Kinetics and Time−Temperature Equivalence of Polymer Degradation

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We studied the hydrolysis kinetics of amorphous polylactide. It was found the hydrolysis rate had a slow-to-fast transition at a certain molecular weight (M_n). This transition was not correlated with the mass loss and water uptake of samples, nor the pH values of testing media. We speculated that this transition was due to the slow diffusion of polymer chain ends. The chain ends did not significantly promote the hydrolysis of samples until their concentrations (∼$1/M_n$) reached a critical value. The degradation tests were also conducted over a temperature range from 37 to 90 °C. A time−temperature equivalent relationship of degradation processes was established and a master curve spanning a time range equivalent to 3−5 years at 37 °C was constructed. This master curve can be used to predict polymer degradation processes based on accelerated tests. The functional time and disappearance time of degradable polymers were also discussed.

Introduction

Biodegradable polymers have been used in various biomedical and pharmaceutical applications such as resorbable sutures, controlled drug release devices, orthopedic fixation parts, and tissue reconstruction grafts.[1−5] The degradation behavior of these materials has been a research focus for several decades. From the point of view of organic chemistry, the hydrolysis of biodegradable polymers is a bimolecular nucleophilic substitution reaction (S_N2), a second order reaction that can be catalyzed by the presence of either acids or bases (Figure 1). The fundamental chemical reaction mechanisms of most hydrolytically biodegradable polymers are thought to be well understood. However, due to the long-chain structures and condensed states of polymers, the detailed hydrolysis of such polymers is much more complicated. For example, polymer bonds in their homopolymers may hydrolyze at different rates compared to that in their copolymers.[6] The polymer bonds near the chain ends may have a different reactivity from those in more remote sites;[7−11] likewise, the reactivity in crystalline domains may be different from that in amorphous domains.[12−16] Also, the diffusion behavior of water, ions, and degradation products (chain segments) are all different and can lead to many transport related phenomena such as auto-acceleration (i.e., hydrolysis products or chain ends catalyze the hydrolysis reaction itself).[17−26] In addition, the competition between reaction and transport processes leads to surface erosion in some materials but bulk erosion in the others. Several papers have reviewed the surface erosion of polymers.[7,27−29] In this paper, we reviewed the major research on the bulk erosion of polymers with the emphasis on physical degradation mechanisms.

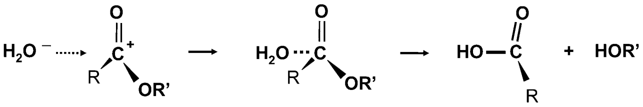

Figure 1. Schematics of ester hydrolysis (nucleophilic substitution reaction (S_N2)).

The first research area is degradation kinetics.[27,30−39] The generally accepted theory is third-order kinetics as proposed by Pitt et al.[31,32] The rationale behind this theory is that the hydrolysis rate depends on the concentration of the polymer bonds, water, and the acidic hydrolysis products (but interestingly, not the H^+ itself). This theory predicts a linear relationship between the logarithm of the polymer molecular weight with degradation time. This prediction fits a number of experimental observations, but a few exceptions have been reported.[33,34] Pitt et al.'s theory does not consider the effects of transport processes of polymers on degradation. Hence, it cannot be used to treat the phenomena related to transport such as surface erosion. Recently, Lyu, Sparer, and Untereker proposed a second order mechanism based on combined reaction and transport.[27] This theory was extended to surface erosion. The erosion velocity and the size of reaction zone were calculated as functions of the hydrolysis rate and the diffusion coefficient of water.

Another important focus is the autoacceleration of hydrolysis of polyesters.[17−26] The hydrolysis of polyesters can produce acidic products (−COOH) in the chain ends. These products can further catalyze the reaction. Due to the restricted diffusion of the chain ends, the acidic polymer fragments can accumulate inside samples and cause faster degradation in the inner part of the specimens.[18−21] Such phenomena were more profound in large-sized specimens and nonbuffered testing media. In buffered pH media, the autoacceleration seemed to be suppressed around neutral pH,[18] which suggested that the autoacceleration might happen preferentially at low pH. However, in low pH buffered solutions, the autoacceleration was not enhanced.[26] Therefore, the effect of the pH of testing media on the degradation is still not well understood. Questions remain include whether the autoacceleration is due to the presence of −COOH or H^+, and how the pH of external testing media affects this acceleration.

A third important area is the effect of temperature on the degradation kinetics.[16,33,40−51] This is not only important to predict the resorbable behavior of the devices in vivo but also

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extremely useful to develop an accelerated degradation test method. Some polymer degradation takes more than 3 years.[14,15] Testing for such a long period is certainly time-consuming. Deng et al. reported an in vitro degradation study of PLGA fibers.[33] The degradation was performed over a temperature range of 27.5−47.5 °C, lower than the glass temperature (T_g) of PLGA (∼ 50 °C). The changes in the strain at break of the materials were found to obey the Arrhenius equation. Tsuji et al. reported another experiment with polycaprolactone (PCL) that was conducted at very high temperatures (>100 °C).[16] Arrhenius behavior was observed as well. These tests were conducted at temperatures that were either higher than the glass transition (or melting) temperature of the materials, or lower than that. Practically, properties of polymers change dramatically from below to above T_g. Therefore, a degradation test within a temperature range from below T_g to above T_g may be needed for a comprehensive understanding of temperature dependence of degradation. However, there have not been very many studies conducted over such temperature ranges to discuss the time−temperature equivalence of degradation for the development of an accelerated testing method.

A fourth important area is the correlations between physical properties (e.g., mechanical and drug release) with the degradation processes.[33,45] One report was performed by Deng et al., who correlated mechanical properties with the molecular weigh of the polymers studied.[33] However, the mechanical properties, drug release behavior, and the degradation processes seemed to be coupled to each other. More detailed understanding is needed to deconvolute these relationships

The degradation of polymers may also depend on sample size, materials processing, composition, and morphology. For example, Sousa et al. found that development of water diffusion channels at nanosacle was critical to the bulk degradation of certain materials.[52] If we summarize the physical portion of degradation research, there were at least two major focuses: (1) hydrolysis kinetics and its dependence on pH, temperature and chemical structure of polymer chains, and (2) transport processes of various chemicals such as water, ions (H^+ and OH^-), pharmaceutical agents, and degradation products of polymers.

In this paper, we report on two things. First we will introduce a method to characterize the hydrolysis kinetics. We compare the experimental results with a second order and a third order kinetics model. In the second part, we will present data from the hydrolysis of PLA over a temperature range from 37 to 90 °C that covers both the use medical temperature range and the glass transition temperature of polylactide. We will demonstrate how to construct a master curve for the hydrolysis of PLA to illustrate the time−temperature equivalent relationship for accelerated testing.

