



Degradation mechanisms of bioresorbable polyesters. Part 2. Effects of initial molecular weight and residual monomer



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ABSTRACT

This paper presents an understanding of how initial molecular weight and initial monomer fraction affect the degradation of bioresorbable polymers in terms of the underlying hydrolysis mechanisms. A mathematical model was used to analyse the effects of initial molecular weight for various hydrolysis mechanisms including noncatalytic random scission, autocatalytic random scission, noncatalytic end scission or autocatalytic end scission. Different behaviours were identified to relate initial molecular weight to the molecular weight half-life and to the time until the onset of mass loss. The behaviours were validated by fitting the model to experimental data for molecular weight reduction and mass loss of samples with different initial molecular weights. Several publications that consider initial molecular weight were reviewed. The effect of residual monomer on degradation was also analysed, and shown to accelerate the reduction of molecular weight and mass loss. An inverse square root law relationship was found between molecular weight half-life and initial monomer fraction for autocatalytic hydrolysis. The relationship was tested by fitting the model to experimental data with various residual monomer contents.

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1. Introduction

Biodegradable polymers are regularly used in the medical field for applications such as sutures, fixation plates, screws and drug delivery. The major benefit over permanent metal orthopaedic devices is that the polymers degrade over a period of months or years to become fully absorbed by the body, therefore negating the need for repeat surgery for removal. It is important to understand the degradation and factors that affect this process. In this study the effects of initial molecular weight and residual monomers are considered, neither of which are fully understood at present. Initial molecular weight significantly affects degradation as has been shown by several experimental publications [1–6]. If the initial molecular weight of biodegradable polymers varies by an order of magnitude, so too does the number of polymer chains and therefore the number of scissions required to halve the molecular weight. In addition, the ratio of end scission to random scission is likely to be higher for lower molecular weight samples which have a higher ratio of bonds at the chain ends. Mass loss may also be affected by initial molecular weight since more monomers will be produced if there is a greater number of chain ends, due to a

greater rate of end scission. Experimental results in which samples of different initial molecular weights show the same trends should actually be interpreted as evidence for different rates of chain scission. The effect of initial molecular weight depends of the type of hydrolysis such as noncatalytic random scission, autocatalytic random scission, noncatalytic end scission or autocatalytic end scission. These hydrolysis mechanisms are discussed in detail in Part 1 of this series of papers [7] using a mathematical model. The model simulates bulk mass loss due to the diffusion of monomers or oligomers out of the polymer. Significant mass loss due to surface erosion is not typically expected for the polymers considered in this study. In addition, substantial mass loss may occur when the polymer begins to break apart in the very late stages of degradation, by which time the model is no longer valid. A monomer is produced by each end scission, whereas oligomers are produced when a random scission occurs near a chain end. One aim of this paper is to understand the effects of initial molecular weight and relate them to the fundamental hydrolysis mechanisms. Simulations are conducted using a more detailed version of a previously developed mathematical model [8–11].

A polymer may contain residual monomer that remains from polymerization or is thermally generated from processing techniques such as melt extrusion. The initial monomer content in biodegradable polymers has been shown to have an impact on the

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degradation trends [6,12–14]. In all experiments of which the authors are aware, the rate of degradation has been accelerated by an increased initial monomer content. The acceleration can be substantial. In the experiments of Paakinaho et al. [12] residual monomers accelerated the rate of degradation of inherent viscosity and strength by approximately one order of magnitude. The experimental data in the literature [6,12–14] support the theory of autocatalysis in which the degradation is catalysed by the acid chain ends of residual monomers. The initial monomer is not expected to affect degradation, which is purely noncatalytic in nature. In this study, the effect of residual monomer is analysed by simulations with the mathematical model detailed in Part 1 [7]. It should be noted that many of the experimental degradation studies prior to the year 2000 could have high residual monomer contents due to their processing conditions although this was rarely measured and thus is not detailed in the publications. It is of critical importance that residual monomer is measured or removed for present and future experiments of biodegradable polymers in order for their degradation characteristics to be fully analysed.

Initial molecular weight and residual monomer were chosen for analysis because they have a significant effect on degradation and are not fully understood. As a result of the lack of clear understanding, these factors are often not discussed in the analysis of experimental data. The simple trends identified in this work can be used to estimate the effects of both factors. The mathematical model is ideally suited for the analysis of initial molecular weight and initial monomer content because both factors are directly implemented in it. Initial molecular weight is almost always stated in experimental publications, so the findings of this study can be used when analysing historical experimental data. Although residual monomer is not always measured, it can be estimated to some degree if polymer processing conditions are known in detail and it has been measured more often in recent years.

