Time-of-Flight Secondary Ion Mass Spectrometry Studies of Hydrolytic Degradation Kinetics at the Surface of Poly(glycolic acid)

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ABSTRACT: This paper presents a new approach for studying the hydrolytic degradation kinetics of biodegradable polymers using time-of-flight secondary ion mass spectrometry (ToF SIMS). In this study, in vitro hydrolytic degradation of polyglycolic acid (PGA) has been carried out at 37 °C in aqueous saline buffer solutions of different pH values. The molecular weight distribution of hydrolysis products was obtained from the ToF SIMS spectra. The average molecular weight of the hydrolysis products calculated from the ToF SIMS spectra is a function of hydrolysis time. Hydrolysis kinetics equations for PGA based on solid/liquid heterogeneous reaction conditions are established. A good linear relationship was obtained using this kinetics equation. The reaction rates observed in this study generally agree with observations reported in the literature. Kinetics constants for the hydrolytic degradation of PGA at different pH values have been obtained. This new approach demonstrates that ToF SIMS can be a powerful and fast technique in the study of degradation kinetics of biodegradable polymers. Using ToF SIMS, the hydrolysis kinetics of biodegradable polymers can be explored in the range of hours with in-vitro methods.

Introduction

Poly(glycolic acid) (PGA) is the simplest member in the family of poly(α-hydroxyl acid)s. Because of its biodegradability, PGA and its copolymers have been used in clinical applications and developing new biomedical applications for a few decades since its first application in absorbable sutures.[1,2] Understanding and controlling the degradation rate of PGA has been a primary research focus in the design and development of biomedical devices. Investigations of the hydrolytic degradation of PGA have been conducted both in vitro and in vivo. In early studies of PGA as absorbable sutures, investigations were mostly carried out in the bulk phase, often combined with histological observations. Pavan and co-workers[3] conducted comparative studies on PGA with catgut by histomorphological examination and mechanical measurements. Chu et al. reported results on the correlation between the hydrolytic degradation of PGA and the crystallinity,[4,5] thermal and morphological properties[6] of samples, and the effect of buffer solutions.[7] It was believed from these studies that the hydrolytic degradation of PGA proceeds through two main stages: the first stage is in the amorphous region and the second stage in the crystalline regions. The crystallinity of the material therefore changes during hydrolytic degradation. There is an initial increase and then a slower gradual decrease in crystallinity.[4] Annealing treatments of PGA resulted in initial higher levels of crystallinity. However, more rapid degradation was observed on the annealed samples.[6] Degradation in buffered saline solution reduced the tensile strength more rapidly than in unbuffered solution, in which the pH value decreased to 2.5 from the initial value of 5.0. Vert and co-workers conducted extensive studies on the hydrolytic degradation of PGA and poly(lactic acid) (PLA) and copolymers in vivo and in vitro.[8−11] The hydrolytic degradation of PGA/PLA polymer devices was found to be rather complex, especially for massive devices. The degradation of the polymer matrix inside and outside of the device can be significantly different due to the difference in mass transfer. The biodegradation rates of microspheres prepared with lactide/glycolide were investigated in vivo with rats.[12−14] Homogeneous degradation was thought to occur for microsphere drug delivery devices.[14]

However, the kinetics of hydrolytic degradation of PGA, like many other biodegradable polymers, are still far from fully understood. Part of the reason is that the hydrolytic degradation of biomedical devices made of PGA is influenced by many factors, besides the structure, molecular weight, and composition of the polymer. For example, the morphology and porosity of PGA samples, which are closely related to the history of sample preparation, influence the hydrolytic degradation significantly due to the variation of the water diffusion rate in the polymer matrix. External factors such as additives, device dimensions, sterilization procedures, and the site of implantation may also change the hydrolytic degradation rate in vivo significantly. The determination of the hydrolytic degradation kinetics of the polymer, therefore, is important for the fundamental understanding of hydrolytic degradation of PGA in vivo and, furthermore, can be used in optimization of polymer structure, morphology, and formulation for specific applications.

The experimental determination of hydrolytic degradation kinetics in vivo is extremely time-consuming, taking months to carry out full course experiments on PGA implants.[15−17] Therefore, establishing faster and

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more reliable methods for experimentally determining hydrolytic degradation kinetics of biodegradable polymers is a highly desirable experimental goal.

A range of methods for studying hydrolytic degradation kinetics of polyesters in vitro has been employed. For instance, Pitt and co-workers[18] carried out in vitro hydrolysis kinetics studies of polyesters in both solid polymer films and in solution. The hydrolysis was measured by gravimetric weight loss and molecular weight change using GPC for solid polymer samples. In solution phase, the hydrolysis was monitored by dissolution of the polymer in aqueous THF solution and measuring the molecular weight change using GPC. Verger and co-workers[19] designed an experimental procedure using monolayer spreading on aqueous solution to investigate the hydrolysis of polyesters at the monolayer/subphase interface. The monolayer of PLA was kept at constant surface pressure while the surface area was measured periodically. The hydrolytic rate was related to the surface area based on the dissolution of oligomers into the water subphase due to hydrolysis of the ester bond. It is not clear how the kinetics of monolayer degradation would relate to the kinetics of etching of devices made of PGA. Zhang and Ward[20] used IR spectroscopy in the quantitative determination of the change of end group concentration during hydrolytic degradation of polyesters. However, few of the currently used techniques can examine hydrolyzed samples in a morphology similar to that in practical application of the polymeric devices. It is understood that[9] the hydrolytic degradation of poly(lactic-*co*-glycolic acid) (PLA/GA) devices is a complex reaction−diffusion balance. Therefore, studying the hydrolytic degradation of PGA in the sample format similar to that in practical applications is of practical importance.

