degradation medium, the following parameters were determined as a function of degradation: (1) the amount of lactic (LA)/glycolic acid (GA) in buffer solution, (2) the mass loss of the polymers, and (3) the decrease in weight average molecular weight ($\bar{M}_w$) and the changes of molecular weight distribution (MWD) of the polymers.

EXPERIMENTAL

Materials

PLA and PLGA were prepared by bulk ring-opening polymerization of lactide or lactide/glycolide using stannous octoate as initiator.[3] PLA and PLGA were

* To whom correspondence should be addressed.

Journal of Applied Polymer Science, Vol. 43, 2099–2106 (1991)
 CCC 0021-8995/91/112099-08$04.00

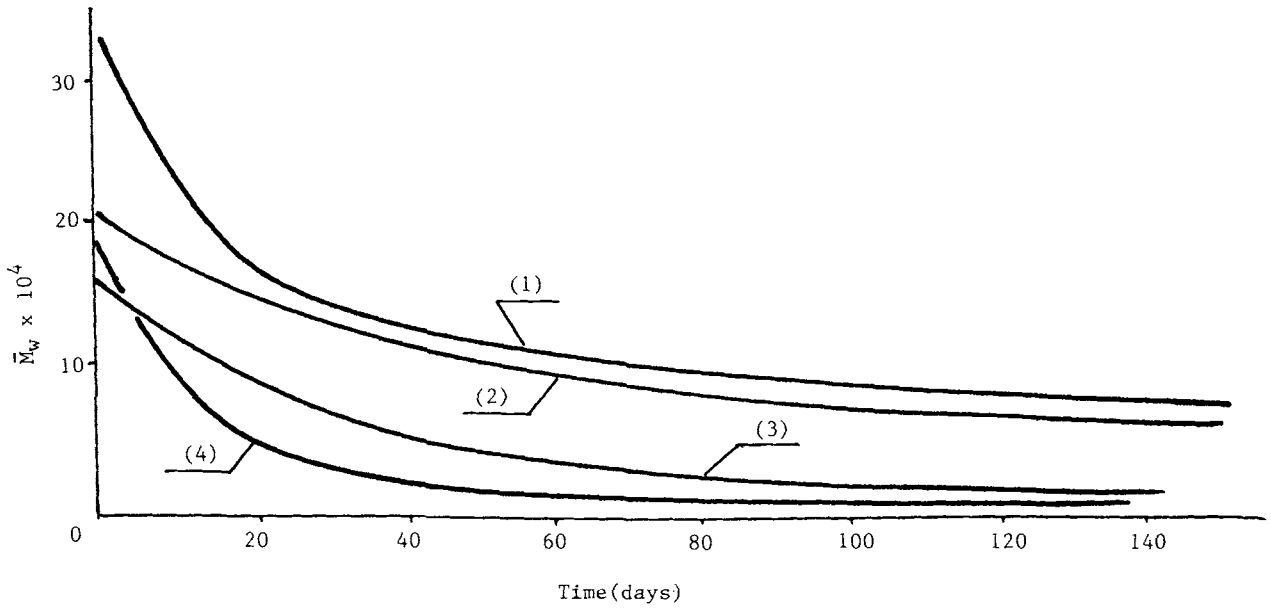

Figure 1 Plots of weight average molecular weight ($\bar{M}_w$) as a function of time: (1) PLA ($\bar{M}_w$ 3.2 × 10^5); (2) PLA ($\bar{M}_w$ 2.0 × 10^5); (3) PLGA (10% GA); (4) PLGA (20% GA).

characterized by IR and NMR, and molecular weight and distribution of molecular weight were measured by gel permeation chromatography (GPC). The composition of PLGA was calculated from the ratios of absorbance at 4.75 and 5.76 ppm. PLA and PLGA microspheres were prepared by a solvent evaporation process.[4] The microspheres with diameters of 65–100 μm were obtained by sieve and chosen for the degradation test.

Degradation *In Vitro*

The following polymers in the forms of 65–100 μm microspheres were chosen for the degradation study:

1. PLA $\bar{M}_w$ 2.0 × 10^5.
2. PLA $\bar{M}_w$ 3.2 × 10^5.
3. PLGA 10% GA $\bar{M}_w$ 1.6 × 10^5.
4. PLGA 20% GA $\bar{M}_w$ 1.7 × 10^5.