Experimental Section

Sample Preparation and Degradation Testing. Poly(L-lactide-co-L,D-lactic actide) (70/30) random copolymer (PLA), from the Boehringer Ingelheim company (Germany), was used in the present study. This polymer is amorphous and has a glass transition temperature of 55 °C. The samples for degradation testing were discs (12.5 mm in diameter and 1 mm in thickness) cut from compression-molded sheets. The number average molecular weight and polydispersity index of the molded samples were 290 kg/mol and 1.03. Degradation was performed by immersing the discs in various testing solutions (Table 1), at various temperatures (37−90 °C), and for various periods (up to 500 days). For each data point, three different discs were used. In order to track the weights of samples, the discs were immersed individually in vials with the amounts of testing solutions being about 50 times the weights of discs tested. The vials were agitated at a frequency of about 10 turns per min in ovens. The testing solutions were refreshed weekly to monthly to ensure that the pH values of the solutions remained unchanged during the testing.

Table 1. The Composition of Testing Solutions

pH	solution composition
0	HCl water solution
2	HCl water solution
7.4	PBS[a]
12	NaOH water solution

[a] Phosphate-buffered solution was made per the following formulation: sodium hydroxide, 0.156 g; KH_2PO_4, 0.680 g; sodium chloride, 0.1g; water added to 100 mL. 0.02 wt % of NaN_3 was added to the solution to prevent bacterial proliferation.

Characterization. At each time point, three different discs were sampled. Water uptake was measured with a micro-balance (Metler Toledo) that can detect weight change at the microgram level. All the samples were weighed three times: before testing (initial W_i), after being tested for each scheduled durations but without drying (W_w), and later after being carefully dried (W_d). Water uptake was calculated from $(W_w - W_d)/W_d$, the weight loss was calculated from $(W_i - W_d)/W_i$. At each time point, molecular weight of the samples was measured from the dried samples with gel permeation chromatography (GPC) (Agilent 1100 unit equipped with Phenogel 5 micron columns) using tetrahydrofuran (THF) as the mobile phase with a flow rate of 0.7 mL/min. Absolute molecular weight was obtained for all the samples based on the coupled light scattering (measured at 18 angles with Dawn EOS, Wyatt) and RI detection (Optilab DSP, Wyatt). The value of dn/dc needed for the calculation of molecular weight was determined to be 0.048. All the data points were the average of at least three repeats.

Results and Discussions

Hydrolysis Kinetics. Prior to the study of the reaction kinetics, it is worthwhile discussing how to characterize the hydrolysis reaction. The hydrolysis rate of polymers should be characterized with either the generation rate of the reaction products or the consumption rate of the reactants. However, because the polymer samples contain many chains with a plurality of molecular weights, a polymer chain that is the product of one reaction event can also be the reactant in a subsequent reaction. Therefore, it is not feasible to characterize the hydrolysis rate by the generation rate of polymer chains. However, the products of the hydrolysis are the newly formed chain ends; the increase of the chain end concentration as a function of time measures the hydrolysis process. The chain end concentration at any time is proportional to $1/N$, where N is the number of repeat units of a chain that is equal to the molecular weight of the chain at that time (M_n) divided by that of monomers or repeat units (M_0). Therefore, the quantity of $1/M_n$ versus degradation time characterizes the degradation product generation process. It is interesting that only a few papers reported $1/M_n$ as a function of time.[53,54] Most papers simply reported the molecular weight or the logarithm of the molecular weight. Although these two parameters are indicative for the degradation progress, neither of them directly leads to a measure of the exact hydrolysis rate.

The quantity $1/M_n$ was measured as a function of time for the solid PLA discs tested in aqueous PBS (pH 7.4) at 37 °C. The results are plotted in Figure 2A. $1/M_n$ increased linearly with the degradation time, which indicates the PLA degraded at a constant rate. When Mn for the remaining samples reached 100 ∼ 110 kg/mol (at about 250 days), the increasing of $1/M_n$ became faster. This indicates the hydrolysis had accelerated.

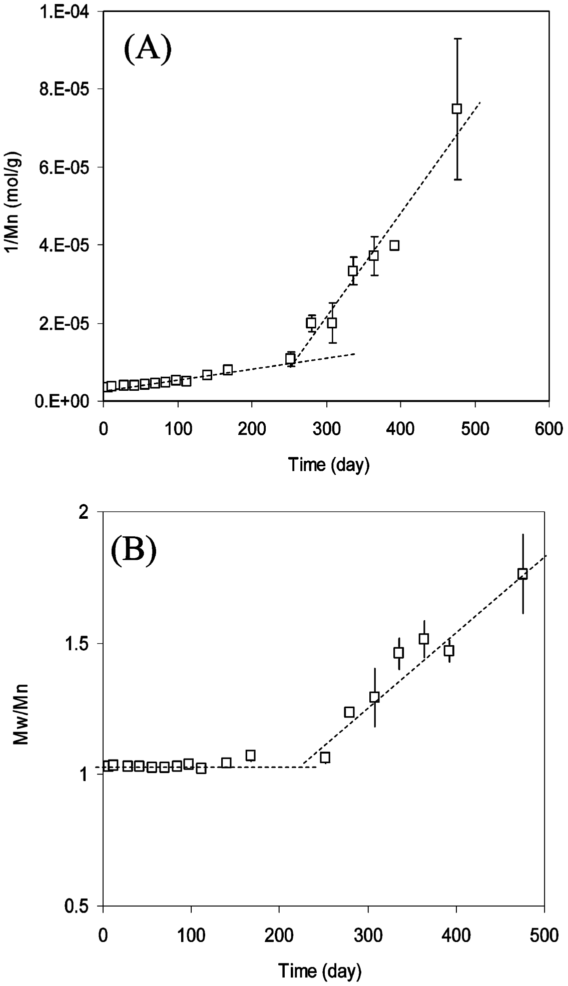

Figure 2. (A) Inverse of number average molecular weight vs degradation time of solid PLA samples that were tested in PBS (pH 7.4) aqueous solution at 37 °C. (B) The polydispersity index (M_w/M_n) for the same test.

The ratio of the weight average molecular weight (*Mw*) to the number average molecular weigh (*Mn*), the polydispersity index (*PDI*), reflects the molecular weight distribution broadness. As shown in Figure 2B, *PDI* was nearly a constant in the beginning. But when the $1/M_n$ accelerated, *PDI* increased quickly, indicating the molecular weight distribution became broad.

The increases in both the degradation rate and the molecular weight distribution broadness seem to suggest there are different hydrolysis kinetics before and after this inflection in degradation rate. There are a few factors that might account for this increase in the degradation rate: e.g., a possible increase in water uptake in the polymer samples, a catalysis by −COOH chain end groups, and so on. However, as it will be shown, this increase in degradation rate is a complicated process.