In our previous papers,[21,22] we have described a new approach for the ToF SIMS study of biodegradable polymers. It demonstrated that the hydrolytic degradation products of PGA can be detected in ToF SIMS as intact molecular ions. In this paper, we present the results of a ToF SIMS study of the hydrolytic degradation of PGA under various conditions and the approach of direct experimental determination of PGA hydrolytic degradation kinetics using ToF SIMS. In this approach, the low molecular weight oligomers of hydrolytic degradation products are ionized as intact molecular ions. A distribution of molecular ions of hydrolytic degradation products has been observed in the ToF SIMS spectra. This distribution of intact oligomer molecules is followed as a function of hydrolysis time. The average molecular weight of the hydrolysis products at the sample surface, therefore, can be obtained from the ToF SIMS spectra. Kinetics analysis of the hydrolytic degradation has been conducted using the ToF SIMS data. Because no specific sample preparation is required in ToF SIMS analysis, this approach demonstrates that samples of biomedical implants can be directly investigated using ToF SIMS without any modification. This eliminates the possibility of introducing other factors that may alter the nature of biomedical implants.

The effect of pH conditions of the hydrolysis environment on the degradation kinetics of PGA was also investigated.

Experimental Section

High molecular weight PGA samples were obtained as a generous donation from Dr. Peter Jarrett of Davis & Geck Division of American Cyanamid Company (One Casper St., Danbury, CT). Physiological buffer solution ISOTON II (pH = 7.4) was purchased from Coulter Diagnostics (a division of Coulter Electronics, Inc., Hialeah, FL). Potassium carbonate−potassium borate−potassium hydroxide buffer solution (pH = 10.0 at 25.0 °C) and potassium hydrogen phthalate buffer solution (pH = 4.0 at 25.0 °C) were purchased from Fisher Scientific. All solutions were used as received without further purification or treatment. Hydrochloric acid was purchased from Fisher Scientific. Sodium hydroxide was purchased from J. T. Baker, Inc. (Phillipsburg, NJ). Reagent grade hexanes and chloroform were purchased from Aldrich for surface cleaning. All solvents were used as received.

PGA disk samples were made by melt-press to ca. 1 mm thick and cut to 8 × 8 mm. Before preparing the disk samples, PGA plates were cut to small pieces and ultrasonically cleaned in hexanes and chloroform, 10 min in each solvent. Aluminum foil was precleaned using the same solvents. PGA plates were placed between aluminum foil sheets and pressed at 200 °C, and then the aluminum sheets were peeled off for the PGA samples. There was no contamination observed for untreated PGA samples in the low mass-to-charge range of ToF SIMS spectra as before (data are not shown).[21,22] Typical contamination might have resulted in signals from residual Al_2O_3 (e.g., $^{27}Al^+$) or signals from low mass organic contaminants, which would not be present above 300 Da.

All hydrolysis treatments were performed at 37.0 ± 0.2 °C using a constant-temperature bath (Fisher circulator model 73). PGA disk samples were immersed in 14 mL of aqueous hydrolysis solution prefilled in 25 mL vials. The whole vial containing the PGA sample and solution was placed in the isothermal water bath. PGA samples were washed carefully with distilled water after the hydrolysis experiments to remove the majority of inorganic salts from the sample surfaces and then vacuum-dried. The posthydrolysis samples were then stored in air-sealed vials for ToF SIMS analysis.

Hydrolysis experiments were conducted in neutral buffer condition (ISOTON II, pH = 7.4), sodium hydroxide adjusted ISOTON II solution (pH = 10.0), potassium carbonate−potassium borate−potassium hydroxide buffer solution (pH = 10.0), and potassium hydrogen phthalate buffer solution (pH = 4.0) to examine the hydrolysis degradation under various pH conditions. The pH values of the solutions were monitored using a Digital Ionalyzer, model 501 of Orion Research, Inc. (Cambridge, MA). No pH value changes were observed for hydrolysis experiments in all buffer solutions beyond ±0.1 units, and the largest pH value change in the sodium hydroxide adjusted pH 10.0 ISOTON II solution was 0.45 ± 0.3 units up to 24 h of hydrolysis time.

ToF SIMS analysis was conducted using a Physical Electronics 7200 time-of-flight secondary ion mass spectrometer equipped with a cesium ion gun and a channel plate detector. The primary ion gun was operated at 8 keV for all experiments. Static mode was used in all acquisitions with primary ion current of 0.3 pA. The pulse width of primary ion current was 1.0 ns. The total ion dosage in each spectral acquisition was no more than 1×10^{11} ions/cm^2. An electron neutralizer was operated during all spectral acquisitions in pulsed mode at low electron energy with a target current under 1 μA for charge compensation. A time resolution of 1.25 ns per step was used for good signal-to-noise ratio at high m/z range. Data reduction was performed using Physical Electronics TOFPak software (version 2.0). Relative peak intensities were obtained by converting the spectra to ASCII file format and integrating peak areas using the data analysis function built-in in Origin (Microcal Software, Inc, Northampton, MA). The surface molecular weight and distribution were calculated by peak area using Googly software.[23]