Microspheres of 150 mg were placed in a screw-capped phial containing 15 mL 0.2*M* phosphate buffer solution (pH 7.4). The degradation was carried out in a thermostatically controlled orbit shaker at 100 rpm and lasted over a period of 21 weeks at 37 ± 0.5°C. Samples were taken out at regular intervals and centrifuged to remove the buffer, then washed with distilled water and dried at vacuum at room temperature.

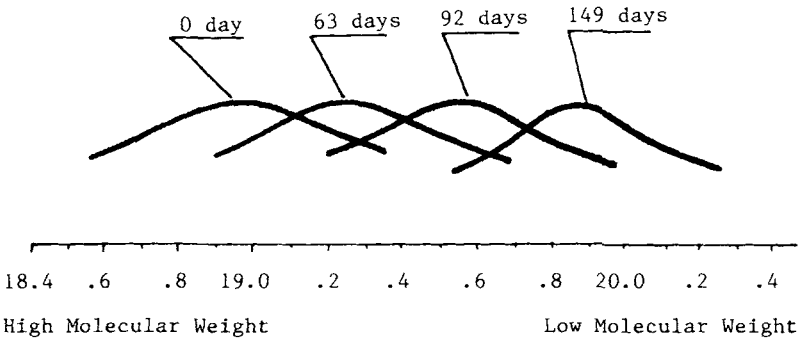

Figure 2 Molecular weight distributions of PLA ($\bar{M}_w$ 2.0 × 10^5) *in vitro* degradation.

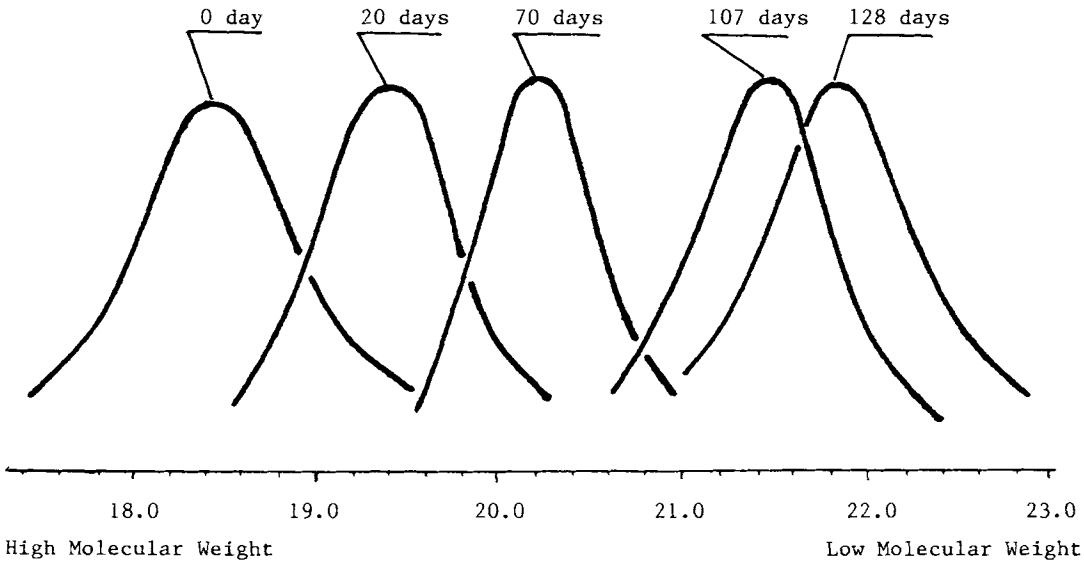

Figure 3 Molecular weight distribution of PLGA (10% GA) *in vitro* degradation.