The mathematical model is fitted to experimental data containing various weight fractions of initial monomer, and also to experimental data containing various initial molecular weights. The experimental data discussed in this study are for poly(lactide) or poly(glycolide) homo- and copolymers because a large number of experimental publications consider these polymers in the literature. The fittings serve to demonstrate the ability of the model to consider both factors and to relate the degradation trends to the underlying hydrolysis mechanisms. The authors are not aware of any models for chain scission of biodegradable polymers that have included initial monomer content to date. It should be noted that the mathematical model used here is purposely over complicated. The intention here is to use the model (i) to identify the individual hydrolysis mechanisms that are prominent in experimental studies, and (ii) to understand the effect of various factors with regards to specific hydrolysis mechanisms. Once the effects of each individual factor are understood, it is then possible to simplify the model by eliminating the unimportant factors. Currently, the model is used to understand experimental results rather than to predict the degradation based on simple information including the polymer type, polymer microstructure, molecular weight distribution and degradation medium.

2. The mathematical model

The mathematical hydrolysis model is described in Part 1 [7]. Eqs. (1)–(5) here are only repeated to help explain how the initial molecular weight and residual monomer affect the model. All the model parameters and units are given in Table 1 for reference. The rate of random scission R_{rs} is given by:

$$\frac{dR_{rs}}{dt} = k_{r1}C_e + k_{r2}C_e \left(\frac{C_{acid}}{1 - X_c} \right)^n \quad (1)$$

and the rate of end scission R_{es} is given by:

$$\frac{dR_{es}}{dt} = k_{e1}C_{end} + k_{e2}C_{end} \left(\frac{C_{acid}}{1 - X_c} \right)^n, \quad (2)$$

which differs from Eq. (1) in that the reactant is chain ends C_{end} for end scission instead of amorphous ester bonds C_e for random scission. Separate reaction constants are used for noncatalytic random scission k_{r1} , autocatalytic random scission k_{r2} , noncatalytic end scission k_{e1} , and autocatalytic end scission k_{e2} . The initial molecular weight affects the rate of end scission from the outset since for a lower initial molecular weight there are more initial chains N_{chain0} and therefore more chain ends as given by:

$$C_{end} = 2N_{chain} = 2N_{chain0} + 2(R_{rs} - (R_{ol}/m)), \quad (3)$$

in which the concentration of random scissions R_{rs} and ester units in oligomers R_{ol} are both zero at the start of degradation. The rate of end scission therefore increases linearly with the number of chains and inversely with initial molecular weight. The rate of random scission in Eq. (1) does not increase in the same manner because it is not directly dependent on the number of chain ends. The rate of end scission to random scission therefore increases. If molecular weight reduction is due to random scission and mass loss is due to end scission as suggested in Part 1 [7], mass loss may be expected to occur earlier for a lower initial molecular weight. A greater rate of end scission results in more monomers C_m and therefore a greater concentration of acid catalyst C_{acid} as given by:

$$C_{acid} = C_m + (C_{ol}/m). \quad (4)$$

This means the rate of autocatalytic hydrolysis increases, for both random and end scission, and the ratio of autocatalytic to noncatalytic scissions increases. Another major effect of increasing the value of N_{chain0} , due to lower initial molecular weight, is that the relative increase of N_{chain} due to each random scission is reduced. In other words, increasing the terms in brackets on the right-hand side of Eq. (3) during degradation becomes less significant as N_{chain0} increases. This affects the degradation of the number-averaged molecular weight, calculated by:

$$M_n = \frac{(C_e + \omega X_c)M_0}{N_{chain}}, \quad (5)$$

which depends primarily on the increase of N_{chain} . For a lower initial molecular weight the effect of each random scission on M_n is reduced. The balance between an increased rate of random scission and reduced relative effect of each random scission depends on the values of the reaction rate constants k_{r1} , k_{r2} , k_{e1} and k_{e2} .

As the initial monomer content increases, the initial concentration of acid catalyst also increases since C_m increases in Eq. (4). This results in two main effects: (i) the rate of autocatalytic chain scission increases, and so too therefore does the rate of M_n reduction and ratio of autocatalytic to noncatalytic hydrolysis; and (ii) the relative increase in C_{acid} for the same number of scissions is reduced since C_m has a larger initial value in Eq. (4). As a result of point (ii), the rate of autocatalytic random scission does not increase to such a great extent during degradation. Point (i) may shift the molecular weight–time curve, as discussed in Part 1, from noncatalytic to autocatalytic in appearance. Point 2 may have the opposite effect. The balance between these effects depends on the reaction rate constants k_{r1} , k_{r2} , k_{e1} and k_{e2} .

3. The effect of initial molecular weight

The effect of initial molecular weight on the degradation of molecular weight and mass loss is analysed for several different types of hydrolysis including noncatalytic random scission, autocatalytic random scission, noncatalytic end scission and autocatalytic

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