Theory and Calculation

The hydrolytic degradation reaction of polyesters in aqueous solution is shown in Figure 1. It is generally agreed that two steps are involved in the polymer

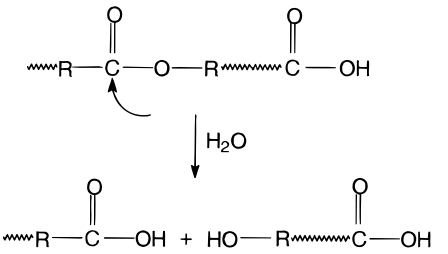

Figure 1. Scheme for hydrolytic degradation of polyesters.

degradation.[24] In the first step, random chain scission occurs, which results in a decrease in polymer molecular weight. Certain changes in polymer properties such as tensile strength and morphology may be associated with this step, but no weight loss of the polymer sample should be involved. The second step starts when the degradation-generated oligomers become small enough to desorb from the sample surface and diffuse into the surrounding liquid phase. Random chain scission and weight loss of the polymer sample take place simultaneously in this step until the process of polymer erosion is completed. In this step, the hydrolysis occurs in two different forms simultaneously. One is the heterogeneous degradation of the solid polymer sample at the solid/liquid interface. The other is the homogeneous hydrolytic reaction of oligomers in the solution phase. In the present study, only the hydrolytic degradation of the solid polymer sample at the solid/liquid interface is considered; therefore, there is no difference in terms of the reaction kinetics between the first and second step of hydrolytic degradation. Chain scission starts at the moment when the polymer sample is placed in contact with the solution and continues until erosion of the solid sample is completed at a reaction rate associated with certain reaction conditions.

Various reaction mechanisms have been proposed in the literature[18,25−27] for the hydrolytic degradation of polyesters, in particular the autocatalytic mechanism[26] and nonautocatalytic mechanism.[27] In the autocatalytic mechanism, it is thought that the hydrolysis reaction of the polyester is catalyzed by the reaction product, the carboxylic acid. This mechanism applies to the homogeneous reaction in which the reactant and product have free motion and interaction in the solution phase. For the heterogeneous reaction at the solid/liquid interface, the motion of the carboxylic acid end groups is restricted by the solid polymer matrix. Therefore, the concentration of carboxylic acid available for reaction at the interface depends only on the solution composition. In cases when the solution composition is constant (such as buffered solution or in well-circulated systems), a pseudo-first-order reaction rate is observed; therefore, the autocatalytic effect of the reaction products will not be considered as an issue in this study.

Consider that the reaction shown in Figure 1 occurs at the solid/liquid interface without counting the influence of the concentration of carboxylic acid on the PGA hydrolysis reaction. The hydrolysis reaction rate law is expressed as

$$\frac{\mathrm{d[E]}}{\mathrm{d}t} = -k[\mathrm{E}][\mathrm{H_2O}] \tag{1}$$

where [E] is the molarity of ester linkages in the solid polymer matrix and [H_2O] the concentration of water in the liquid phase. When the concentration of water is

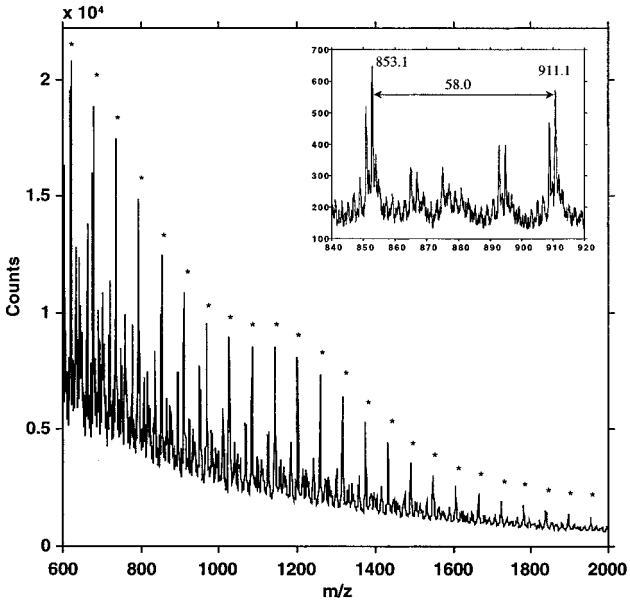

Figure 2. Sample ToF SIMS spectra of hydrolyzed PGA showing the molecular ion peaks and the molecular ion distribution. The spectrum was taken on a PGA sample hydrolyzed in neutral saline solution for 4 h.

a constant, the equation becomes

$$\frac{\mathrm{d[E]}}{\mathrm{d}t} = -k'[\mathrm{E}] \tag{2}$$

in which $k' = k[\mathrm{H_2O}]$ is the apparent reaction constant. Let D_t being the degree of polymerization at time t; by relating [E] to D, eq 2 can be integrated to give

$$\ln \frac{D_t - 1}{D_t} = \ln \frac{D_0 - 1}{D_0} - k't = c - k't \tag{3}$$

where c is a constant and D_t the average degree of polymerization at the sample surface at time t of hydrolysis. Thus, the plot of $\ln(D_t - 1)/D_t$ versus reaction time t should give a straight line, in which the starting molecular weight determines the intercept of the straight line only. This result is same as Pitt's derivation[27] although based on different assumptions.