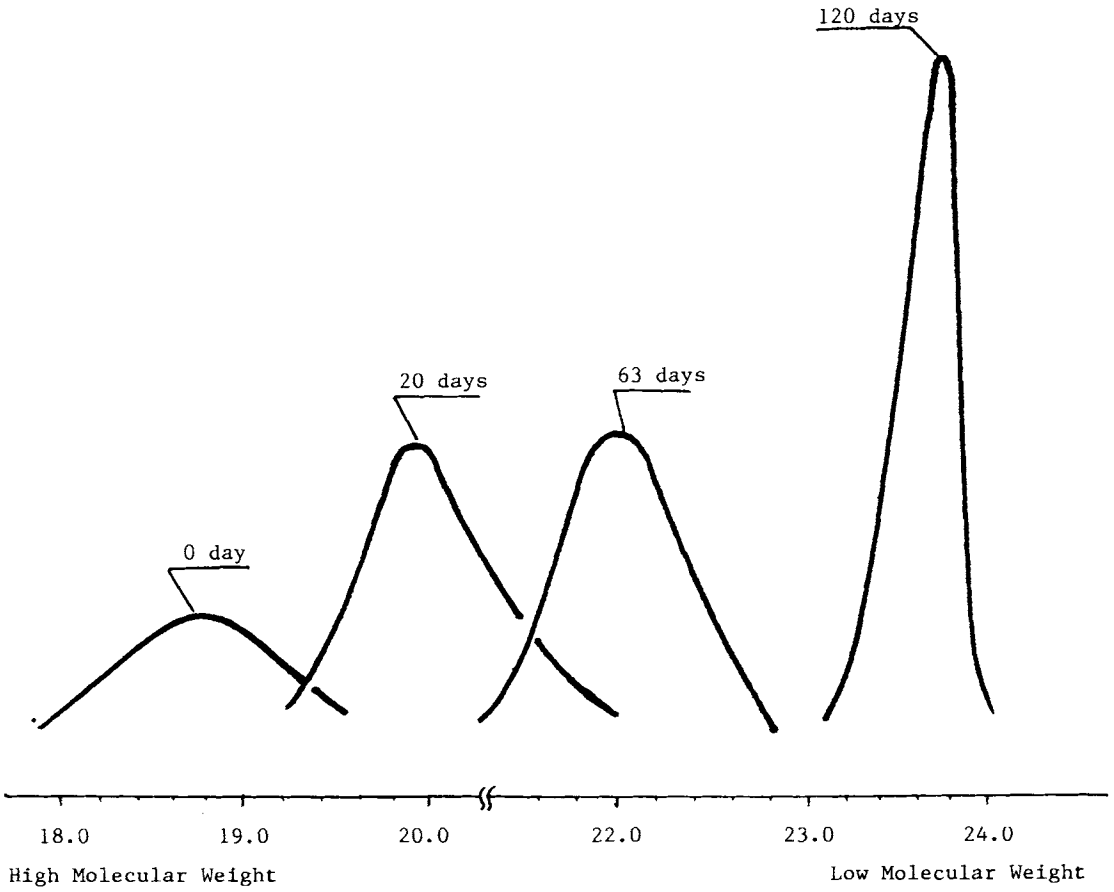

Figure 4 Molecular weight distributions of PLGA (20% GA) *in vitro* degradation.

