2462 *Macromolecules* **2009**, *42*, 2462−2471

Improved Mathematical Model for the Hydrolytic Degradation of Aliphatic Polyesters

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Received October 3, 2008; Revised Manuscript Received February 6, 2009

ABSTRACT: The objective of this study was to develop a mathematical model that describes and even predicts the hydrolytic degradation of aliphatic polyesters. From literature, it is known that the main process of degradation of aliphatic polyesters is the autocatalytic hydrolysis of ester bonds. Because of this hydrolysis, polymer chains are cleaved and the molecular weight will decrease. With time, the molecules become small enough for the system to start losing weight, since the small molecules dissolve in the aqueous medium. In addition, the crystallinity can change during degradation and influence the degradation rate of the polymer and the monomer ratio of a copolymer. In order to test the model several aliphatic polyesters were synthesized. The degradation behavior of these polymers was investigated by placing them in an aqueous environment (pH = 7.4) at 37 °C. At certain time intervals, samples of the polymers were taken and analyzed. A mathematical model was developed based on the autocatalytic hydrolytic degradation mechanism of aliphatic polyesters and verified with the measured results. Up to now, no models are known that include the autocatalytic hydrolysis behavior of aliphatic polyesters. The calculations of the new developed model are compared with measured results. It shows that it describes the concentration change of all polymer chains present as function of the degradation time. Hence, the change in molecular weight distribution, the decrease of the average molecular weight and the mass loss of the polymer as function of the degradation time can be predicted. This is a major advancement with respect to any earlier developed model. The only unknown input parameter for the model is the hydrolysis rate constant. The mathematical model is valid for semicrystalline as well as amorphous polymers and for copolymers.

Introduction

Polymers are among the most widely used materials in life. One of the valuable properties includes their tong term stability. However, for some applications, a shorter lifetime is desired, such as biomaterials for medical, pharmaceutical, and ecological purposes. The degradation behavior of polymers has been intensively investigated, as well as the mechanism of their degradation.[1−4] The type and speed of the erosion of a degradable polymer depends on the polymer and the environment wherein it takes place. One of the main groups of degradable polymers is the group of the aliphatic polyesters. Nowadays, these polymers are used in different applications such as drug delivery devices, surgical implants (e.g., bone screws) or in disposable materials. During the design of a product, made from a degradable aliphatic polymer, information about the degradation rate of the polymer is of major interest in order to choose the right polymer with the desired properties. In addition, it was observed that the main process of degradation of aliphatic polyesters is the hydrolysis of the ester bonds in the polymer chain, which was found to be an autocatalytic process. Because of the hydrolysis, the molecular weight decreases during the degradation process. With time, the molecules become small enough to dissolve in the bulk medium and hence the system starts losing weight. The objective of this work is to develop a mathematical model which can describe and even predict the degradation of the aliphatic polyesters in an aqueous environment. The improvement with respect to existing models[5−12] is that our model takes into account the autocatalytic effect of generated carboxylic acid groups on the hydrolysis.

General Considerations

The hydrolytic degradation mechanisms of poly(ϵ-caprolactone) (PCL), polylactide (PLA), polyglycolide, and their copolymers are similar,[12−14] and a similar model can be used to describe the degradation. In literature the majority of the studies on the degradation of polyesters is focused on PLA and its copolymers. Therefore, the theory of the hydrolytic degradation mechanism of poly(α-hydroxy acids) is mainly based on the results of PLA degradation, supported with findings of degradation studies of PCL and its copolymers.

At first, water diffuses into the amorphous regions of the polymer. The densely packed crystalline regions are inaccessible for water.[15] The ester bonds in the polymer backbone are hydrolyzed in the amorphous domains in the presence of water. This is a random chain scission process catalyzed by the presence of acid. The penetration of water into aliphatic polyesters is much faster than the hydrolysis rate of the ester bonds.[16] Therefore the degradation of aliphatic polyesters is a bulk erosion process.[17−19] In previous studies by Li and coworkers,[20,21] it was found that PLGA films exhibited faster degradation behavior in the center than at the surface of the material, when exposed to an aqueous environment. The degradation of the polymer surface is affected by the environment and it is found that the difference in degradation of the core and of the surface is smaller in a buffered environment than in a nonbuffered aqueous environment.[20] When polymer samples are small, a linear relationship between the degradation rate and the particle size was observed.[22] On the other hand,

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10.1021/ma802222m CCC: $40.75

when the polymer samples are very large, water needs more time to diffuse into the core of the sample. Although water has already penetrated the skin and enhances degradation, the core remains unaffected, because water has not reached the core jet. Every polymer has its own specific critical dimension from which samples exceeding that dimension show surface erosion instead of bulk erosion. According to Von Burkersroda for poly(α-hydroxy acids) this is about 7.4 cm.[16]

Upon degradation, the number of carboxylic acid groups in the polymer will increase leading to a dramatic decrease of pH inside the polymer matrix to as low as pH 2 *in vivo*[23] and a significant increase of autocatalytic degradation. The encapsulation of buffer salts may neutralize the internal pH, but affects the erosion profile negatively.[24] The degradation rate is also affected by other encapsulations (e.g., catalyst,[24] salts,[25] fatty acid ester,[26] acidic or basic excipients[27,28]).

Upon hydrolysis the molecular weight of the polymer decreases because of the random chain scission process. When the oligomers become small enough, they will dissolve in the medium,[29] and hence mass loss of the polymer will start. For poly(D,L-lactide-*co*-glycolide) this mass loss starts after several days.[20,21,29,30] Ultimately, the polymers degrade into their oligomeric and monomer hydroxy acids. Also the oligomers, which are dissolved in the medium, degrade into their monomeric hydroxy acids.[31,32] When the term "monomers" is used, this refers to "monomeric hydroxy acids" in this study.

Initially, semicrystalline polymers reveal an increase in crystallinity during a degradation study in water.[19] The increase in crystallinity is due to a slight swelling of the amorphous domains, which causes an increase of the chain flexibility. This allows further crystallization of the polymer. This crystallization was also found upon absorption of water in nylons.[33] Beside this increase of crystallinity, the crystallinity of the polymer can also increase by aging. Some amorphous, aliphatic polyesters can form semicrystalline residues during degradation.[34] Whether a poly(α-hydroxy acid) is amorphous or semicrystalline and whether it can form semicrystalline residues during degradation depends on the following: the comonomer ratio, the average block length of the copolymer, and the process conditions during the preparation of the polymer. According to Hakkarainen and Vert, the crystalline regions start to degrade when most or all of the amorphous regions have disappeared and the water slowly penetrates into the crystalline regions.[19,35]

The monomer ratio of aliphatic copolyesters has a strong influence on the degradation, because of two main reasons. One is, if the polymer consists mainly or completely of one type of monomer, it is often semicrystalline and the degradation of the completely polymer will be slower than that of a complete amorphous polymer. If the polymer has a high amount of one kind of monomer, it is possible that degradation may give semicrystalline residues under selected degradation conditions.[35] The other cause is that the hydrolysis rate of one type of ester bond is faster than that of other ester bonds. Different studies of PLGA copolymers have shown that the chain scission of glycolic acid bonds is faster than that of lactic acid bonds.[19−21] Other aliphatic copolyesters like those based on caprolactone have not been as intensively investigated as PLGA. However, they clearly show that the degradation process is a random hydrolytic chain scission and that the rate of the degradation also strongly depends on the monomers used and the ratio of the copolymers.[13,36−38]