The molecular weight of hydrolysis products is calculated from the molecular ion peak intensities of ToF SIMS spectra. Figure 2 shows a typical molecular ion distribution of the hydrolysis products of PGA. The spectrum was acquired from a disk sample of PGA hydrolyzed in neutral solution for 4 h. Each of the star-marked peaks is an intact molecular ion peak. The intensity displayed in *counts* represents the population of the molecule at each particular molecular weight. It is possible that lower mass oligomers would have higher ionization probabilities than higher mass oligomers. This phenomenon has been reported by our group for PDMS molecular weight distribution in SIMS and MALDI.[28] In the present study we cannot evaluate this. So, we assumed that all oligomers have the same ionization potential. The error that would result from this assumption would shift the reported apparent M_n to a lower value. By integrating only the area of the molecular peaks, the molecular weight distribution is obtained in this study. To improve the precision in data reduction, all of peaks with the same repeat number will be integrated and summed in the next PGA study

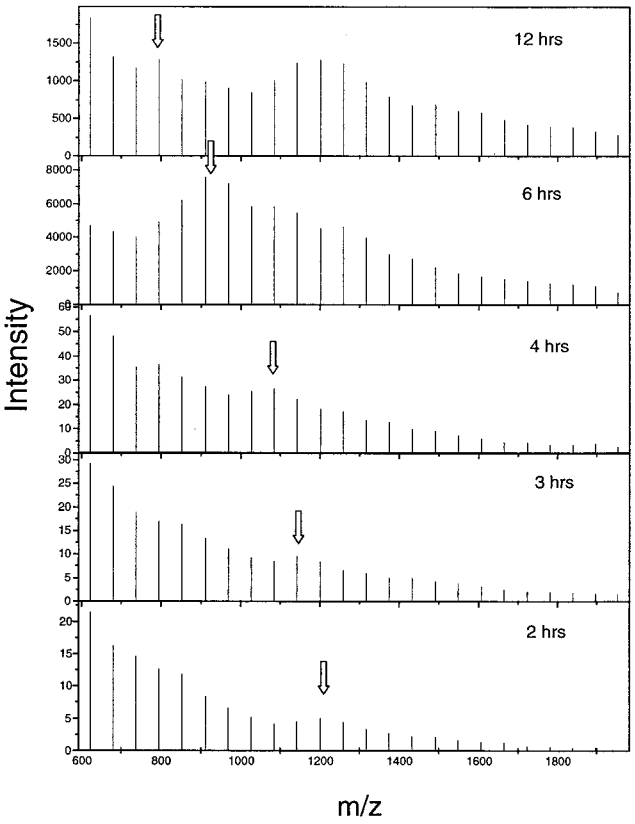

Figure 3. Plots of molecular weight distribution of different hydrolysis time, calculated from ToF SIMS spectra of PGA samples hydrolyzed in neutral saline solution.

for the direct comparison of change in bulk crystallinity vs the hydrolytic surface degradation rate.[29] Figure 3 is an example of the molecular weight distributions calculated from the ToF SIMS spectra for PGA hydrolyzed in neutral saline solution for different times. A multiple molecular weight distribution can be seen growing and second crest of the distribution (marked with arrows in Figure 3) moving toward lower molecular weight as the hydrolysis time increases. This phenomenon can be confirmed by referring the apparent M_n change calculated in Table 1. Despite the presence of multiple peak crests, we treated all distribution similarly and calculated one global M_n. In future work we will examine the origin of multiple distribution.

The average molecular weight (M_n) was calculated using the intensities obtained from the integration of the molecular ion peaks (the data of Figure 3) in place of the number of molecules in each molecular weight. This calculation was performed using the Googly software.[23] The average degree of polymerization at time t is defined as the average number of repeat units in the hydrolysis products:

$$D_t = \frac{M_n - 18}{58} \tag{4}$$

where 18 is the mass of the end groups and 58 the mass of PGA repeat unit.

Results of Kinetics Analysis

The average molecular weight (M_n and M_w) and the degree of polymerization with respect to the hydrolysis time calculated using eq 4 for the hydrolysis experiments conducted in different solutions are listed in Table 1. The degree of polymerization data plotted versus hydrolysis time using eq 3 are shown in Figure 4a−d. As discussed above, the molecular weight at the sample surface continuously decreases during the hydrolysis experiments until the oligomers become small

Table 1. Hydrolysis Results of PGA[a]

time (h)	M_n	M_w	D_t
pH 7.4 ISOTON II Physiological Buffer Solution			
2	1269.9	1306.6	21.6
3	1243.2	1274.1	21.1
4	1101.1	1144.5	18.7
6	1041.6	1121.9	17.6
12	1034.3	1128.2	17.5
pH 4.0 Acidic Buffer Solution			
1	1159.9	1213.5	19.7
3	1093.6	1156.7	18.5
6	1038.5	1144.2	17.6
12	1033.1	1130.3	17.5
NaOH Adjusted pH 10.0 ISOTON II Solution			
1	1243.7	1306.2	21.1
2	1114.2	1226.1	18.9
3	1018.2	1082.1	17.2
4	986.6	1043.9	16.7
pH 10.0 Basic Buffer Solution			
2	1129.8	1214.5	19.2
3	1105.9	1192.1	18.8
4	1068.9	1147.3	18.1
6	1035.7	1128.2	17.5
12	1020.2	1117.2	17.3
24	1038.7	1130.3	17.6

[a] Data contain 5% relative standard deviation.