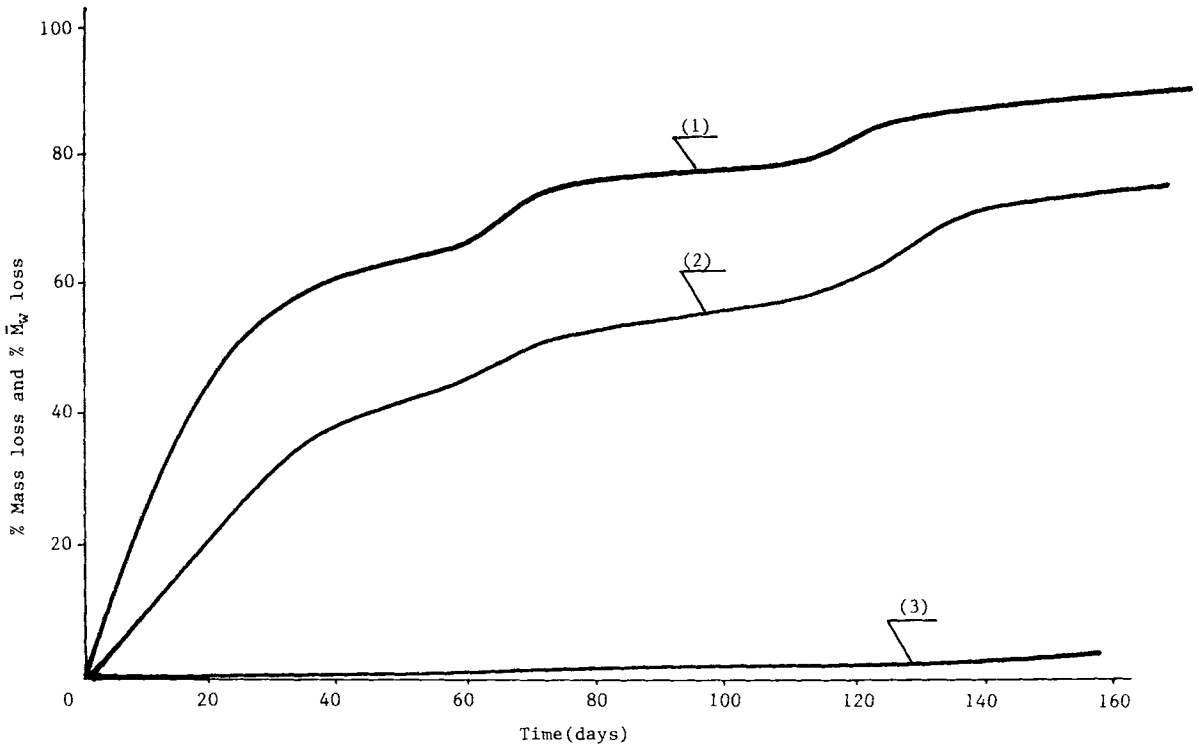

Figure 5 Mass loss and molecular weight loss of PLA *in vitro* degradation: (1) % $\bar{M}_w$ loss of PLA ($\bar{M}_w$ 3.2×10^5); (2) % $\bar{M}_w$ loss of PLA ($\bar{M}_w$ 2.0×10^5); (3) % mass loss of PLA ($\bar{M}_w$ 2.0×10^5, 3.2×10^5).