When poly(α-hydroxy acids) are immersed in an aqueous environment, the polymer starts to absorb water, which causes swelling of the polymer. Two types of water are found within the copolymer, bulk water and bound water.[39] Water which is absorbed in the free volume in the amorphous phase of the polymer, acts as a plasticizer and reduces the glass transition temperature. Also, during the water uptake of the polymer, voids filled with water are formed.[40] They are formed out of prevoids that are present in the polymer material. The total swelling of the polymer depends on the swelling of the polymer coils[41] and the forming of voids.[40]

When the chain parts become so small that the polymer material starts to lose mass, the structure of the polymer device becomes very porous and the medium penetrates the porous structure and penetrates into the polymer. The surface of the polymer that is exposed to the medium becomes very large and the degradation of the polymer is more and more controlled by surface degradation.[22] Variation in ion strength of the environment has no influence on the copolymer chain scission, but it has influence on the amount of water uptake. The higher the ionic strength, the lower the concentration of absorbed water will be. The variation in pH of a media with similar ionic strength has no influence on the hydrolysis of the polymer chain or the water uptake.[39] This is an indication that the polymer is impermeable for ionized species. However, when the pH exceeds 13, the erosion kinetics of PLA and PLGA change into a linear mass loss profile, indicating that surface erosion is the degradation mechanism for higher pH values.[16]

A polymer with carboxylic acid end groups degrades faster than a polymer without carboxylic acid end groups, because the presence of carboxylic acid groups accelerates the autocatalytic chain scission process from the very beginning of the degradation process.[42] The rate of hydrolysis also depends on the temperature at which the degradation process takes place. The higher the temperature, the faster the degradation rate will be.[43]

Degradation of a polymer generally refers to all the effects observed during the decay of the polymer. With the term hydrolysis of the polymer, the chain scission of the polymer chain is meant.

The New Model

The hydrolytic degradation of aliphatic polyesters is caused by the hydrolysis of the ester bond in the polymer main chains and this is an autocatalytic mechanism. In this study, the degradation of the aliphatic polyesters is performed in an aqueous environment. Thus, water is present in a bulk amount and, therefore, the water concentration remains constant during the degradation of the polymers. The hydrolysis rate equation is

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

where [E] is the concentration of ester bonds, [A] is the concentration of acid, k is the reaction rate constant of hydrolysis of the ester bond, and t is the time of the hydrolysis process. All the concentrations mentioned are molar concentrations and not mass concentrations.

A polymer chain (P) consists of a number of ester bonds (i), so the rate of hydrolysis of one polymer chain with chain length n can be written as follows:

$$\frac{\mathrm{d}[\mathrm{P}_n]}{\mathrm{d}t} = -nk[\mathrm{P}_n][\mathrm{A}] \tag{2}$$

In eq 2, every ester bond in the polymer chain is considered to have the same hydrolysis rate (k). Also, the equation is based on a specific chain length of a linear polymer chain, whereas normally polymers consist of a mixture of different chain lengths (P_i). Only the degradation of the longest polymer chain in the entire polymer mass is described with eq 2. The degradation of the polymer chain with one less ester bond can be written as follows:

$$\frac{\mathrm{d}[\mathrm{P}_{n-1}]}{\mathrm{d}t} = 2k[\mathrm{P}_n][\mathrm{A}] - (n-1)k[\mathrm{P}_{n-1}][\mathrm{A}] \tag{3}$$

For all the other chain lengths (i), it is as follows:

$$\frac{\mathrm{d}[\mathrm{P}_i]}{\mathrm{d}t} = 2\sum_{m=i+1}^{n} k[\mathrm{P}_m][\mathrm{A}] - ik[\mathrm{P}_i][\mathrm{A}] \tag{4}$$

During the degradation, monomers are also formed [P_0] and the rate of their formation is expressed with the following equation:

$$\frac{\mathrm{d}[\mathrm{P}_0]}{\mathrm{d}t} = 2\sum_{i=1}^{n} k[\mathrm{P}_i][\mathrm{A}] \tag{5}$$

Differential eqs 2 to 5 cannot be solved separately. They form a system of coupled differential equations that can be expressed in the following matrix notation:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} P_0 \\ P_1 \\ \vdots \\ P_i \\ \vdots \\ P_{n-1} \\ P_n \end{bmatrix} = k[\mathrm{A}]\begin{bmatrix} 0 & 2 & \cdots & 2 & \cdots & 2 & 2 \\ 0 & -1 & & & & 2 & 2 \\ \vdots & & \ddots & & \iddots & & \vdots \\ 0 & & & i & & & 2 \\ \vdots & & \iddots & & \ddots & & \vdots \\ 0 & 0 & & & & -n+1 & 2 \\ 0 & 0 & \cdots & 0 & \cdots & 0 & -n \end{bmatrix}\begin{bmatrix} P_0 \\ P_1 \\ \vdots \\ P_i \\ \vdots \\ P_{n-1} \\ P_n \end{bmatrix} \tag{6}$$

In the previous equation P_i represents the concentration of a polymer chain with i ester bonds. As the amount of ester bonds in a polymer chain is proportional to the polymer chain length, the vector of P_0 to P_n can be seen as a linear molecular weight distribution.

Carboxylic acid end groups, autocatalytic for the ester hydrolysis, are formed during hydrolysis and the time dependence of the concentration of the carboxylic acid groups has to be incorporated into the equation. The concentration of carboxylic acid end groups in the polymer at time t for polymers with an initial carboxylic acid end group is expressed with the following equation:

$$[\mathrm{A}] = \sum_{i=0}^{n} [\mathrm{P}_i] + [\mathrm{A}]_0 \tag{7}$$

If the polymer has a noncarboxylic acid end group at the start of the degradation, the total concentration of polymer chains before the start of the hydrolysis process (symbol $[\mathrm{P}_i]_0$) has to be subtracted (see eq 8):

$$[\mathrm{A}] = \sum_{i=0}^{n} [\mathrm{P}_i] - \sum_{i=0}^{n} [\mathrm{P}_i]_0 + [\mathrm{A}]_0 \tag{8}$$

The acid concentration at time t ([A]) is the sum of the total concentration of monomers and polymer molecules present at time t ([P_i]) plus a constant ($[\mathrm{A}]_0$). The constant $[\mathrm{A}]_0$ includes the concentration of acid which is initially present due to the additives in the polymer and the amount of water dissolved in the polymer (see eq 7).