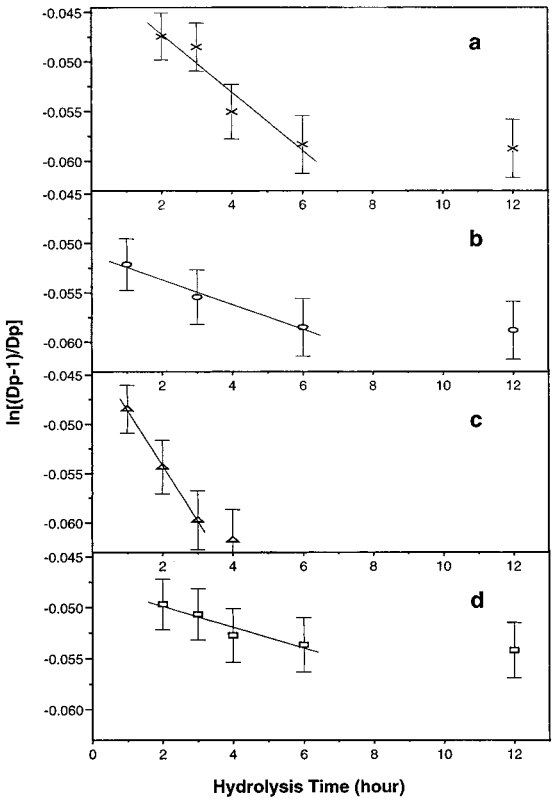

Figure 4. Semilog plot of degree of polymerization versus hydrolysis time using eq 3: a, PGA disk sample hydrolyzed in ISOTON II physiological buffer solution (pH = 7.4); b, hydrolyzed in potassium hydrogen phthalate buffer solution (pH = 4.0); c, hydrolyzed in sodium hydroxide adjusted ISOTON II solution (pH = 10.0); d, hydrolyzed in potassium carbonate−potassium borate−potassium hydroxide buffer solution (pH = 10.0).

Table 2. PGA Hydrolysis Reaction Constants[a]

solution	pH	k' (s^{-1})	k (s^{-1} mol^{-1})	R^2
ISOTON II	7.4	0.0029	5.2×10^{-5}	0.92
acidic buffer	4.0	0.0013	2.3×10^{-5}	0.98
ISOTON II/NaOH	10.0	0.0055	9.9×10^{-5}	0.99
basic buffer	10.0	0.0013	2.3×10^{-5}	0.98

[a] 5% relative standard deviation applies to reaction constant results.

enough to diffuse into solution. Then the molecular weight at the sample surfaces becomes stable when the surface ester bond scission and the desorption of small oligomers reach a steady state. This is exemplified by the plots (Figure 4) using eq 3 without exception. The first few points show good linear relationships as predicted by eq 3, and extra points at longer hydrolysis times show leveled values with respect to hydrolysis time. In Figure 4, one extra point is shown in each plot to illustrate this relationship. The reaction constants are calculated by regression using the first few data points in the linear relationship.

As an example, Figure 3 shows the results of the calculated molecular weight distributions from the ToF SIMS spectra of PGA hydrolyzed in neutral solution. The calculation range of molecular ion peaks was chosen from 600 to 2000 Da in all data analyses in this study for consistency although molecular ion peaks beyond this range were observed in some ToF SIMS spectra of hydrolyzed samples.[18] Those peaks should not significantly influence the results in average molecular weight calculations because the major contribution comes from the peak crest that represents the most probable molecular weight distribution.

The reaction constants obtained from the slopes of the linear regression using eq 3 are listed in Table 2, in which k' is the apparent reaction constant and k is the absolute reaction constant at the specified solution acidity. A relative standard deviation of 5% was estimated for the reaction constants using error propagation theory,[30] indicating good reproducibility of data for this method.

Figure 4a is the semilog plot of degree of polymerization of the hydrolysis in neutral ISOTON II buffer solution versus hydrolysis time using eq 3. A reaction constant of $(5.2 \pm 0.3) \times 10^{-5}$ s^{-1} mol^{-1} resulted from this linear regression. The point for 12 h of hydrolysis time shows that the molecular weight at the sample surface has reached steady state in about 6 h. The equilibrium could also be due to factors related to diffusion in the polymer matrix.

The hydrolysis under acidic buffer conditions (potassium hydrogen phthalate buffer solution, pH = 4.0) also reached equilibrium in about 6 h, as shown in Figure 4b. However, the reaction constant obtained from this regression shows a slower reaction rate. The degree of polymerization data shown in Table 1 indicate that, in the acidic buffer solution, the surface molecular weight decreases quickly at the beginning of the reaction, suggesting that the higher H_3O^+ concentration in solution caused faster initial reaction, but after the initial period, the reaction proceeds at a lower rate. The same phenomena were also observed in the literature for similar studies in acidic solution.[19] This will be discussed further in the next section.