To get insight into the hydrolysis we first checked whether there is a transition in water uptake in the polymer within the same time frame. As shown in Figure 3A, the percentage of water absorbed in the polymer was about 1 wt-% for up to almost 400 days. From the inset of Figure 3A, it can be seen that the polymer was saturated by water within about 2 days. Therefore, there was no transition related to the water absorption at the time when the degradation rate started to increase (about 250 days). Therefore, the transition in degradation rate was not related to water uptake. From the inset in Figure 3A, the diffusion coefficient of water (*D*) in PLA can be estimated to be 6.4 × 10^{-8} cm^2/s at 37 °C base on the following equation[55]:

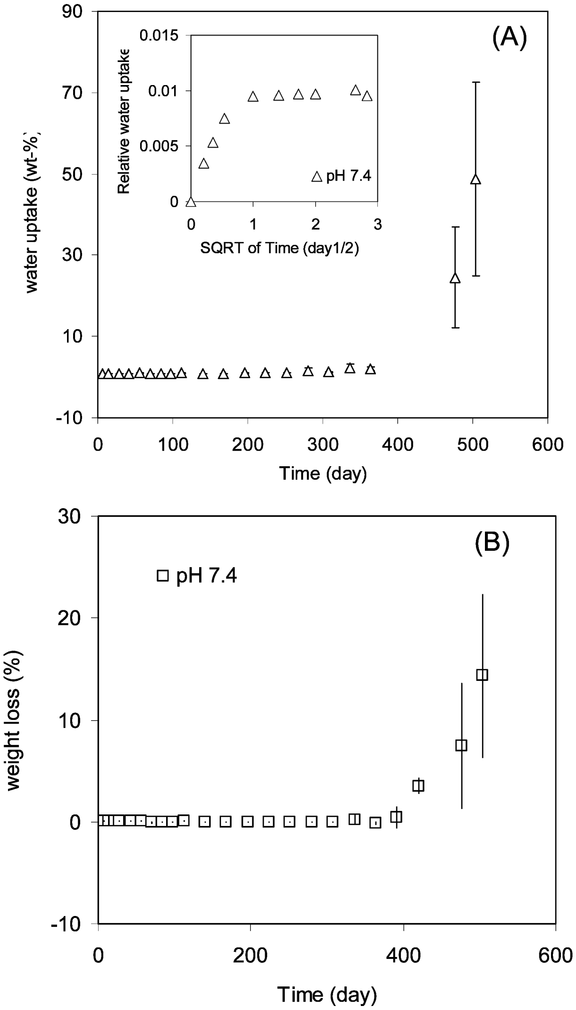

Figure 3. Water uptake (A) and weight loss (B) of PLA samples tested in pH 7.4 solution at 37 °C. Significant changes in both the water uptake and the weight loss occurred at about 400 days after testing started. The inset in plot A indicates the water saturation process from which the diffusion coefficient of water was estimated.

$$x(t) = 2\left(\frac{Dt}{\pi l^2}\right)^{1/2} \tag{1}$$

Where x(t) is the percentage of water absorption, *l* is the sample thickness. Weight loss of the sample was also plotted (Figure 3B). It can be seen that the significant weight loss started at about the same time (∼ 400 days) as when the water swelling started to increase. At this time, the molecular weight of samples was 20 to 25 kg/mol. These results indicate the increase in degradation rate was not co-incident with the weight loss.

The next question is how the chain end −COOH groups affected the hydrolysis reaction. Because the hydrolysis reaction is between the reactive bonds (esters) and water molecules, it is reasonable to assume the reaction rate is proportional the concentration of the ester groups (C_R) and water (C_S). (We will not distinguish ester groups and reactive bonds because these two are the same for polyesters such as PLA, PCL, PGA, etc.) If the water and ester bond concentrations are the only factors, the reaction should be controlled by second-order kinetics:

$$\frac{d[\mathrm{COOH}]}{dt} = k_2 \cdot C_S \cdot C_R \tag{2}$$

Where k_2, C_S, and C_R are the kinetic constant, the saturated concentration of water in polymer, and the concentration of reactive esters. Substituting $N \gg 1$, [COOH] = C_B/N, and $C_R = C_B(1 - 1/N)$ (where C_B is the total bond concentration in polymer, including both the reactive bonds and chain ends) and integrating eq 2, we have[27,53]

$$\frac{1}{M_n} = \frac{1}{M_{n0}} + \frac{1}{M_0} k_2 \cdot C_S \cdot t \qquad (3)$$

It is interesting that the second-order kinetic model leads to a linear relationship between $1/M_n$ and time that is exactly the same as the relationship to characterize the hydrolysis kinetics discussed in the beginning of this section. This result allows one to calculate the kinetic constant from Figure 2. Thus the slope of the $1/M_n \sim t$ curve is equal to k_2C_S/M_0. However, the slope increased after the molecular weight was lower than about 100 kg/mol (Figure 2A). The water concentration C_S was measured to be constant (Figure 3A). Therefore, the kinetic constant, k_2, must have increased.

One can propose that the chain end −COOH can increase the hydrolysis rate because the −COOH can dissociate into $-COO^-$ and H^+ that can catalyze the reaction. If the hydrolysis rate is assumed to be proportional to [COOH] in addition to C_S and C_R, we would have third order kinetics as proposed by Pitt et al. [31] This kinetic relationship is

$$\log(M_n) = \log(M_{n0}) - k_3 \cdot C_B \cdot C_S \cdot t \qquad (4)$$

Another possible kinetic relationship can be obtained by assuming the hydrolysis rate is proportional to $[H^+]$ that has a square root relationship with [COOH] (since, at equilibrium, $K[COOH] = [H^+][COO^-] = [H^+]^2$). In such a case, the reaction would follow 2.5th order kinetics. The kinetic equation of the 2.5th order reaction is

$$\frac{d[COOH]}{dt} = k_{2.5} \cdot (K \cdot [COOH])^{1/2} \cdot C_S \cdot C_R \qquad (5)$$

Where, K is the dissociation constant of −COOH. The relationship between molecular weight and time then is

$$\left(\frac{1}{N}\right)^{1/2} = \left(\frac{1}{N_0}\right)^{1/2} + \frac{1}{2} k_{2.5} \cdot (K \cdot C_B)^{1/2} \cdot C_S \cdot t \qquad (6)$$

The experimental data were fitted to eq 4 and 6 for the third and 2.5th order reaction kinetics. The results are plotted in Figure 4A,B. As shown, neither plot has a linear relationship. Similar to the $1/M_n \sim$ time curve, it appears that the hydrolysis goes through two kinetic processes with different rates. This simply indicates that the hydrolysis rate is not constantly proportional to either [COOH] or $[H^+]$. Actually, a hydrolysis rate not proportional to $[H^+]$ has been observed with both solid samples and polymer solutions.[30,31] The literature results of the relationships between the degradation rates and [COOH] are mixed. Pitt et al. observed a linear relationship with PCL solid samples.[31] However, Deng et al. did not observe the same relationship with PLGA fiber samples. They observed that the hydrolysis rate increases with time,[33] similar to that shown in Figure 4A of the present paper.