To describe the degradation of a polymer, eqs 6 and 7 have to be combined. This results in a set of nonlinear differential equations:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} P_0 \\ P_1 \\ \vdots \\ P_i \\ \vdots \\ P_{n-1} \\ P_n \end{bmatrix} = k\left(\sum_{i=0}^{n} [\mathrm{P}_i] + [\mathrm{A}]_0\right) \times \begin{bmatrix} 0 & 2 & \cdots & 2 & \cdots & 2 & 2 \\ 0 & -1 & & & & 2 & 2 \\ \vdots & & \ddots & & \iddots & & \vdots \\ 0 & & & i & & & 2 \\ \vdots & & \iddots & & \ddots & & \vdots \\ 0 & 0 & & & & -n+1 & 2 \\ 0 & 0 & \cdots & 0 & \cdots & 0 & -n \end{bmatrix}\begin{bmatrix} P_0 \\ P_1 \\ \vdots \\ P_i \\ \vdots \\ P_{n-1} \\ P_n \end{bmatrix} \tag{9}$$

If a polymer is semicrystalline, parts of the polymer chain are excluded from degradation because they are incorporated in the crystals, where water cannot, or only hardly, penetrate. Therefore, no degradation in the crystals occurs. However, water can penetrate into the amorphous domains,[15,19,35] and hence, the ester bonds in the amorphous phase are available for degradation.

To calculate the correct hydrolysis rate, the concentration of ester bonds in the total polymer sample has to be reduced with the molar fraction of ester bonds present in the crystalline domains (φ_C). The applied characterization techniques, almost exclusively based on dissolving the entire polymer material, are only able to analyze the complete polymer sample. To correct for this in the model, the concentrations of each polymer chain length and the concentrations of the ester bonds in eq 9 have to be multiplied with the amorphous fraction (φ_A) or ($1 - \varphi_\mathrm{C}$).

It is not possible to construct a matrix in which every possible monomer sequence distribution of a copolymer chain consisting of two or more monomeric units is presented. A polymer chain consisting of 1000 monomer units of two different types has $2^{1000} \approx 10^{300}$ possibilities to be arranged. This number is far too large to use in calculations with our current computer technology. Additionally, it is not possible to detect each individual monomer sequence of the polymer chains, however the total concentration of each polymer chain lengths can be characterized.

The total amount of different types of ester bonds present in the polymer can be determined. A copolymer that consists of two different monomeric units (A and B) has the following four types of ester bonds: A−A, A−B, B−A, and B−B, respectively symbolized as E_1, E_2, E_3, and E_4. Of course, this approach can be extended with numerous types of ester bonds (E_m). Each different type of ester bond has its specific hydrolysis rate constant (k_{E_1} to k_{E_m}). It is postulated that the overall hydrolysis rate (k) can be expressed as in eq 10. Herein χ_{E_i} is the molar fraction of each corresponding type of ester bond (E_i).

$$k = x_{\mathrm{E}_1}k_{\mathrm{E}_1} + x_{\mathrm{E}_2}k_{\mathrm{E}_2} + \cdots + x_{\mathrm{E}_\mathrm{m}}k_{\mathrm{E}_\mathrm{m}} = \frac{[\mathrm{E}_1]}{\sum_{i=1}^{m}[\mathrm{E}_i]}k_{\mathrm{E}_1} + \frac{[\mathrm{E}_2]}{\sum_{i=1}^{m}[\mathrm{E}_i]}k_{\mathrm{E}_2} + \cdots + \frac{[\mathrm{E}_m]}{\sum_{i=1}^{m}[\mathrm{E}_i]}k_{\mathrm{E}_m} \quad \text{or} \quad k = \sum_{i=1}^{m} x_{\mathrm{E}_i}k_{\mathrm{E}_i} \tag{10}$$

During degradation the ratio of E_1 to E_m ester bonds changes. To know what the fraction of ester bonds E_1 to E_m is, the concentration of ester bonds at each time interval has to be calculated. The reaction rate equations for the decrease of the concentration of ester bonds are:

$$\begin{aligned}\frac{\mathrm{d}[\mathrm{E}_1]}{\mathrm{d}t} &= -k_{\mathrm{E}_1}[\mathrm{E}_1][\mathrm{A}]\\ \frac{\mathrm{d}[\mathrm{E}_2]}{\mathrm{d}t} &= -k_{\mathrm{E}_2}[\mathrm{E}_2][\mathrm{A}]\\ &\vdots\\ \frac{\mathrm{d}[\mathrm{E}_m]}{\mathrm{d}t} &= -k_{\mathrm{E}_m}[\mathrm{E}_m][\mathrm{A}]\end{aligned} \tag{11}$$

In eq 11 $[\mathrm{E}_1]$ to $[\mathrm{E}_m]$ are the concentrations of ester bonds of respectively E_1 to E_m, [A] is the concentration of acid, k_{E_1} to k_{E_m} are the reaction rate constants of hydrolysis of the ester bond of respectively E_1 to E_m, and t is the time of the hydrolysis process. The set of nonlinear differential equations (eq 11) can be written in a matrix notation.

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix}E_1\\E_2\\\vdots\\E_m\end{bmatrix} = \begin{bmatrix}-k_{\mathrm{E}_1} & 0 & 0 & 0\\ 0 & -k_{\mathrm{E}_2} & 0 & 0\\ 0 & 0 & \ddots & 0\\ 0 & 0 & 0 & -k_{\mathrm{E}_m}\end{bmatrix}\begin{bmatrix}E_1\\E_2\\\vdots\\E_m\end{bmatrix}[\mathrm{A}] \tag{12}$$

With eq 12, the concentration of ester bonds (E_1 to E_m) can be calculated at each time interval during degradation. The acid concentration [A] in the copolymer depends on the amount of chains present in the polymer and is given by eq 7 for polymers with a carboxylic end group or can be described with eq 8 for polymers with a noncarboxylic end group. These equations are directly coupled by means of eq 9.

The set of linear differential equations (eq 12) can be used to calculate the concentration of ester bonds at a certain time interval. With this information the overall hydrolysis rate at that time interval can be calculated (eq 10). To describe the degradation of a copolymer eq 9 and eq 10 have to be combined, This new equation is coupled with the equation which describes the concentration of ester bonds present in the copolymer sample (eq 12). This finally results in the next set of nonlinear differential equations.

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix}E_1\\E_2\\\vdots\\E_m\end{bmatrix} = \begin{bmatrix}-k_{\mathrm{E}_1} & 0 & 0 & 0\\ 0 & -k_{\mathrm{E}_2} & 0 & 0\\ 0 & 0 & \ddots & 0\\ 0 & 0 & 0 & -k_{\mathrm{E}_m}\end{bmatrix}\begin{bmatrix}E_1\\E_2\\\vdots\\E_m\end{bmatrix}\left(\sum_{i=0}^{n}[\mathrm{P}_i] + [\mathrm{A}]_0\right)$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix}P_0\\P_1\\\vdots\\P_i\\\vdots\\P_{n-1}\\P_n\end{bmatrix} = \left(\sum_{i=1}^{m} x_{\mathrm{E}_i}k_{\mathrm{E}_i}\right)\left(\sum_{i=0}^{n}[\mathrm{P}_i] + [\mathrm{A}]_0\right) \times$$

$$\begin{bmatrix}0 & 2 & \cdots & 2 & \cdots & 2 & 2\\ 0 & -1 & & & & 2 & 2\\ \vdots & & \ddots & & \iddots & & \vdots\\ 0 & & & i & & & 2\\ \vdots & & \iddots & & \ddots & & \vdots\\ 0 & 0 & & & & -n+1 & 2\\ 0 & 0 & \cdots & 0 & \cdots & 0 & -n\end{bmatrix}\begin{bmatrix}P_0\\P_1\\\vdots\\P_i\\\vdots\\P_{n-1}\\P_n\end{bmatrix} \tag{13}$$

This set of coupled differential equations can be solved with the Runge–Kutta algorithm.[44] Equation 13 is valid for copolymers with a carboxylic acid end group. For copolymers with a noncarboxylic acid end group, the subtraction of the initial concentration of polymer chains (as in eq 8) has to be implemented in the term for the acid concentration (term: $\Sigma[\mathrm{P}_i] + [\mathrm{A}]_0$).