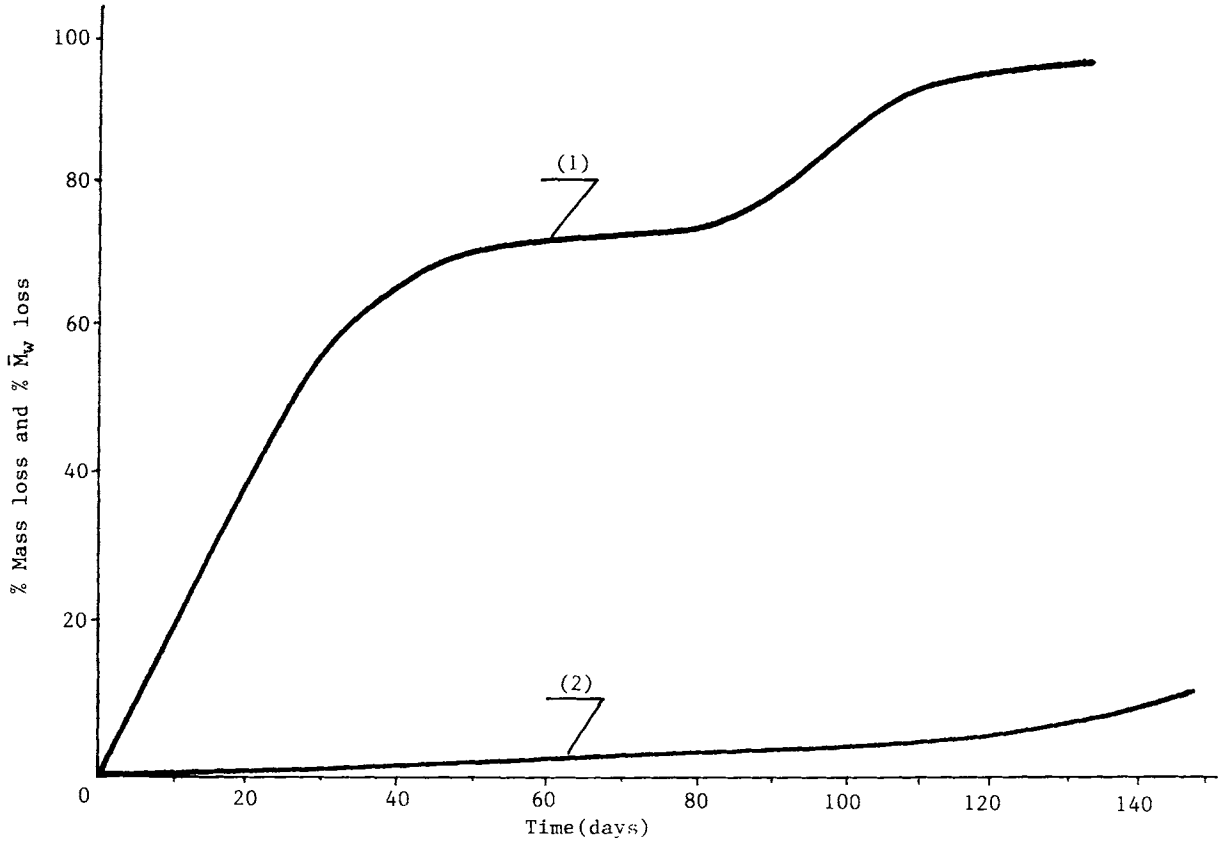

Figure 6 Mass loss and molecular weight loss of PLGA (10% GA) *in vitro* degradation: (1) % $\bar{M}_w$ loss; (2) % mass loss.

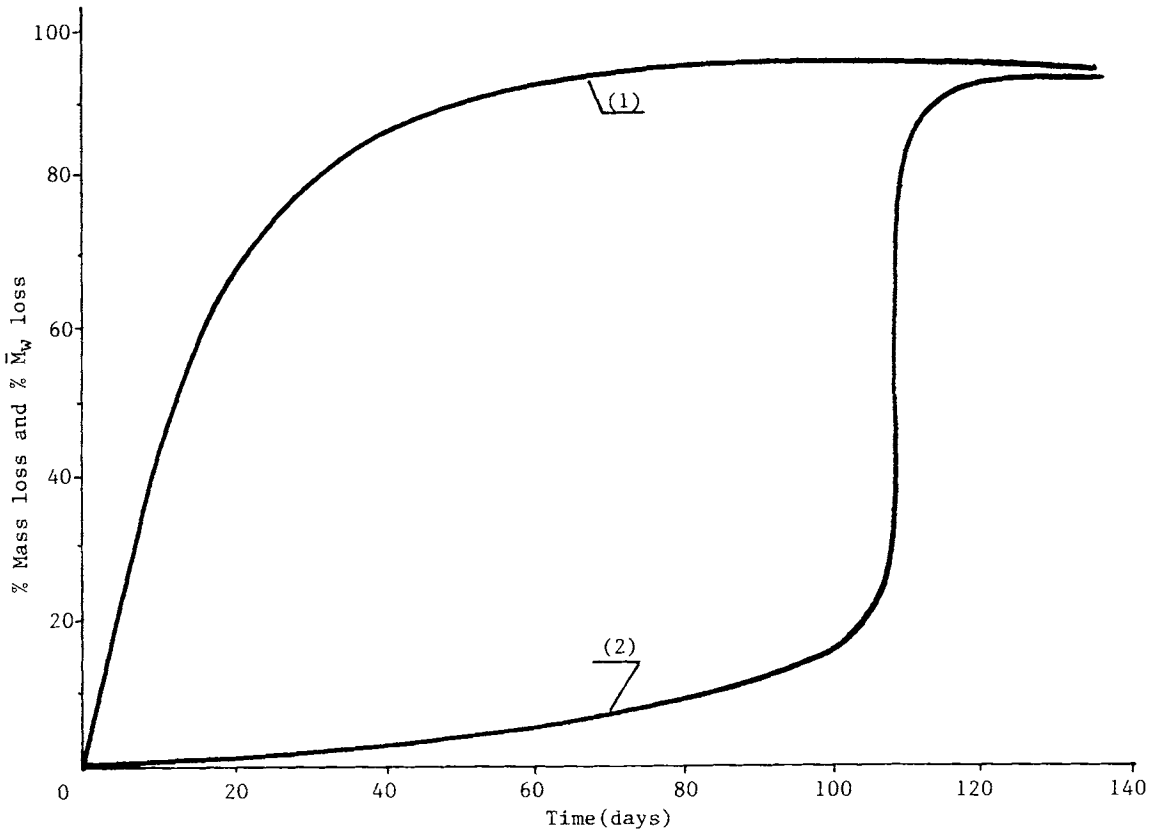

Figure 7 Mass loss and molecular weight loss of PLGA (20% GA) *in vitro* degradation: (1) % $\bar{M}_w$ loss; (2) % mass loss.

Estimation of Degradation

The degree of degradation was estimated from the decrease in $\bar{M}_w$ and changes in MWD, from the mass loss and the amount of LA/GA generated as the final degradation product in buffer solution, and from the morphological changes of microspheres.