In order to understand this discrepancy, we need to examine the two fundamental properties: reactivity and diffusivity of all the reactants. Chemical reaction between two or more groups not only needs these reactive groups to be chemically active but also requires them to be able to move close to each other. A reaction volume has been defined to quantify this effect.[27] The diameter of the reaction volume is defined as the distance that the reactants can diffuse within the time that is needed for a reaction event. The kinetic equations mentioned above are valid only inside the reaction volume. This situation is termed reaction control. Outside the reaction volume, the above equations are no longer valid, and the reaction is termed diffusion control.

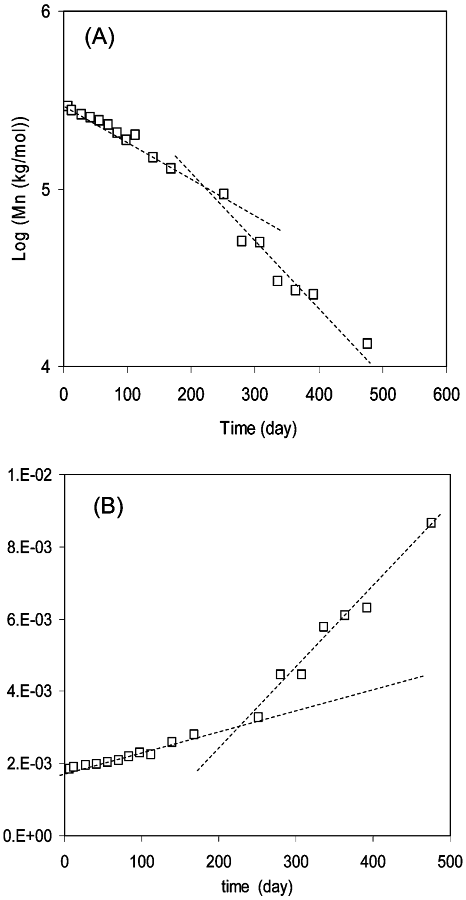

Figure 4. A, logarithm of the molecular weight as a function of degradation time of solid PLA samples tested at 37 °C in PBS solution (pH 7.4). This relationship should be linear if the degradation follows third-order kinetics. B, $(1/M_n)^{1/2}$ as a function of degradation time for the same test. This relationship is based on the kinetics in which the reaction rate is proportional to $[H^+]$. However, as indicated, neither curve was linear over the total testing time range.

Besides the reaction volume, each chemical group has an occupancy volume that is equal to the total sample volume divided by the number of that chemical group. Occupancy volume is larger than the physical volume of reactive groups. In order for the above equations to be valid within the entire sample, the reaction volume has to be equal to or greater than the occupancy volume for all the reactants. It has been theoretically confirmed that if the hydrolysis reaction is between water and polymer bonds only, it is reaction-controlled, and eqs 2 and 3 are valid for the entire sample volume.[27] The reason is that the diffusion of water is fast enough so that it can explore the occupancy volumes of water and reactive bonds. However, when the chain ends are involved in reaction, they have a much larger occupancy volume (N times of that of bonds or water). But at the same time, their reaction volume is much smaller because their diffusion coefficient is much lower than that of water.[56] This difference is especially significant for polymers with high molecular weights and at a temperature below its Tg. Under these conditions, diffusion of chains is extremely slow and even hardly observed.[56] So, it is very possible that within

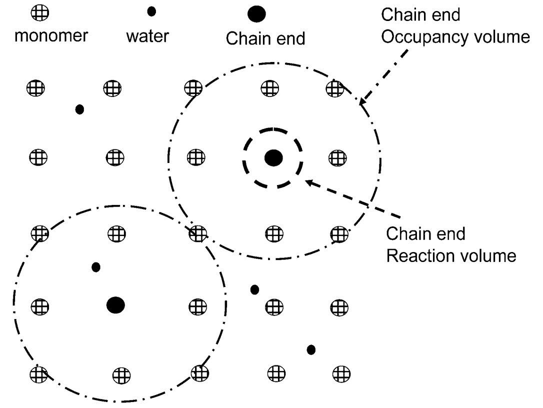

Figure 5. Schematics of reaction volume and occupancy volume of water, reactive bonds, and chain ends of PLA. The reaction volume of chain ends is smaller than their occupancy volume. The reaction involved by the chain ends is limited within reaction volume.

the reaction time the chain ends cannot explore the entire volume of the sample but just a fraction of it (ϕ). As a result, even if the chain ends can catalyze the hydrolysis, they can be effective only in the part of sample volume that the chain ends can reach through diffusion. In the rest of the sample, the hydrolysis reaction is mainly between water and polymer bonds and follows second order kinetics.

The parameter ϕ can be estimated as the follows. The occupancy volume of a chain ends is equal to the total volume of sample divided by the number of chain ends. It is equal to $N\cdot V_0$, where V_0 is the monomer volume. The time interval between two reaction events is about $1/(k_3C_SC_B)$ and the distance that a catalytic chain end can diffuse within this time interval is $(D/(k_3C_SC_B))^{1/2}$, where D is the diffusion coefficient of chain ends. Then, the volume fraction of accelerated reaction is,

$$\phi \sim (D/k)^{3/2}/(N\cdot V_0) \qquad (7)$$

Where, $k \sim k_3C_SC_B$. When $\phi < 1$, the hydrolysis would be dominated by the second order reaction or non-accelerated reaction. When $\phi > 1$, the hydrolysis might be dominated by the auto-accelerated reaction. The transition region is $\phi \sim 1$. It should be pointed out that $\phi > 1$ means the chain ends can diffuse through their entire occupancy volumes. It does not mean there is extra volume introduced. In this sense, ϕ is a ratio of the reaction volume to the occupancy volume.