During degradation, monomeric and oligomeric degradation products can dissolve in the medium, causing a mass loss of the polymer sample, which can easily be calculated. When the maximum molecular weight of oligomers that can dissolve in the medium is known, the total mass loss can easily be calculated by adding up the total amount of monomers and oligomers having the same or lower molecular weight as the just soluble oligomer. When oligomers and monomers are dissolving in the medium, these have to be excluded from the equations calculating the acid formation in the polymer (eqs 7 and 8). Then, i does not start at 0 but at the number of ester bonds present in the smallest or lightest insoluble oligomer, and when only monomers dissolve, i starts at 1.

An assumption in this model is the absence of swelling of the polymer. This assumption can be justified by the small amount of water which is present in the amorphous phase of the polymer.

In the results and discussion part of this paper, the new, improved hydrolytic degradation model will be experimentally validated for several types of aliphatic (co)polyesters.

Experimental Section

Preparation of the Polymers. The synthesis of poly(ϵ-caprolactone) (PCL) and poly(4-methylcaprolactone) with either a carboxylic acid end group (P4MC) or with a benzyl alcohol end group (P4MC-BA) were performed as described by De Geus et al.[45] Poly(D,L-lactide) (PLA) and poly(D,L-lactide-*co*-glycolide) with a monomer ratio of 53:75 (PLGA 53:47) and a ratio of 75:25 (PLGA 75:25) were obtained from Purac.

The polymers PCL, PLA, PLGA 53:47, and PLGA 75:25 were placed in a melt-indexer (Tinius Φ Olsen, model MP993). Then, after an equilibrium time to allow complete melting, the material was extruded into a rod through a die with a diameter of 2.0 mm, by pressing it with a piston loaded at higher temperatures (PCL at 75 °C and PLA, PLGA 53:47, and PLGA 75:25 at 140 °C). The other polymers were thick viscous liquids and therefore could not be processed into rods.

Degradation Experiments. The degradation of the polymers was performed in Phosphate Buffered Saline (PBS-buffer). The next PBS-buffer was prepared. In a glass vessel of 20 L, 174.165 g of $\mathrm{Na_2HPO_4}$, 37.3602 g of $\mathrm{NaH_2PO_4 \cdot 2H_2O}$, 0.7059 g of NaCl, 7.6310 g of $\mathrm{NaN_3}$ and 15002.6 g of Milli-Q water were weighed. A top stirrer was placed in the vessel, and the medium was stirred for 1 h. Subsequently, the medium was degassed by purging it with helium for at least 1 min.

The mass of the clean test-tubes was determined with an analytical balance, before adding the rods and buffer solution. Subsequently, several amounts of polymer from each batch were individually weighed in the test-tubes/bottles to be analyzed for the different time intervals and PBS-buffer was added. The test-tubes were placed in an oven at 37.0 °C. At certain time intervals the polymers were sampled by removing the PBS-buffer with a syringe. The remaining polymer was vacuum-dried (15 mbar) at ambient temperature for at least 12 h. Mass loss of the polymer was gravimetrically determined.

Measurements. SEC analysis was carried out using a Waters GPC equipped with a Waters 2695 - Alliance pump, injector (50 μL) and a column oven (40 °C). Several detectors were used at a temperature of 40 °C: a Waters 996 Photo Diode Array detector, a Viscotek 250 Dual detector (viscosity detection + differential refractive index detection) and a Waters 2414 differential refractive index detector. Three MIXED-C 5 μm 300 × 7.5 mm columns were used. Tetrahydrofuran (Biosolve, stabilized with BHT) was used as eluent at a flow rate of 1.0 mL/min. Calibration curves were obtained using polystyrene (easy cal.; Polymer Laboratories,

Table 1. Eluent Used for HPLC Analysis: Methanol, Water, and as Additive 0.1% Acetic Acid

gradient: time	% H_2O	% MeOH
0	90	10
20	0	100
25	0	100
28	90	10

Table 2. Results of Average Molecular Weight of the Polymers before and after Ram-Extrusion

	before extrusion		after extrusion		
polymer	M_n (kg/mol)	M_w (kg/mol)	M_n (kg/mol)	M_w (kg/mol)	diameter rod (mm)
PCL	n/a	n/a	14.8	59.5	1.4
P4MC[a]	n/a	n/a	9.4	32.0	n/a
P4MC-BA[a]	n/a	n/a	5.0	21.8	n/a
PLA	12	34	12	34	1.5
PLGA 53:47	16	78	14	63	2.0
PLGA 75:25	15	90	13	79	2.3

[a] The samples were thick viscous liquids.

$M = 580$ to $M = 7.1 \times 10^6$ g/mol). Data acquisition was performed using the Waters Empower2 (all detectors) and Viscotek Ominisec4 (Viscotek Viscosity and Waters DRI). The melting points and the crystallinity of the polymers were determined with differential scanning calorimetry (DSC). The applied instrument is a DSC Q100 V9.4 Build 287. The sample was cooled down to −50.0 °C and heated to +150.0 °C at a rate of 10 °C/min. From the first heating curve the crystallinity of the polymers was determined using the melt enthalpy of the crystalline phase. For poly(ϵ-caprolactone), the melt enthalpy, ΔH_m, for 100% crystalline material is 139.4 J/g.[46] To determine the dissolved polymer fragments 1.5 mL buffered medium was transferred into a crimp cap vial. Then, the samples were placed in the chromatographic system (HPLC), being an Agilent 1100 series with a degasser (G1322A), quaternary pump (G1311A), autosampler (G1313A) with an injection volume of 1 μL, column compartment (G1316A) at a temperature of 25 °C, and detector UV-DAD (G1315B) signal A ($\lambda = 254$ nm, bw = 8 nm) and the mass spectrometer used was an Agilent MSD type SL (G1946D) with spray chamber settings as follows.: drying gas temperature, 350 °C; drying gas flow, 13 L/min; nebulizer pressure, 30 psi; capillary voltage, 4000 V; AP-ESI mode, positive. Subsequently, the samples were processed and data acquisition was performed using the HP Chemstation version A10.01 (Hewlett-Packard) software. A Column Zorbax RX-C8 (2.1 × 150 mm; $d_p = 5$ μm) was used. The used eluent and gradient are described in Table 1. The flow rate was 0.25 mL/min.