A much faster reaction rate was observed under the basic conditions for sodium hydroxide adjusted ISOTON II solution, as shown in Figure 4c, while a slower rate

Table 3. Comparison of Chemical Composition in ISOTON II and Potassium Carbonate−Potassium Borate−Potassium Hydroxide Buffer Solutions

ISOTON II	potassium carbonate−potassium borate−potassium hydroxide buffer solution
sodium chloride	potassium carbonate
potassium chloride	potassium hydroxide
monosodium phosphate	potassium borate 5 hydrate
disodium phosphate	disodium EDTA dihydrate
disodium EDTA	
sodium fluoride	

was observed in the potassium carbonate−potassium borate−potassium hydroxide buffer solution at the same pH (both pH = 10.0). The adjustment of pH using sodium hydroxide has slightly reduced the buffer capacity of sodium hydroxide adjusted pH 10.0 ISOTON II solution; the change in pH value after 24 h hydrolysis treatment was $\Delta(pH) = 0.45 \pm 0.3$ for the NaOH adjusted pH 10.0 ISOTON II solution. The reaction constant for the sodium hydroxide adjusted ISOTON II solution was $(9.9 \pm 0.5) \times 10^{-5}$ s^{-1} mol^{-1}, about double the rate in neutral ISOTON II buffer solution. However, hydrolysis in the potassium carbonate−potassium borate−potassium hydroxide buffer solution was remarkably slow; the reaction constant was only $(2.3 \pm 0.2) \times 10^{-5}$ s^{-1} mol^{-1}. The slower reaction rate in this basic buffer solution may be explained by the generation of a Lewis acid during the hydrolytic degradation of PGA in the potassium carbonate−potassium borate−potassium hydroxide buffer solution. A comparison of chemical composition of the solutions is given by Table 3. As shown in Table 3, the basic buffer solution contains potassium borate, which the ISOTON II solution does not. It is well-known that the hydrolytic degradation in basic aqueous solution involves bond breaking of acyl−oxygen linkages in the polyester backbone by nucleophilic attack of hydroxide ion to form acid and alcohol groups as degrading products, and in high-pH media the borate ion goes directly to boron tetrahydroxide.[31]

$$B_4O_7^{2-} + 2OH^- + 7H_2O \rightarrow 4B(OH)_4^- \qquad (5)$$

Hence, the boron tetrahydroxide ions generated in pH 10.0 solution would be reacted with carboxylic acid end groups produced during the hydrolysis treatment to finally yield boric acid, a Lewis acid, the amount of which would be proportional to the hydrolytic degradation rate of PGA in the basic buffer solution.

$$B(OH)_4^- + H^+ \rightarrow B(OH)_3 + 2H_2O \qquad (6)$$

To evaluate the effect of borate in the buffer solution, potassium borate was added to sodium hydroxide adjusted pH 10.0 ISOTON II solution to a concentration of 0.02 M, followed by 24 h hydrolysis treatment. The change in pH value was $\Delta(pH) = 0.14 \pm 0.2$ for the NaOH adjusted pH 10.0 ISOTON II solution with borate. When comparing it with the pH change for NaOH adjusted pH 10.0 ISOTON II solution without borate, it can be seen that the borate in aqueous solution plays a role to resist changes in pH. Therefore, generation of boric acid, a Lewis acid, could have a retardation effect on this nucleophilic reaction. Figure 5 shows the molecular distribution of the hydrolysis products in the potassium carbonate−potassium borate−potassium hydroxide buffer solution. For all samples hydrolyzed in