When samples have very high molecular weight, ϕ may be less than 1. Thus, the hydrolysis may follow a second-order kinetics first, then as N decreases the reaction changes to a third-order kinetics. The transition indicated in Figure 2A and Figure 4A may reflect such crossover. Figure 2A indicated that the onset of the crossover was at a molecular weight of about 100 kg/mol. This molecular weight corresponds to a chain end occupancy volume with a diameter of about 6 nm (density of PLA = 1.24 g/cm^3; reaction volume diameter $\sim$[(100 kg/1.24 g/cm^3/(6.02 $\times$ 10^{23})]$^{1/3}$ $\sim$ 6 nm). Taking the reaction time scale as 10^{7}s (see below), we can estimate the diffusion coefficient of polymer chain ends of the present PLA to be 2×10^{-20} cm^2/s at 37 °C. Similarly, we can estimate the diffusion coefficient of chain ends of PLGA at 37.5 °C based on the data reported by Deng et al.[33] The result is 5×10^{-20} cm^2/s (the transition molecular weight was about 10 kg/mol). These results indicate that the chain ends of PLGA and PLA have similar diffusion coefficients around 37 °C. This is reasonable because these two polymers are similar in structure and also in glass transition temperature (about 50−55 °C). The values of the estimated diffusion coefficients were reasonable. As reported in reference 56, polystyrene and poly(methylmethacrylate) have diffusion coefficients of about 10^{-15} to 10^{-18} cm^2/ s at a temperature about 10 °C higher than their glass transition temperatures. In the present study, the molecular weight of PLA is much higher. The testing temperature was about 10−15 °C lower than the Tg of the polymer. Therefore, the diffusion coefficients should be much lower (typically, several orders of magnitude reduction in kinetic rates can be observed when temperature goes down cross T_g and polymers change from rubbery to glassy state).

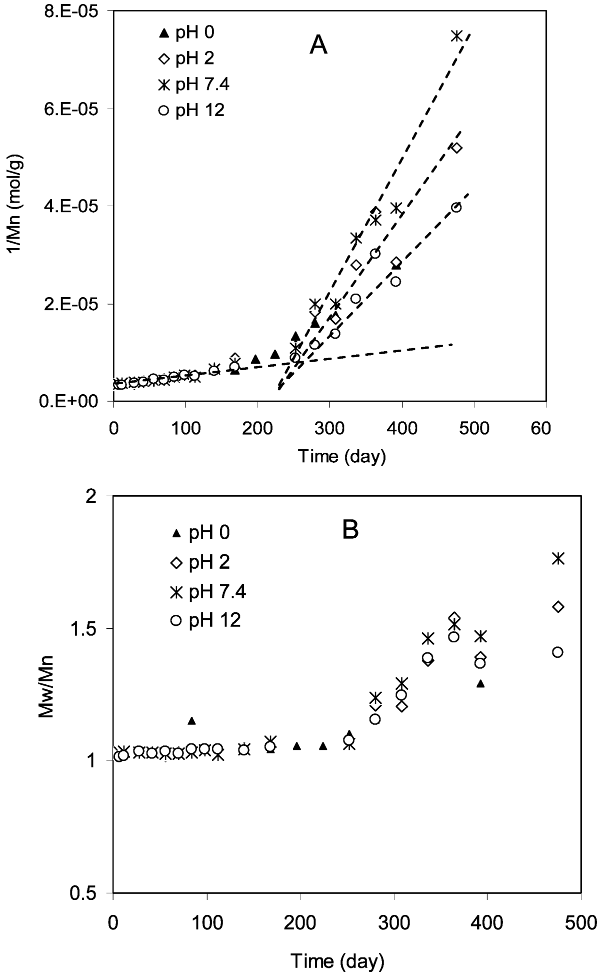

Figure 6. Solid PLA sample degradation conducted by immersing them in aqueous solutions with pH ranging from 0 to 12. The initial degradation kinetics was the same for all conditions. (A) 1/M_n vs time and (B) molecular weight distribution versus time.

As indicated by eq 7, the fraction of volume within which the chain ends catalyze hydrolysis reaction increases as the hydrolysis rate decreases, the molecular weight decreases, and the diffusion coefficient of chain increases. The hydrolysis rate of PCL is slower than that of PLA, and even slower than that of PLGA. Therefore, it is more likely to observe chain end catalysis effects in PCL than in PLA or PLGA. This may explain why the PCL hydrolysis followed a third order kinetics as observed by Pitt et al.[31] However, there are kinetic transitions in both the PLA and PLGA. The transition molecular weight (M_A) of PLGA (10 kg/mol)[33] is lower than that of PLA (100 kg/mol) because PLGA is more reactive than PLA. In principle, any factor, e.g., temperature, that can cause changes in k and D will cause change in M_A and, further, in the kinetic transition.

Because of the possible cross over from second-order to third-order kinetics, the experimental data can be treated with eqs 3

Table 2. The Hydrolysis Rate Constants of Solid PLA in Solutions of Different pH. The Numbers in Braces are the Standard Deviation[a]

pH	0	2	7.4	12
k_2 (M^{-1} s^{-1})	0.4 (0.07) × 10^{-10}	0.4 (0.05) × 10^{-10}	0.4 (0.04) × 10^{-10}	0.4 (0.02) × 10^{-10}
k_3 C_BC_S (s^{-1})	6.0 (0.5) × 10^{-8}	6.5 (1.6) × 10^{-8}	8.0 (0.9) × 10^{-8}	7.0 (1.5) × 10^{-8}
k_3 (M^{-2} s^{-1})	6.2 (0.5) × 10^{-9}	6.8 (1.7) × 10^{-9}	8.4 (1.0) × 10^{-9}	7.5 (1.6) × 10^{-9}

[a] $C_S = 0.56$ M, $C_B = 17.2$ M.

and 4 separately. For example, the PLA degradation before the transition can be fitted to the second order reaction kinetic if a coefficient of about 0.4 × 10^{-10} M^{-1} s^{-1} is used. The data points after the transition can be fitted to the third order kinetics using a different constant about 8 × 10^{-8} s^{-1}. However, it should be pointed out that the discussion here is qualitative. Quantitative analysis of the data needs measurements of the diffusion of chain ends. Unfortunately, measurements of diffusion of polymers below T_g are rare because it is extremely slow. The present paper is interested in a transition from a slower reaction without chain end catalysis to a faster reaction with the catalysis. Whether the faster catalysis reaction is a third order or not is still debatable and practically may not be very critical. In reality, the kinetic data alone may not be sufficient to distinguish the two mechanisms. This can be seen in Figures 2A and 4A,B, where it seems the hydrolysis after the transition fits all second-, 2.5th-, and third-order kinetic relationships.

The degradation of solid PLA was also conducted in media with pH values ranging from 0 to 12 (Figure 6). Similar results were observed as shown in Figure 2A. A transition occurred at about the same molecular weight for all the pH values. The degradation rates of the two regimes were essentially the same for all the pH media (Table 2). Such results indicate that the testing solution pH did not affect the bulk degradation of the polymers significantly. This was likely due to the low permeability of polymer to the ions of the test solutions.