Results and Discussion

Synthesis and Extrusion of the Polyesters Based on 4-Methylcaprolactone or ϵ-Caprolactone. The syntheses of the different polymers PCL and P4MC, both with and without carboxylic acid end groups, were performed as described before.[45] The molecular weight and molecular weight distribution of the obtained polymers were determined with SEC and were measured before and after the ram-extrusion (see Table 2). The crystallinity of 66% for PCL was determined with DSC. The NMR results of P4MC-BA showed that in this case benzyl alcohol was only incorporated in 20% of the polymer chains. The remaining 80% of the polymer chains had a carboxylic acid end group. This high amount of carboxylic acid end groups in the polymer can have several causes, for example the enzyme or another component used during reaction was not dried well, or due to the long reaction times and poor isolation toward humid air, water could have diffused into the reaction vessel.

Ram-extrusion of the different polymers (PCL with carboxylic acid end group, PLA and PLGA with noncarboxylic acid end group) was performed. The molecular weight and molecular weight distribution of the obtained polymers were determined with SEC before and after ram-extrusion, except for PCL which was only analyzed after ram-extrusion. P4MC and P4MC-BA were viscous liquids and therefore not processed with the ram-extruder. The results are presented in Table 2.

Table 3. Determined Mark−Houwink Parameters

polymer	a (-)	s_d of a (-)[b]	K (dL/g)	s_d of K (dL/g)
PCL	0.810	0.018	0.00013	2×10^{-5}
P4MC/ P4MC-BA[a]	0.680	0.026	0.00032	8×10^{-5}
PLA	0.737	0.032	0.000176	8×10^{-5}
PLGA 75:25	0.610	0.020	0.00051	11×10^{-5}
PLGA 53:47	0.726	0.032	0.000176	6×10^{-5}

[a] The average value of those two is taken because it is the same polymer only with a different end group. [b] s_d is the standard deviation.

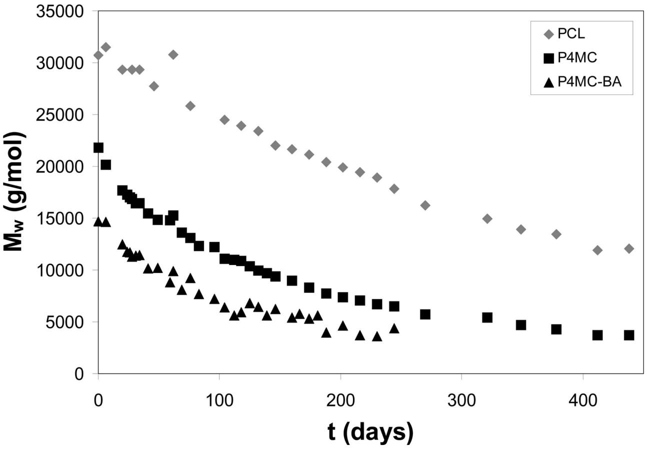

Figure 1. Weight average molecular weight degradation profile of PCL, P4MC, and P4MC-BA only determined on the remaining polymer.

The reduction in molecular weight of the copolymers PLA and PLGA after ram-extrusion is between 6 and 20%. The time of exposure of the polymer to the elevated temperatures during ram-extrusion was not measured, so the extend of degradation can only be used as an indication. The SEC chromatograms also showed that the samples did not contain unreacted lactide, glycolide ϵ-caprolactone or 4-methylcaprolactone, and therefore there is no influence of the unreacted compounds on the degradation (e.g., initial mass loss).[47]

Determination of Polymer Parameters. The polymer chain length decreases during degradation. When oligomers are obtained, mass loss starts as these oligomers dissolve in the buffer surrounding the polymer. The molecular weight of the oligomers that dissolved in the buffer was determined with HPLC-MS. Oligomers consisting out of 4 or less monomeric hydroxy acids of the polymers PCL, P4MC and P4MC-BA dissolved in the buffer, which corresponds with a molecular weight up to 500 g/mol. For PLGA 53:47, oligomers with a molecular weight up to 850 g/mol dissolved in the buffer (ca. 13 monomeric units). This value corresponds with values found in the literature for PLA.[31] It is reasonable to assume that the oligomers of PLGA 75:25 with a molecular weight up to 850 g/mol also dissolve in the buffer. This data has been used in the model to determine the mass loss curves (see Figures 9 and 11) Using Triple-SEC, the Mark−Houwink parameters (a and K) of the different polymers were determined. The determined data is presented in Table 3.

Hydrolytic degradation of the polymers. During the evaluation of the results the weight average molecular weight (M_w) of the different samples is preferred above number average molecular weight (M_n), because M_n is very sensitive toward small variations in the integration of the chromatogram. In Figure 1 the M_w of the polymers, PCL, P4MC-BA and P4MC is depicted as a function of degradation time. In Figure 2, the

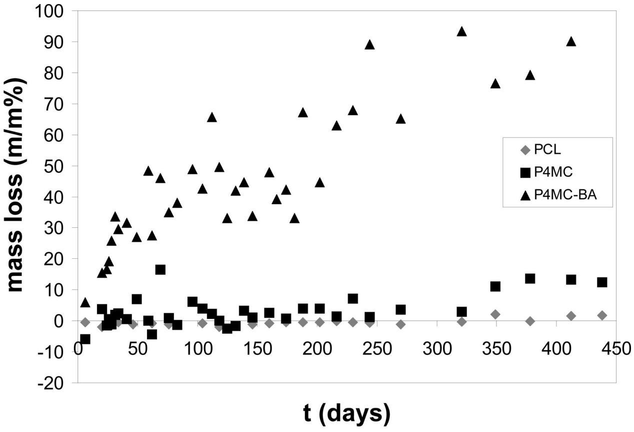

Figure 2. Mass loss during degradation of PCL, P4MC, and P4MC-BA.

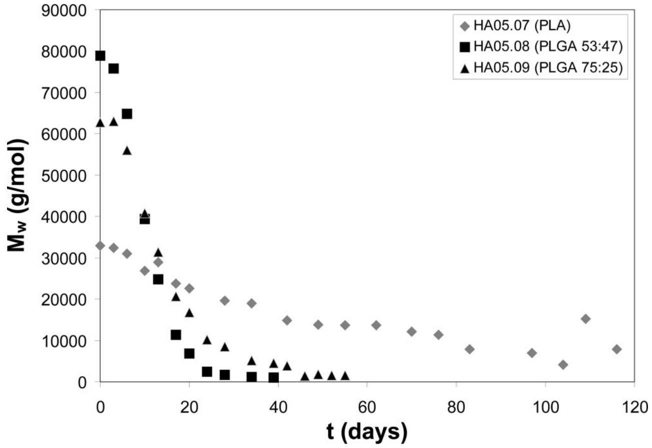

Figure 3. Weight average molecular weight development during degradation of PLA, PLGA 75:25, and PLGA 53:47, only determined on the remaining polymer.