$\bar{M}_w$ and MWD was measured by GPC in THF at 25°C with polystyrene as reference. Mass loss was calculated for each sample by comparing the dry weight remaining at a specific time with the initial weight. The amount of LA/GA was determined at different degradation periods with the titrimetric method described by Stetzlers and Smulin.[5] All samples after degradation were examined by SEM (S-450, Japan) to observe their morphological changes.

RESULTS AND DISCUSSION

The decrease in $\bar{M}_w$ of four polymer microspheres is shown in Figure 1. The rate of $\bar{M}_w$ decrease of PLA with higher molecular weight was faster at the beginning of degradation; afterward, the tendency of the $\bar{M}_w$ to decrease for both PLA was almost the same. The decrease in $\bar{M}_w$ of PLGA (10% GA) was slightly faster than that of PLA, whereas PLGA (20% GA) was much faster than the other three polymers in the $\bar{M}_w$ decrease. These results indicate that the molecular weight of these polymers do not significantly affect the rate of the $\bar{M}_w$ decrease and that the $\bar{M}_w$ decrease is strongly related to the composition of the polymer. Degradation is enhanced with the increase of GA content; this may be contributed to the increasing hydrophilic and decreasing hindrance. The degradation of polyester depends on many factors, such as the degree of crystallinity, hydrophobic or hydrophilic properties, and steric effect. Since PLA and PLGA (GA < 70%) are amorphous, the degradation is related mainly to hydropholic/hydrophilic properties and steric effects.

No significant changes in $\bar{M}_w/\bar{M}_n$ were observed from the GPC spectrum of PLA and PLGA (10% GA) (see Figs. 2 and 3) except PLGA (20% GA)