Accelerating Tests by Varying Temperature. We conducted PLA hydrolysis at four different temperatures: 37, 55, 70, and 90 °C for up to 18 months. The glass transition temperature of PLA (55 °C) was within this range. The concentration of hydrolysis products ($1/M_n$) versus time for each temperature is plotted in Figure 7A. As expected, the hydrolysis is faster at higher temperature. At each temperature, hydrolysis was slow in the beginning followed by an acceleration period. However, this rate difference was less significant at higher temperatures. This suggests, at high temperatures, the increase in chain end mobility may be more profound than that in hydrolysis reaction rates. Therefore, the autoaccelerated degradation may be more favorable at elevated temperatures. However, when the molecular weight of the samples was low enough (2−3 kg/mol), the sample started to break up into small particles. At this point, the molecular weight leveled off. This probably was because the low molecular weight products started to dissolve in testing solutions. The molecular weight at which PLA becomes soluble in water is about 2−3kg/mol. Similar level-off were also observed in other studies.[6,7]

The data before and after the kinetic transition were treated based on second and third order kinetic equations (Figure 7B). The slopes of the curves (k_2C_S/M_0 and $k_3C_SC_B$) were calculated and plotted on a log scale as functions of $1/T$ as shown in Figure 8A,B. If the reaction obeys the Arrhenius equation (eq 8), a linear relationship should be observed. The degradation at high-temperature ($>T_g$) did obey the Arrhenius equation, which is similar to that reported by Tsuji et al.[16] However, the data points at 37 °C did not follow the trend defined by the data obtained at higher temperatures. Therefore, the overall hydrolysis of the solid PLA did not obey the Arrhenius equation over the total testing temperature range. This strongly suggested that the temperature effects on hydrolysis need to be studied over a temperature range from below T_g to above T_g for a comprehensive understanding:

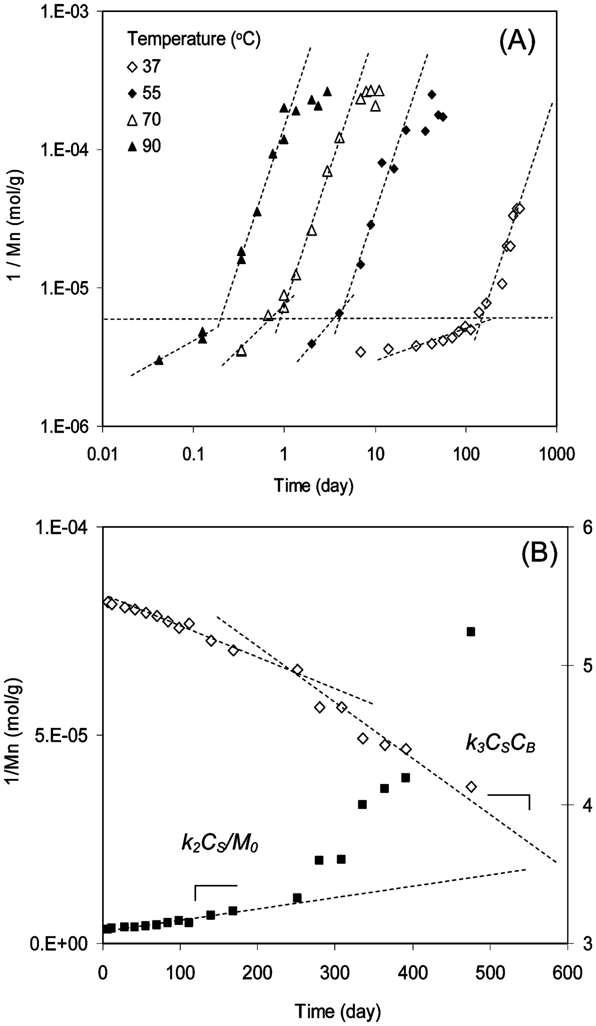

Figure 7. Degradation of solid PLA samples in PBS (pH 7.4) at various temperature. Complete hydrolysis (visual disappearance of samples) was observed at both 70 °C (day 16) and 90 °C (day 2 to 3). Panel A is a plot of $1/M_n$ vs log(t). Panel B shows the calculation of k_2C_S/M_0 and $k_3C_SC_B$ from curves of $1/M_n$ vs time and log(Mn) vs time for the degradation at 37 °C.

$$k = k_0 \cdot e^{-(E/RT)} \tag{8}$$

where, E is the activation energy, R is the gas constant, and k_{l0} is the collision frequency.

It is not surprising that the reaction of the polymers do not fit the Arrhenius equation. In fact, many kinetic processes of polymers do not obey the Arrhenius equation, but can be described with the following (Vogel−Tammann−Fulcher, or VTF) equation:[57]

$$k = k_0 \cdot e^{-[E/R(T-TS)]} \tag{9}$$

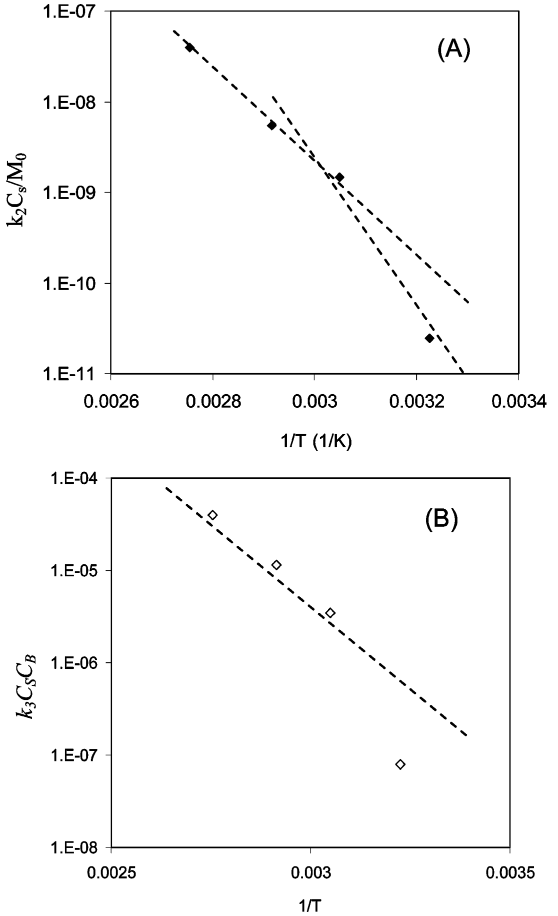

Figure 8. Log plot of the degradation rates before the transition (k_2C_S/M_0) (A) and after the transition ($k_3C_SC_B$) (B) vs reciprocal temperature. The nonlinear relationships indicated the degradation kinetics do not obey the Arrhenius equation within the present testing temperature range (37−90 °C).