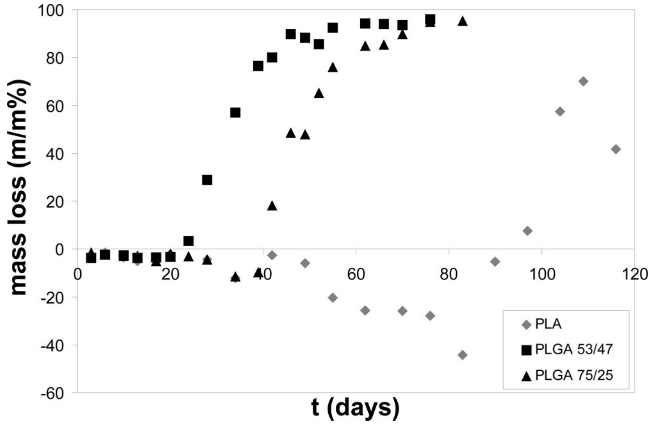

Figure 4. Mass loss during degradation of PLA, PLGA 75:25, and PLGA 53:47.

mass loss of the polymers, is presented as a function of time. The M_w s of the polymers PLA, PLGA 75:25 and PLGA 53:47 versus time are presented in Figure 3. The mass losses of polymers PLA, PLGA 75:25 and PLGA 53:47 versus time are presented in Figure 4.

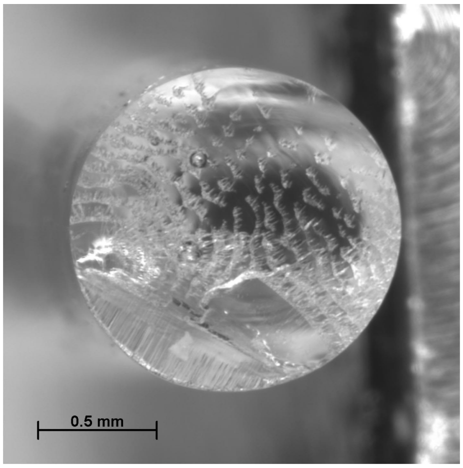

Figure 5. Cross section of the initial PLA rod.

A decrease in molecular weight of all polymers is observed. When the molecular weight becomes too low the polymers start to lose weight, due to the dissolution of oligomers in the buffered medium.[20,30] P4MC-BA has a very low initial molecular weight and therefore mass loss starts immediately. The observed patterns in Figure 1 to Figure 4 indicate that the degradation occurs via a bulk erosion process. In the initial period without mass loss, the molecular weight of the polymer already decreases. This observed decrease in molecular weight without mass loss can only be observed when bulk erosion takes place, as polymer chains are cleaved in the entire sample.

The change of molecular weight of the polymer during degradation shows a typical S-shaped curve which can be divided in three stages (Figure 3). Although originally these polymers possessed noncarboxylic acid end groups, conditions during ram extrusion may cause some hydrolysis, thereby introducing a small amount of carboxylic acid end groups. Due to the low concentration of carboxylic acid groups the decrease in molecular weight is slow in the first stage. In the second stage, more carboxylic acid end groups have been formed, which accelerates the hydrolysis reaction. Therefore the rate of decrease in the molecular weight increases. In the last stage the low concentrations of ester bonds slows down the degradation and the decrease of molecular weight. For polymers with relatively high initial carboxylic acid end group concentrations at the start of the degradation (e.g., PCL, P4MC, and P4MC-BA) the degradation curve starts in the second stage of the degradation process.

The initial molecular weight of the polymers PLA, PLGA 75:25, and PLGA 53:47 are respectively 34, 63, and 79 kg/mol (see Figure 3). By coincidence the polymer with a high GA-content has a higher molecular weight. The weight average molecular weight of the copolymer with a high GA-content decreases faster than for the copolymer with a lower GA-content. The degradation curves even cross each other (see Figure 3), which proves that the hydrolysis of GA ester bonds is faster than the hydrolysis of LA ester bonds.

During the degradation of PLA rods a white skin was formed (see Figure 5 and Figure 6). Also the mass of the rods seemed to increase after ca. 50 days (see Figure 4). The center of the rod was very viscous whereas the skin layer was more brittle. DSC results show that there were no crystals present in the remaining rod. From IR-spectroscopy and thermal gravimetrical analyses (TGA) free water was detected in the skin layer. This shows that during degradation a porous skin layer was formed by penetration of the PBS-buffer. The degradation of the skin was probably slowed down by the presence of PBS-buffer and this PBS buffer was not removed by the drying procedure. The presence of the buffer also neutralizes the formed carboxylic acid in the skin, washes the formed oligomers away and slowes down the degradation. In the core of the rod the hydrolysis rate increased because of accumulation of carboxylic acid end groups, which are not washed out so easily. In the developed

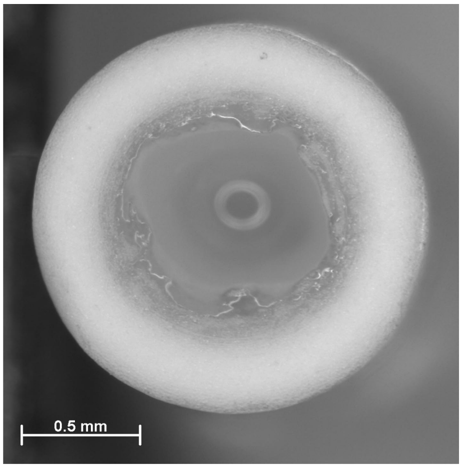

Figure 6. Cross section of the PLA rod after 70 days of degradation.

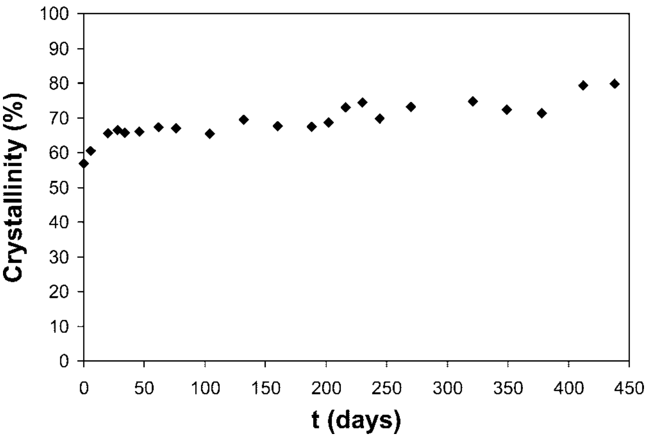

Figure 7. The crystallinity of the polymer phase during degradation of PCL.

model, surface degradation is not incorporated. As a consequence, only the first 28 days of the degradation curve can be used to determine the hydrolysis rate constant of PLA.

This difference between core and skin degradation of PLA causes inhomogeneous samples at the end of the degradation. This explains the deviations in the molecular weight degradation profile (see Figure 3) and in the mass loss degradation profile (see Figure 4).

All polymers were amorphous at the start and during degradation, except for PCL. In Figure 7, the crystallinity of PCL is presented as a function of the degradation time.

It seems that the crystallinity slightly increases during degradation. This can be explained by water penetration into the amorphous domains. The amorphous domains slightly swell, increasing the chain mobility and (re)crystallization of the polymer can occur. This (re)crystallization mechanism phenomena has been shown for nylons.[33]

Modeling of the Polymer Degradation. To test the new model, all initial characteristics of the polymers were used as input parameter. The initial characteristics are: the molecular weight of the monomeric unit, the molecular weight of the oligomers which dissolve into the surrounding medium, the monomer ratio of the copolymers, the crystallinity, the type of the end group, the concentration of initial carboxylic acid groups present and the complete molecular weight distribution (MWD).