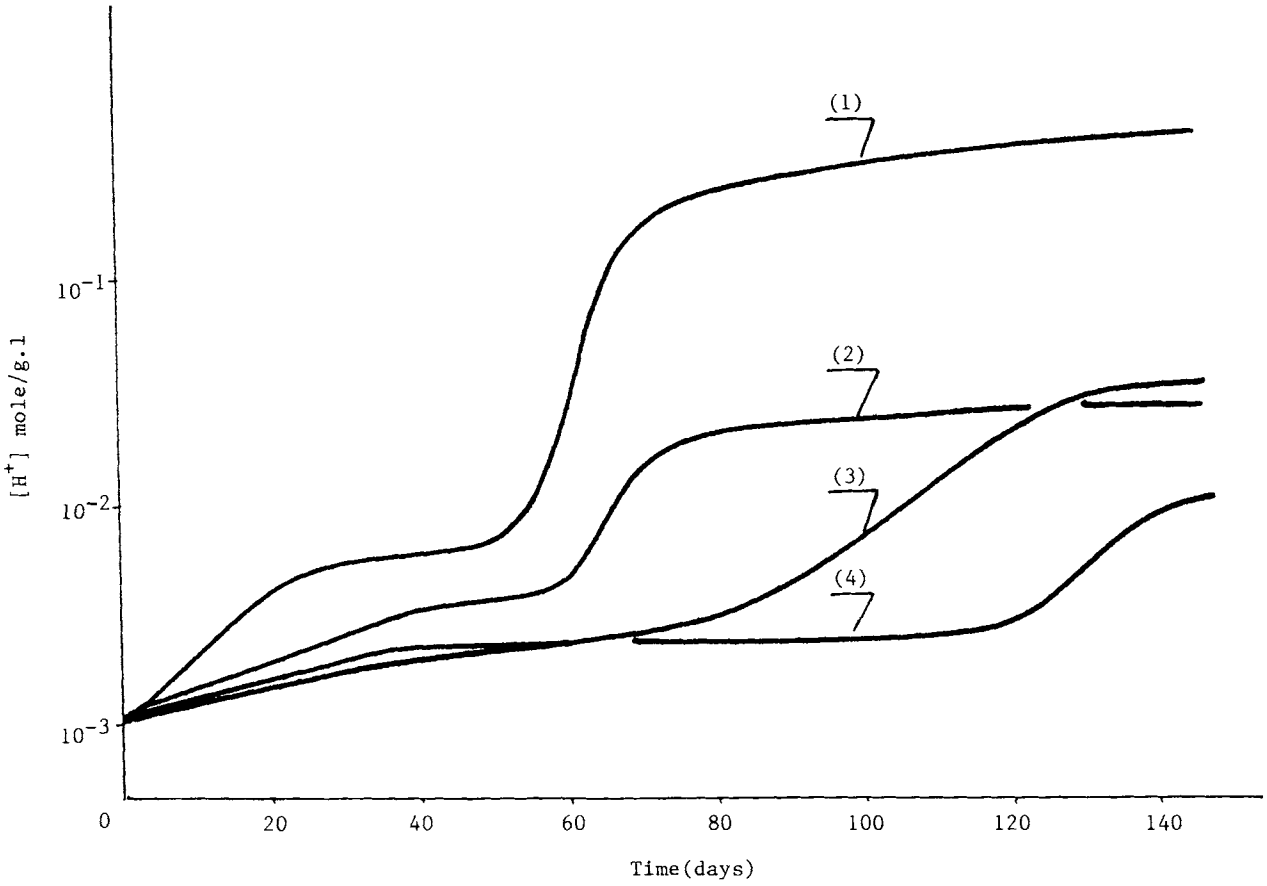

Figure 8 Amount of $[H^+]$ generated at pH 7.4 buffer solution: (1) PLGA (20% GA); (2) PLGA (10% GA); (3) PLA ($\bar{M}_w$ 3.2×10^5); (4) PLA ($\bar{M}_w$ 2.0×10^5).

(see Fig. 4) in our experiment. After 120 days degradation, PLGA (20% GA) decomposed into low molecular weight species with narrow MWD. Since PLA and PLGA hydrolytically degrade at random, it is possible, theoretically, that a narrow MWD product will appear by the end of degradation. In this experiment, the mass loss of PLA and PLGA (10% GA) was less than 5.0% after a predetermined degradation time; the degradation was not complete, so no narrow MWD was observed; and the mass loss of PLGA (20% GA) was 97%—nearly total degradation.

For PLA microspheres of two $\bar{M}_w$ 2.0×10^5 and 3.2×10^5 after 149 days degradation, the mass loss was 2.2 and 2.0%, respectively. PLGA (10% GA) and PLGA (20% GA) were 5.0 and 97%, respectively, after 120 days. This tendency was quite similar to that observed in $\bar{M}_w$ decrease profiles. Figures 5–7 show the curves of % mass loss and % $\bar{M}_w$ loss. The mass loss was slower than the loss in $\bar{M}_w$; this suggests that the mass loss continues until a fraction of low species that is soluble in the degradation medium is generated from the polymers.

The amount of LA/GA reflects the number of end groups in the polymer matrix being degraded. PLGA degrades much faster and produces more end groups, and higher molecular weight PLA has a faster degradable rate at the beginning and also produces more end groups, which conforms to the results shown in Figure 8.

Scanning electron micrography of four polymer microspheres before degradation and all samples after degradation were taken to observe the morphological changes during degradation. PLA and PLGA microspheres had a smooth, round surface before degradation [see Fig. 9(a)]. After 149 days degradation, PLA still had a smooth, round surface and remained spherical. After 113 days degradation, fissures appeared on the surface of PLGA (10% GA) microspheres, although they were approximately