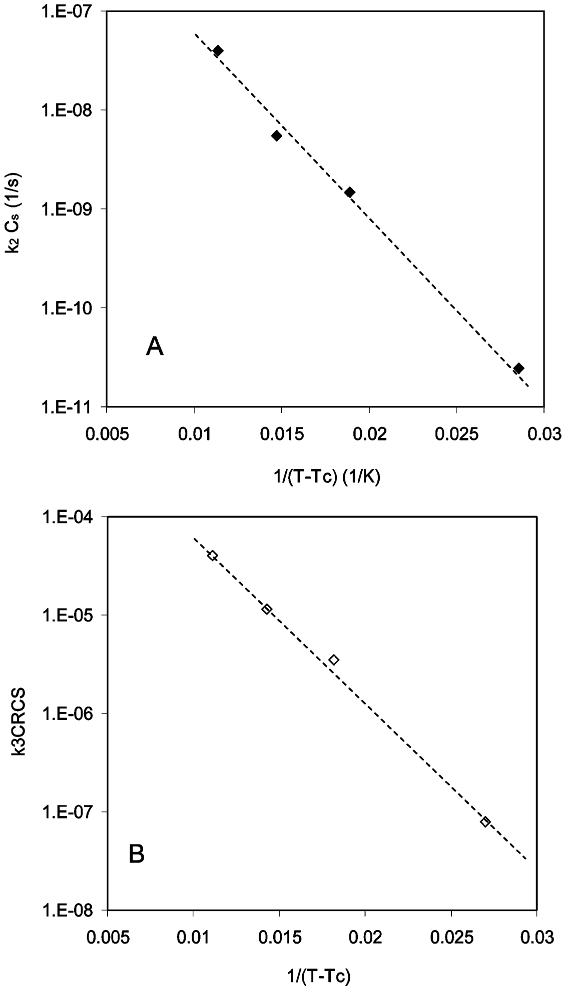

Figure 9. The degradation rates (k_2C_S/M_0) (A) and $k_3C_SC_B$ (B) vs $1/(T-T_S)$. Linear relationships indicate the degradation kinetics obeyed the VTF equation.

where T_s is a reference temperature at which the conformation entropy of the polymer chains approaches zero. This is analogous to the thermodynamic zero temperature (0 °K) for small molecules. This reference temperature usually is about 50 °C below the glass transition temperature of the polymers.[58] If the kinetic constants are re-plotted as a function of $1/(T - T_S)$ with $T_S = 0$ °C, linear relationships are observed for the hydrolysis both before and after the kinetic transition (Figure 9). This suggests that the hydrolysis reaction fits the VTF equation with a reference temperature being 55 °C lower than the PLA glass transition temperature (55 °C). The parameter E/R of eq 8 can be estimated to be about 390K. The VTF equation can be converted into the familiar Williams−Landel−Ferry equation

$$\log(\alpha_T) = \frac{C_1(T - T_1)}{C_2 + (T - T_1)} \tag{10}$$

by taking $C_1C_2 = E/R$ and $C_2 = T_1 - T_S$. In this equation, α_T is the factor to shift the data obtained at temperature T to overlap with that at T_1 (temperature of interest, e.g., 37 °C in the present paper).

Substituting the fitting parameters ($C_1 = 10.5$ and $C_2 = 37$ °C) into eq 10, the time factors ($1/\alpha_T$) to shift the degradation data curves of 55, 70, and 90 °C to overlap with that of 37 °C (T_1) were calculated (31, 144, and 496). Applying these values to the curves of Figure 7A, the data points for all four temperatures overlapped well and formed a master curve (Figure 10). This master curve represents a temperature range from below to above T_g. It can be easily read from the master curve that it would take more than 4 years for this type of PLA to completely degrade and disappear at 37 °C. This predicted time is long, but it is comparable with the result of PLLA observed by Tsuji et al., where more than 85% of the sample still remained after 3 years of degradation testing.[15]

Not only can the hydrolysis kinetics ($1/M_n$ vs time) be treated with the VTF equation, but the water uptake and polymer weight loss can also be reasonably transformed into master curves with this equation by using the same shifting parameters. These results are plotted in Figure 11A,B.

Predicting the time it takes for the whole sample to disappear was an important part of the degradation experiments. At 37 °C, the weight loss of the samples was relatively small even after 18 months. However, at 90 °C, the samples disappeared within 2−3 days. The molecular weight of the disappearing polymer gel was about 2−3 kg/mol. The master curve obtained based on the time−temperature superposition (Figures 10 and 11) predicts that this polymer will disappear in pH 7.4 medium at 37 °C after 3 to 5 years. This demonstrates the powerful predicting ability of the VTF or WLF equation for studying degradation processes in polymers.

It is worthwhile to review the entire degradation in amorphous polymers. Based on the present studies, there are four phases in the solid PLA degradation process (Figure 12). The first phase is the diffusion of water into the polymer during which the whole

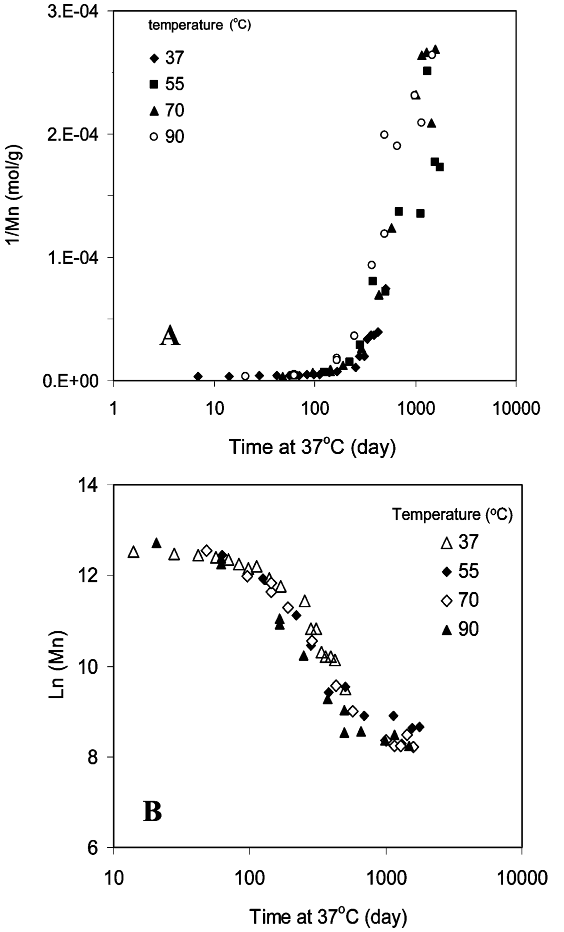

Figure 10. Master curve for the solid PLA degradation at 37 °C obtained by shifting the results obtained at higher temperatures using the time−temperature equivalent relationship (WLF or NTF equations). As for Figure 7, the plots show $1/M_n$ (A) and $\ln(M_n)$ (B) vs $\ln(t)$.

sample can become saturated within a short period of time. In the second phase, the polymer hydrolyzes at a constant rate that is controlled by the water concentration within it. The third phase starts when there are enough polymer chain ends generated (at molecular weight M_A), and thus the hydrolysis is accelerated. After the chains further degrade, some of them become small enough (M_d) that they become soluble in water. Then, significant water swelling and weigh loss start.[6] This is the onset of fourth phase of degradation. The average molecular weight of solid samples at the onset of this phase is larger than M_d, but approaches to it until the whole sample disappears.