The linear MWD of the polymer of interest has to be entered into the set of nonlinear differential equations (eq 9). From SEC analysis a logarithmic MWD is obtained. To transform the logarithmic MWD into a linear MWD the exponent of the molecular weight has to be taken. The value of the dw/dlog(M) has to be divided by the corresponding molecular weight.[48]

Table 4. Determined Hydrolysis Rate Constants (k)

polymer	ester bond	k (L mol^{-1} day^{-1})
PCL[a] ($\varphi_A = 0.33$)	CL−CL	0.421×10^{-3}
P4MC	4MC−4MC	0.398×10^{-3}
P4MC-BA	4MC−4MC	0.423×10^{-3}
PLA	LA−LA	6.44×10^{-3}
PLGA 75:25	GA−GA	10.3×10^{-3}
PLGA 53:47	GA−GA	12.9×10^{-3}

[a] The value of the hydrolysis rate constant of PCL only refers to the amorphous phase. φ_A = fraction of amorphous material.

The data points of the linear MWD are not equidistant and not necessarily correspond to the mass of a monomeric unit. The data points of the measured chromatogram are equidistant. The logarithmic MWD was calculated from the recorded chromatogram with the following procedure. Polystyrene standards with an exactly known molecular weight were injected and with the obtained retention times a calibration curve was constructed. The relation between time and the logarithm of the molecular weight is a cubic equation. To obtain equidistant data points of the molecular weight with the distance of the monomeric unit, all possible chain lengths in the range of the MWD were calculated. Of each chain length the y-axis value was calculated with the closest measured value on the left side and right side by linear interpolation.

The copolymers are formed with two monomers (e.g., A and B) and contain four different ester bonds, namely A−A, B−B, A−B, and B−A bonds. During degradation the types and concentrations of these different ester bonds present in the copolymer were not determined, and therefore these could not be taken into account in the model. For convenience and in first approximation it is assumed that the A−B and B−A bond have a hydrolysis rate which is exactly the average of the two hydrolysis rates for A−A and B−B.

After all (corrected) input parameters were entered into the model, an ODE solver, based on the Runge−Kutta algorithm, was used to solve the set of nonlinear coupled differential equations (eq 9) using the software package Matlab 7.1. In order to calculate the hydrolysis rate constant (k), a bisectional[44] method was used and these results are presented in Table 4. In the bisectional method the calculated M_w was fitted to the measured M_w. This comparison was preferred above fitting with M_n because M_n is very sensitive toward small variations in the integration of the chromatogram and when the complete MWD is used for fitting, the calculation time would be too long.

As can be seen in Table 4, the fitted hydrolysis rate constants of P4MC, P4MC-BA, and PCL are almost identical. This was expected, because the only difference between CL and 4MC is the substituted methyl group on the fourth position of the lactone ring. This methyl group was expected to be too distant from the ester bond to influence its hydrolysis rate. That, after correction for the crystalline fraction, the hydrolysis rate of PCL is almost equal to that of P4MC confirms the assumption that the degradation slowed down proportionally to the crystalline fraction.

The values of the fitted GA-GA hydrolysis rate constants of PLGA 53:47 and PLGA 75:25 are of the same order. The difference can be caused by variations in the measured molecular weights or by the assumption that the hydrolysis rate of GA-LA and LA-GA is not the average of the hydrolysis rate of GA-GA and LA-LA. Too little information is available to distinguish the causes of this variation.

In Figure 8 and Figure 9, the calculated and measured number average molecular weight (M_n), the weight average molecular weight (M_w) and the mass loss of the amorphous polymer P4MC

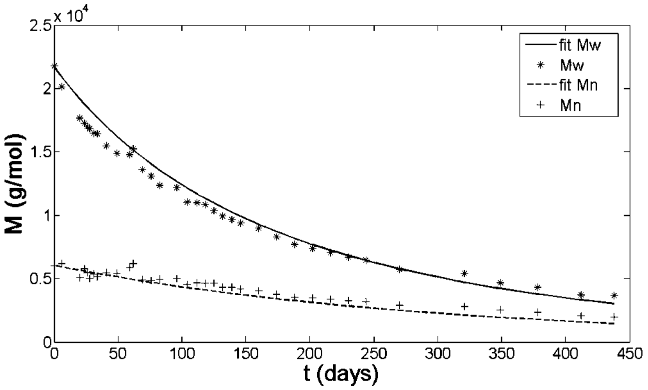

Figure 8. Calculated and measured M_n and M_w degradation profiles of P4MC with carboxylic acid end groups.

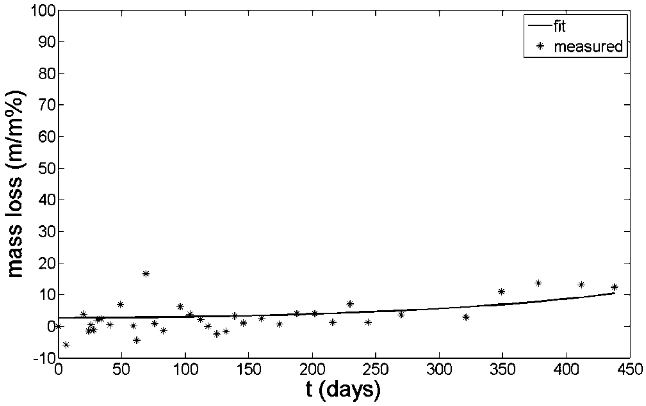

Figure 9. Calculated and measured mass loss degradation profiles of P4MC with carboxylic acid end groups.

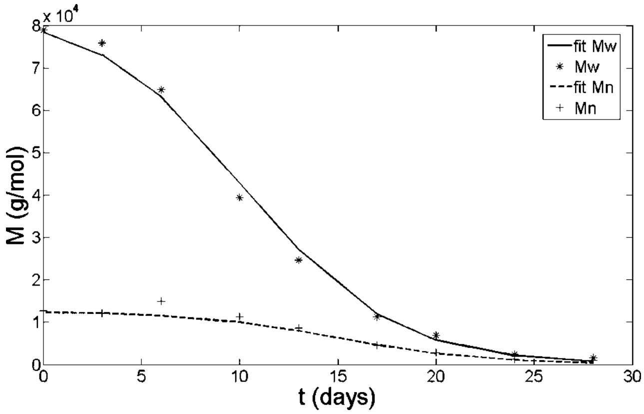

Figure 10. Calculated and measured M_n and M_w degradation profiles of PLGA 53:47 without carboxylic acid end groups.

are presented as a function of hydrolysis time. Figure 10 shows the calculated and measured number and weight average molar masses as a function of time for PLGA 53:47, and Figure 11 shows the calculated and measured weight loss for this copolymer.

All calculated molecular weight degradation profiles (Figure 8 and 10) are almost identical to the measured values (M_n and M_w). The model can predict both M_n and M_w, and hence it can be concluded that it is able to predict the complete MWD. Also, the model seems to be valid both for polymers with (see Figure 8) and without carboxylic acid end groups and for copolymer systems (see Figure 10).