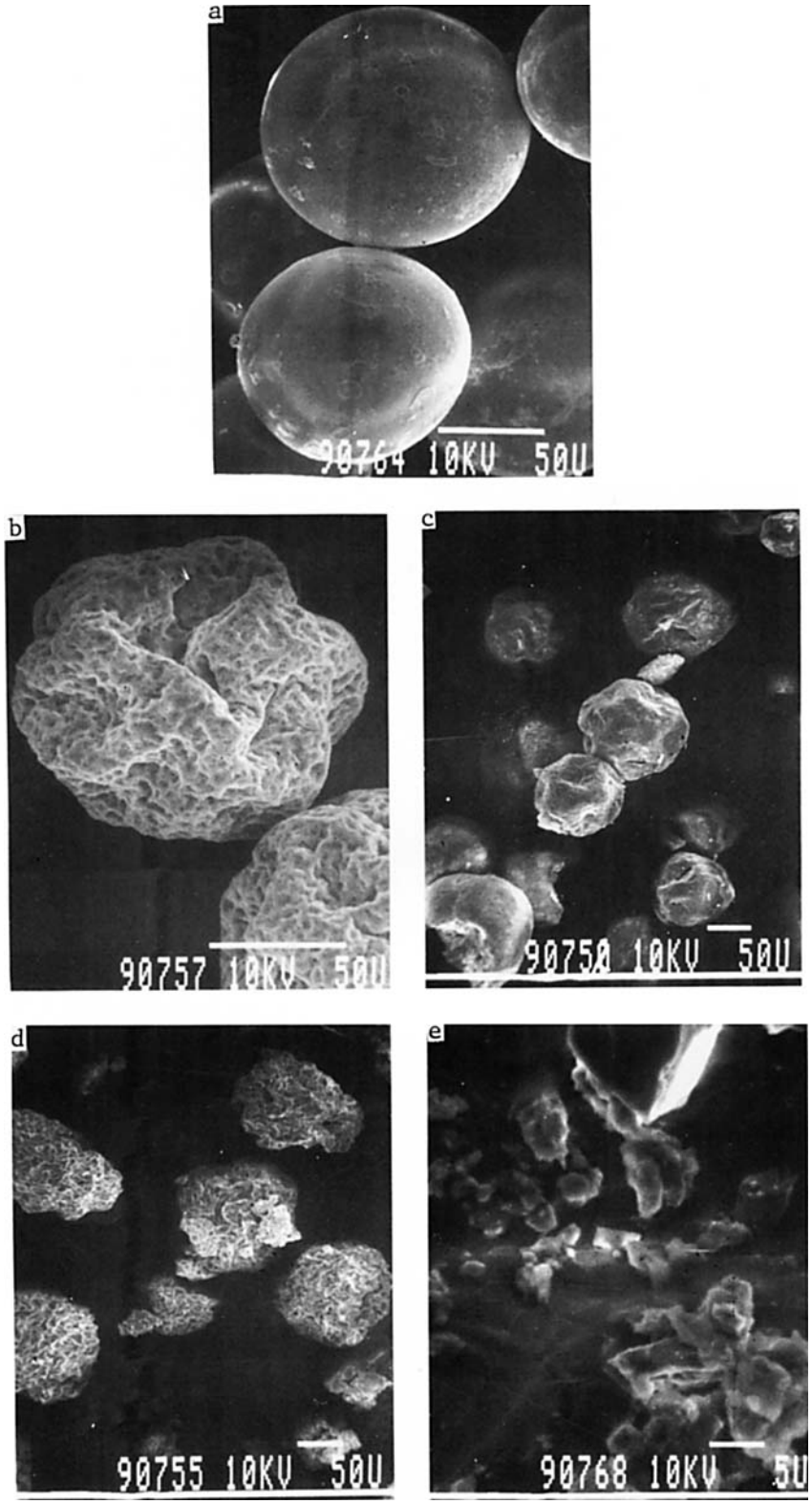

Figure 9 Scanning electron micrographs of (a) PLA microspheres before degradation; (b) PLGA (10% GA) microspheres after 113 days degradation; (c) PLGA (10% GA) microspheres after 142 days degradation; (d) PLGA (20% GA) microspheres after 63 days degradation; (e) PLGA (20% GA) microspheres after 142 days degradation.

spherical [see Fig. 9(b)], whereas after 142 days degradation, small fragments were observed [see Fig. 9(c)]. Compared with PLGA (10% GA) microspheres, PLGA (20% GA) microspheres showed apparent fissures on their surface after only 63 days degradation; meanwhile, a few small fragments were seen [see Fig. 9(d)]. PLGA (20% GA) microspheres completely decomposed into small fragments after 142 days degradation [see Fig. 9(e)].

CONCLUSION

It is concluded that the degradation of PLA and PLGA depends mainly on the composition of polymers, i.e., the GA content in polymers, not on the polymer molecular weight. The relatively fast rate of degradation will limit PLGA to long-term applications.

REFERENCES

1. K. Makino and T. Kondo, *Chem. Pharm. Bull.*, **33,** 1195 (1985).
2. A. M. Reed and D. K. Gilding, *Polymer,* **22,** 494 (1981).
3. D. K. Gilding and A. M. Reed, *Polymer,* **20,** 1459 (1979).
4. L. R. Beck, D. R. Cowsar, and D. H. Lewis, *Fertil. Steril.*, **31,** 545 (1979).
5. R. S. Stetzlers and C. F. Smulin, *Anal. Chem.*, **34,** 194 (1962).

Received October 20, 1989
Accepted January 23, 1991