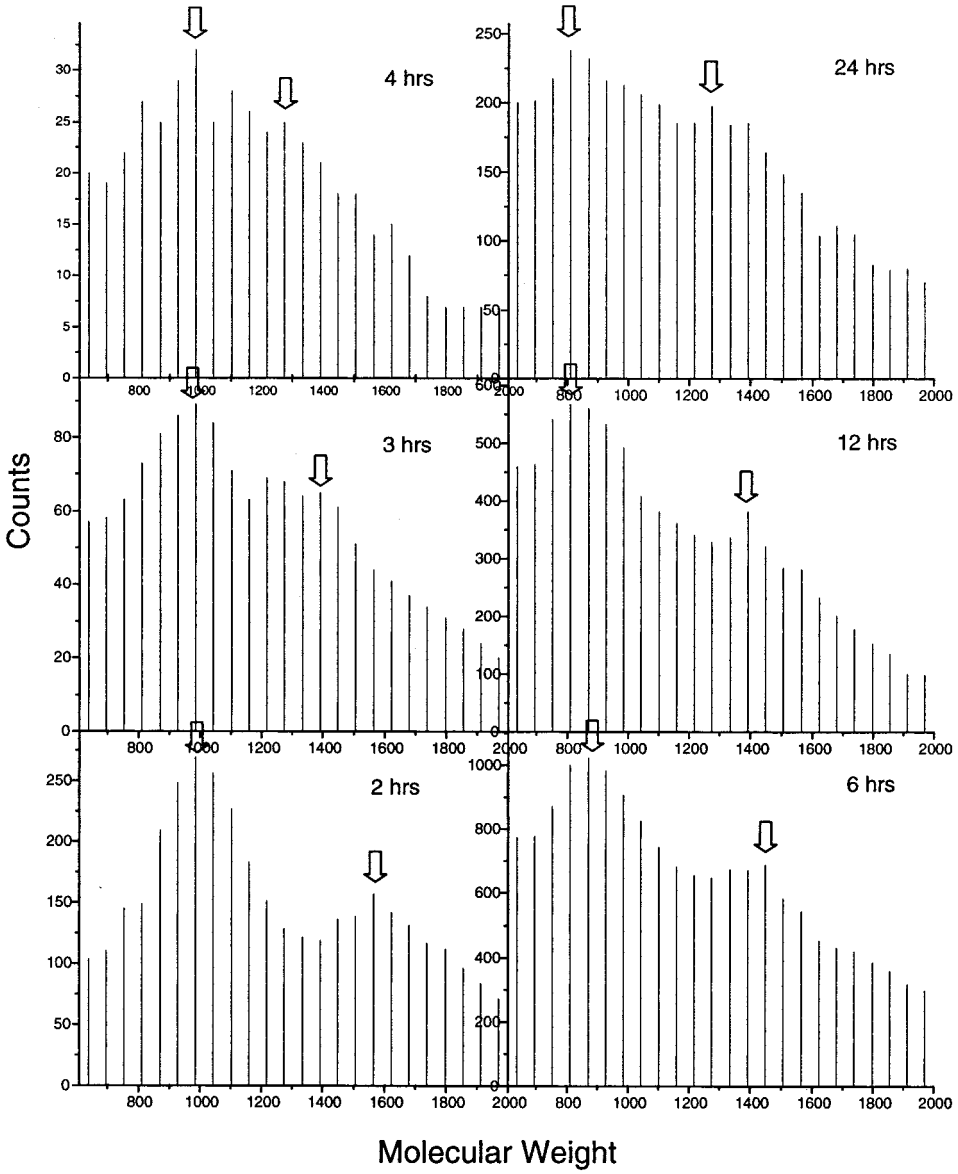

Figure 5. Plot of molecular weight distribution of hydrolysis products shows the double molecular weight distributions for each sample. PGA sample hydrolyzed in potassium carbonate−potassium borate−potassium hydroxide buffer solution (pH = 10.0).

this buffer solution, there is a double distribution at least observed in every ToF SIMS spectrum, as shown in Figure 5 (sometimes, a multiple distribution). One explanation is that a reesterification reaction may have taken place at the sample surface which generated the double distribution. Another possibility is that the second distribution comes from lower layers of the sample. To understand the effect of the PGA surface degradation rate on the change in PGA thermal bulk properties, we are presently investigating the surface degradation kinetics of PGA using other buffer systems to eliminate this unexpected retardation effect of a Lewis acid.[29]

Discussion

We would like to place the results of present study in context with other work on the degradation kinetics of polyesters. The state of understanding of polyester hydrolytic degradation kinetics on the literature is controversial. A few researchers[8−10,18,20,25,26] reported that the hydrolytic degradation of polyesters follows an *autocatalytic* mechanism, in which the carboxylic end group of the polyester generated in the hydrolysis has a catalytic effect. Pitt et al.[18,25,26] used first-order kinetics for the carboxylic functional group in the description of the hydrolysis kinetics of polyesters. Ward et al.[20] used half-order reaction kinetics for the carboxylic functional group in their kinetics studies. The catalytic effect of the carboxyl group was attributed to the neutral carboxylic acid group,[25,26] which is hydrogen-bonded to the ester groups. In this study, the catalyst effect of the carboxylic end group was regulated by the buffer solution as discussed above. The regression results using eq 3 do give reasonably good linear relationships.

However, the reaction kinetic constant of the hydrolysis in acidic buffer solution obtained in this study shows that the reaction rate is slower than that in basic solutions after the reaction is initiated. Similar observations for the hydrolytic degradation of PGA were also reported in the literature. For example, Chu[7] reported that the hydrolysis of PGA was slower when it was hydrolyzed in unbuffered acidic saline solution (with pH value of 5.0 initially to 2.5 at the end of the experiment)

than in buffered neutral saline solution. It was considered that the accumulated acids generated in the hydrolysis gradually retarded the hydrolysis and slowed the degradation rate.[7] This is opposite to that observed by Pitt et al.[18] These controversial results may be due to the fact that the apparent hydrolysis rate and even mechanisms of degradation of this polyester are closely related to the sample dimension and geometry,[9] in addition to the different experimental methods or procedures used in individual studies. It was found that[9,10] large-sized PGA devices hydrolyze quite differently from small particles such as microspheres. This was considered to be due to the significant differences in mass transfer in different sample geometries, as well as different experimental conditions.

Verger and co-workers[19] studied the hydrolysis kinetics of PLA using monolayers. In acidic solution, the reaction rate slowed down remarkably after the first 15 min while the reaction in basic solution was close to linear over the whole reaction period of 1 h. In the first 10 min, however, the reaction rate in acidic solution was noticeably higher than that in basic solution. This is consistent with what we observed in this study, suggesting that the acidity of the solution may not be the catalytic factor.

In the present study, hydrolysis products are selectively observed from the surfaces of hydrolyzed samples. The diffusion process is presumably much faster in the present experimental conditions compared with hydrolysis of the ester bonds. Kinetic analysis showed that using eq 3 gave good linear relationships for all hydrolytic degradation data in saline solutions with different pH values. These results suggest that a systematic study of the mass transfer process in the bulk phase of PGA samples would be helpful to clarify the hydrolysis mechanism of PGA having different morphologies.

Conclusion

In vitro hydrolytic degradation of PGA has been investigated using ToF SIMS in aqueous saline solutions of different pH values. It is demonstrated that, by using the molecular ion peak distribution of hydrolytic degradation products observed in ToF SIMS spectra, the average molecular weight of hydrolysis products can be obtained; the molecular weight is a function of hydrolysis time.