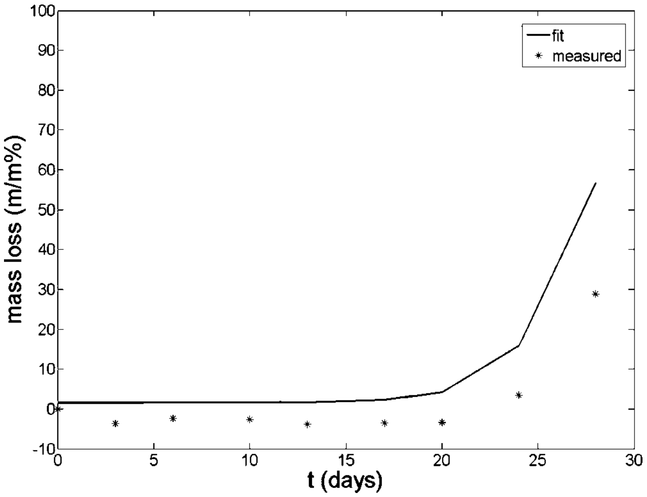

Figure 11. Calculated and measured mass loss degradation profiles of PLGA 53:47 without carboxylic acid end groups.

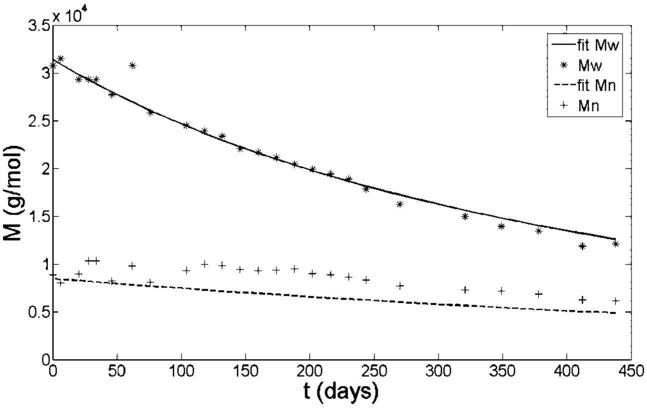

Figure 12. Calculated and measured M_n and M_w degradation profiles of PCL.

The calculated and measured number average molecular weight (M_n) and weight average molecular weight (M_w) of PCL are compared in Figure 12. For the degradation curve only CL ester bonds present in the amorphous phase were taken into account during the degradation. The theoretical (calculated) curve and the measured values are almost identical, which validates the assumption that each polymer chain length and the concentrations of the ester bonds in eq 9 have to be multiplied with the amorphous fraction (φ_A). So, it can be concluded that the model is able to predict the MWD development during hydrolysis of aliphatic polymers, even when a crystalline fraction is present.

The fit of the calculated and measured mass loss degradation profiles is worse than that of the molecular weight curves. The reliability of the observed mass loss is questionable, as due to the used determination method, some systematic errors may have been introduced. One is that during degradation water is absorbed by the polymer and after the applied drying there is probably still some water present, resulting in a lower experimental mass loss. The second introduced error is that in the final stage of the degradation, fragments of the polymer chain become smaller and more hydrophilic until they can dissolve in the water phase. In this stage probably more water is absorbed by the polymer and therefore the concentration of carboxylic acid end groups would slightly decrease, which decelerates the hydrolysis reaction. Hence, this deceleration would also result in a lower experimental mass release. The third reason is that some remaining of the buffer salts can also contribute to an underestimation of the experimental mass loss. After removal of the PBS-buffer with a syringe, some buffer stays behind, and after drying, the buffer salt remains, again reducing the experimental mass loss. The last potential error is that during the removal of the buffer after the degradation, a small amount of nondissolved polymer may have been removed, together with the buffer, by the syringe. This would give an increase of the mass loss during the degradation. This systematic error can be made when viscous polymer samples are investigated, like P4MC and P4MC-BA or in the final stage of the degradation when most of the polymer is degraded into oligomers, which can be very easily removed with a syringe. This explains the large scattering in the measured mass loss curves (see Figures 2 and 4). Nevertheless, it can be concluded that the calculation of the mass loss is reasonable and the observed experimental trend is well predicted.

There are several different existing models to describe the degradation behavior of aliphatic polyesters. First of all there are empirical models like the Monte Carlo model[6,7] and the statistical model.[8] The disadvantage of these approaches is that they are not based on the real mechanism of degradation, which makes it difficult to predict the degradation of the polymer based on the initial polymer properties.

Then, there is the model of Pitt and co-workers[12] and in this model it is assumed that the degradation of aliphatic polyesters follows pseudo first-order kinetics. It is assumed that only the change of the number of carboxylic acid groups influences the rate of hydrolysis, and that the decrease of ester bonds has no influence on the degradation rate and can be neglected. Also, this model describes only the decay of M_n. However, in first order reactions the concentration of the reactant decreases exponentially[49] with time. M_n is proportional to the amount of ester bonds present in a polyester or inversely proportional to the amount of carboxylic acid groups. Therefore, if the hydrolysis of ester bonds follows first order kinetics is should decrease exponentially and not like an S-shaped curve as we found experimentally and with our model (see Figure 10).

In the work of Lyu et al.[10] the hydrolytic degradation is considered only to depend on the amount of ester bonds and water in the polymer and not on the formation of carboxylic acid groups, and it is also assumed that the hydrolysis follows second order kinetics. However, in a second order reaction the decrease of concentration of the reactant as function of time would give a straight line when 1/[reactant] vs time is plotted. This type of function would not describe a S-shaped curve, as we found (see again Figure 10).

In the early 1940s, Simha developed a random chain scission theory to describe degradation and the size distribution of long chain polymers.[9] Herein, it is assumed that every connection between two monomer units in the chain can break at random. In the same work Simha also developed a model where it was assumed that the degradation of the polymer only takes place at the end of the chains. Later Batycky et al. developed a model which is a combination of the random chain scission and the and chain scission models.[11] However, all these three models are based on the assumption that the kinetics is first order and the autocatalytic process (forming of carboxylic acid) was not incorporated into the model.

The model developed in this work takes the formation of carboxylic acid and the decrease of ester bonds into account, which is a mayor improvement in comparison with existing models. Therefore, it describes the autocatalysis effect of the ester hydrolysis by carboxylic acid groups, generated during the hydrolysis process.

Conclusion

The results of the degradation studies on the polymers poly(ϵ-caprolactone) (PCL), poly(4-methylcaprolactone) (P4MC), polylactide (PLA), and the copolymer poly(D,L-lactide-*co*-glycolide) (PLGA) provide a good insight in the degradation mechanism. By combining the results of the decrease in molecular weight and mass loss, it was proven that the degradation is a bulk erosion process.

The newly proposed mathematical model is based on the autocatalytic kinetics of hydrolysis of aliphatic polyesters. This model was designed to describe the concentration of all polymer chains present after a certain degradation time. The experimental results were used as input for the model to determine the hydrolysis rate constant and to calculate the theoretical degradation profile. These calculations show that the model is able to describe the development of the total molecular weight distribution in an accurate way and that it is also able to reasonably predict the mass loss trend of the polymer phase. The mathematical model is also valid for copolymer systems and for systems with a crystalline phase, provided that a correction is introduced for the crystalline fraction.

Acknowledgment. We thank Purac B.V. for sending the polymer samples for free and R. Maalcke of the Hoge School van Arnhem en Nijmegen for his support.

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