The first phase is governed by a water diffusion process. For most samples, the water diffusion coefficient is about 10^{-8} to 10^{-7} cm^2/s, so the first phase takes place quickly (e.g., lasts for days depending on the sample size).[55] The duration of the second phase strongly depends on the initial molecular weight of the samples. This phase cannot be observed if the initial molecular weight is lower than the molecular weight (M_A) at which the auto-acceleration starts. M_A depends on both the reaction and diffusion rates of chain ends. This phase should be sensitive to temperature. The hydrolysis rate during this phase should be more properly described with second order kinetics since the catalytic effects due to the acidic chain ends are insignificant. In the third phase, the hydrolysis might be a third order reaction due to auto-acceleration as Pitt et al. proposed.[31] During the fourth phase, the samples break into small particles, which may enhance the release of small molecular weight acidic degradation products into testing media.[59] These particles can last for long time due to the weakened auto-correlation effects on the hydrolysis. For PLA, the onset molecular weight this phase is about 20−25 kg/mol (Figures 2 and 3). The M_d is about 2−3 kg/mol (Figure 7A).

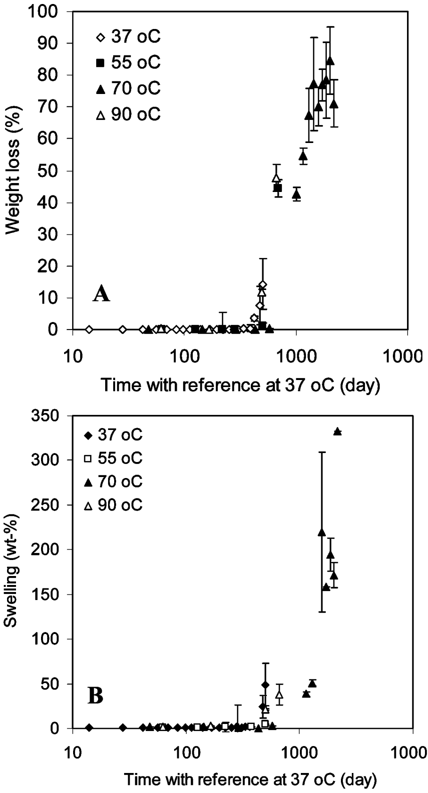

Figure 11. Overlapping of the water swelling and weight loss data for the solid PLA samples in PBS (pH 7.4). The data were measured at four temperatures and shifted based on the time−temperature equivalent parameters determined from Figure 9. The complete disappearance of the samples can be estimated to be about 4 to 6 years.

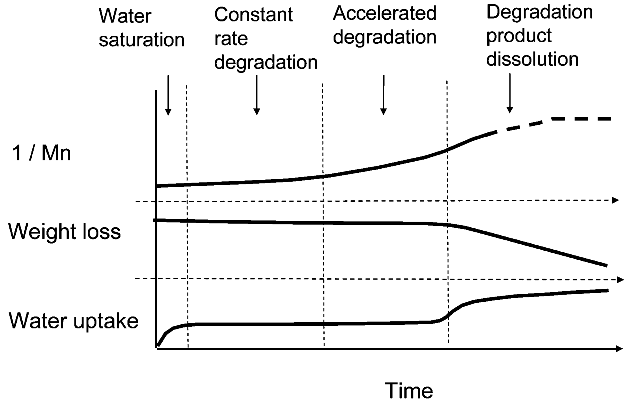

Figure 12. Schematics showing how $1/M_n$, weight loss, and water uptake change during the four phases of degradation.

Hakkarainen, Albertsson, and Karlsson (HAK) proposed an important idea that hydrolysis of polymers proceeded through three stages.[6] During the first stage, solid polymers degrade without significant mass loss. Degradation enters the second stage when mass loss starts. During this stage, molecular weight change slows down. At the time when total mass loss is reached, degradation proceeds to the third stage. During this stage, the soluble oligomers continue to hydrolyze in water until they are completely converted into monomers. It can be seen that the four-phase model of the present study focuses more on the hydrolysis before the mass loss starts. The three-stage model provided detailed insight into the hydrolysis during and after

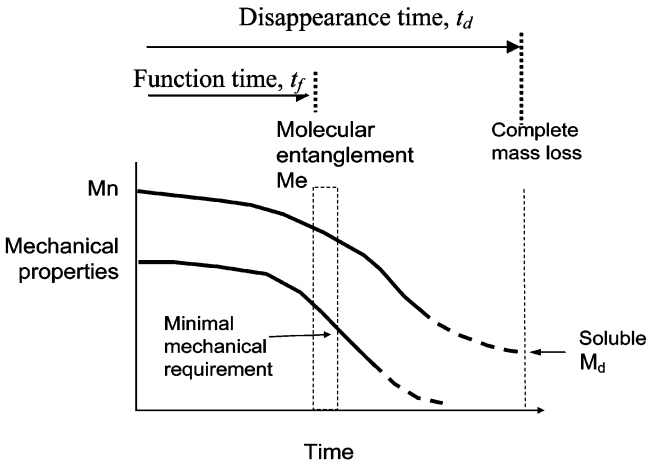

Figure 13. Schematics comparing the changes in M_n and mechanical properties as degradation proceeds.

mass loss. The first three phases of the present model are a stretching of the first stage of Hakkarainen-Albertsson-Karsson’s three-stage model. Therefore, the present model and HAK’s model may be complementary.

Concluding Remarks

For practical applications, there are two important time events (Figure 13). One is the time for degradable devices to perform with physical and mechanical integrity (functional time, t_f), the other is the total time that devices spend from implantation to disappearance (disappearance time, t_d). In order for materials to have good mechanical properties, especially toughness, their molecular weights have to be higher than a certain value M_P that is related to the entanglement molecular weights (M_e) of the materials. For PLA, the entanglement molecular weight is about 8 to 10 kg/mol.[60] The functional time is the duration for the materials to degrade from their initial molecular weight (M_{n0}) to M_p. The disappearance time is determined by the whole process from the initial molecular weight M_{n0}, through M_p, to the soluble molecular weight M_d. For PLA, M_d is 2−3 kg/mol.[6,7,61] Ideally, degradable devices should disappear shortly after completing their physical functions. So, the ratio t_d/t_f should be close to 1. In reality, this ratio might be much larger than 1 because the time for molecules to degrade from M_p to M_d can be long. Prediction of the ratio t_d/t_f may be possible if the parameters mentioned above are measured.

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