The hydrolysis kinetics equation for PGA was established for different systems based on solid/liquid heterogeneous reaction conditions, without considering the concentration of acidic species in solution. Experimental data fit the kinetics equation with good linear relationships. The reaction rates obtained in this study generally agree with observations reported in the literature. Kinetics constants were calculated for the hydrolysis degradation of PGA at different pH conditions using the ToF SIMS data.

This new approach demonstrates that ToF SIMS can be a powerful and fast technique for the study of degradation kinetics of biodegradable polymers. The time scale for obtaining hydrolytic degradation kinetics can be reduced from weeks to the range of hours.

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References and Notes

(1) Schmitt, E. E.; Polistina, R. A. U. S. Patent 3297033, 1967.
(2) Frazza, E. J.; Schmitt, E. E. *J. Biomed. Mater. Res.* **1971**, *1*, 43.
(3) Pavan, A.; Bosio, M.; Longo, T. *J. Biomed. Mater. Res.* **1979**, *13*, 477.
(4) Chu, C. C. *J. Appl. Polym. Sci.* **1981**, *26*, 1727.
(5) Chu, C. C. *Polymer* **1980**, *21*, 1480.
(6) Chu, C. C.; Browning, A. *J. Biomed. Mater. Res.* **1988**, *22*, 699.
(7) Chu, C. C. *J. Biomed. Mater. Res.* **1981**, *15*, 19.
(8) Li, S.; Vert, M. In *Degradable Polymer*; Scott, G., Gilead, D., Eds.; Chapman and Hall: London, 1995.
(9) Vert, M.; Mauduit, J.; Li, S. *Biomaterials* **1994**, *15*, 1209.
(10) Vert, M.; Li, S.; Garreau, H. *J. Biomater. Sci., Polym. Ed.* **1994**, *6*, 639.
(11) Vert, M.; Li, S.; Garreau, H. *Macromol. Symp.* **1995**, *98*, 633.
(12) Beck, L. R.; Cowsar, D. R.; Lewis, D. H. In *Biodegradables and Delivery Systems for Contraception*; Hafez, E. S. E., Van Os, W. A. A., Eds.; MTP Press: Lancaster, UK, 1980; Vol. 1, p 63.
(13) Tice, T. R.; Lewis, D. H.; Dunn, R. L.; Mayers, W. E.; Casper, R. A.; Cowsar, D. R. In *9th International Symposium on Controlled Release of Bioactive Materials*, The Controlled Release Society, 1982.
(14) Tice, T. R.; Tabibi, S. E. In *Treatise on Controlled Drug Delivery*; Kydonieus, A., Ed.; Marcel Dekker: New York, 1992.
(15) Winet, H.; Bao, J. Y. *J. Biomater. Sci., Polym. Ed.* **1997**, *8*, 517.
(16) Eppley, B. L.; Reilly, M. *J. Craniofacial Surg.* **1997**, *8*, 116.
(17) Ashammakhi, N.; Rokkanen, P. *Biomaterials* **1997**, *18*, 3.
(18) Zhu, K. J.; Hendren, R. W.; Jensen, K.; Pitt, C. G. *Macromolecules* **1991**, *24*, 1736.
(19) Ivanova, Tz.; Panaiotov, I.; Boury, F.; Proust, J. E.; Benoit, J. P.; Verger, R. *Colloids Surf. B: Biointerfaces* **1997**, *8*, 217.
(20) Zhang, H.; Ward, I. M. *Macromolecules* **1995**, *28*, 7622.
(21) Chen, J.; Gardella, J. A., Jr. *Macromolecules* **1999**, *32*, 7380.
(22) Gardella, J. A., Jr.; Hernandez de Gatica, N. L. *J. Electron Spectrosc. Relat. Phenom.* **1996**, *81*, 227.
(23) Googly Software, Copyright 1994 Andrew Proctor.
(24) Gopferich, A. *Biomaterials* **1996**, *17*, 103.
(25) Pitt, C. G. In *Biodegradable Polymers as Drug Delivery Systems*; Chasin, M., Langer, R., Eds.; Marcel Dekker: New York, 1990.
(26) Pitt, C. G. In *Biodegradable Polymers and Plastics*; Vert, M., Feijen, J., Albertsson, A., Scott, G., Chiellini, E., Eds.; Thomas Graham House: Cambridge, 1992.
(27) Zhu, K. J.; Hendren, R. W.; Jensen, K.; Pitt, C. G. *Macromolecules* **1991**, *24*, 1736.
(28) Yan, W.-Y.; Mariarz, E. P.; III; Hawkridge, A. M.; Ammon, D. M., Jr.; Grobe, III, G. L.; Gardella, J. A., Jr.; Wood, T. D. *Eur. Mass Spectrom.* **1998**, *4*, 467.
(29) Lee, J.-W.; Gardella, J. A., Jr. *Macromolecules*, submitted.
(30) *Principles of Instrumental Analysis*, 4th ed.; Skoog, D. A., Leary, J. J., Eds.; Saunders College Publishing: Orlando, 1992.
(31) *Advanced Inorganic Chemistry*, 5th ed.; Cotton, F. A., Wilkinson, G., Eds.; John Wiley & Sons: New York, 1988.

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