Degradation mechanisms of bioresorbable polyesters. Part 1. Effects of random scission, end scission and autocatalysis

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ABSTRACT

A mathematical model was developed to relate the degradation trend of bioresorbable polymers to different underlying hydrolysis mechanisms, including noncatalytic random scission, autocatalytic random scission, noncatalytic end scission or autocatalytic end scission. The effect of each mechanism on molecular weight degradation and potential mass loss was analysed. A simple scheme was developed to identify the most likely hydrolysis mechanism based on experimental data. The scheme was first demonstrated using case studies, then used to evaluate data collected from 31 publications in the literature to identify the dominant hydrolysis mechanisms for typical biodegradable polymers. The analysis showed that most of the experimental data indicates autocatalytic hydrolysis, as expected. However, the study shows that the existing understanding on whether random or end scission controls degradation is inappropriate. It was revealed that pure end scission cannot explain the observed trend in molecular weight reduction because end scission would be too slow to reduce the average molecular weight. On the other hand, pure random scission cannot explain the observed trend in mass loss because too few oligomers would be available to diffuse out of a device. It is concluded that the chain ends are more susceptible to cleavage, which produces most of the oligomers leading to mass loss. However, it is random scission that dominates the reduction in molecular weight.

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1. Introduction

A large number of experiments have been conducted to understand the degradation of bioresorbable polymers such as polylactic acid (PLA), polyglycolic acid and polycaprolectone (PCL) [1–31], which are used for various medical applications. A phenomenological mathematical model has been developed by Pan and his co-workers [32–35] to predict the degradation rate of the biodegradable polymers. It was demonstrated that the model is able to fit a wide range of experimental data for changes in molecular weight, mass and crystallinity as functions of degradation time. The purpose of this paper is to present a more detailed model that can be used to relate degradation behaviour to the underlying hydrolysis mechanisms. The mathematical model is used in order to understand how the different hydrolysis mechanisms affect the degradation behaviour, while the models published in our previous work [32–35] are more suitable for the design of devices because they contain fewer parameters that may be difficult to measure experimentally.

The hydrolysis mechanisms being considered include random scission, end scission, noncatalytic hydrolysis and autocatalytic hydrolysis. In noncatalytic degradation, the ester bonds are cleaved in the presence of water, whereas in autocatalytic degradation the hydrolysis reaction is catalysed by the carboxylic acid chain ends of water-soluble oligomers and monomers [1]. In random scission it is assumed that each ester bond in the polymer has an equal chance of chain cleavage, whereas end scission assumes that only ester bonds at the end of polymer chains are cleaved. Experimental evidence for which hydrolysis mechanisms are dominant is conflicting due to the number of factors that affect degradation and the inconsistency between experiments. Shih [36] suggested that end scission is dominant, at approximately 10 times the rate of random scission. However, for a high molecular weight sample, a single random scission has a greater impact on molecular weight than 1000 end scissions, so their experiment actually indicates that random scission controls the molecular weight reduction. The experiment by Schliecker et al. [13] supports the theory of noncatalytic hydrolysis because it was found that the addition of oligomers does not accelerate degradation. Other experiments support the theory of autocatalytic hydrolysis [2,37]. It has been widely observed that degradation occurs faster at the core of large samples

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compared to the surface because oligomers and monomers, which act as catalysts, diffuse out of the polymer near the surface [22].

It has been suggested that a linear relationship between ($1/M_n$) and time, where M_n represents number average molecular weight, indicates noncatalytic hydrolysis [38] and a linear relationship between ($1/M_n$)$^{0.5}$ and time indicates autocatalytic hydrolysis [1,37]. However, there is considerable experimental data in the literature that demonstrates a delay before the reduction of molecular weight [10,22–29], and therefore does not fit either trend. The experiments of Antheunis et al. [27] demonstrate a delay trend when the initial polymer chains do not possess carboxylic acid end groups but no delay when they do. The model here considers hydrolysis to only be catalysed by the acid chain ends of water-soluble oligomers and monomers, not the chain ends of long chains, which may be unable to catalyse hydrolysis due to lack of mobility or may initially not possess carboxylic acid end groups. It is not fully understood which hydrolysis mechanisms are generally most prevalent in degradation experiments. In this paper, an analysis scheme is developed that can quickly identify which hydrolysis mechanisms are likely to be dominant based on experimental data for molecular weight and/or mass loss. The trends of molecular weight degradation and mass loss predicted by the mathematical model for various combinations of noncatalytic/autocatalytic hydrolysis and random/end scission are analysed and translated into the simple analysis scheme. Case studies demonstrate the use of the scheme, and a large set of experimental data from the literature is evaluated to identify the dominant hydrolysis mechanisms. The particular focus of this study is predominantly on poly(lactide) and poly(glycolide) polymers in order to draw unambiguous conclusions regarding their degradation. The effects of initial molecular weight and residual monomer in relation to the hydrolysis mechanism are the subject of a separate paper [39].

2. The mathematical model

The phenomenological model developed by Pan and co-workers [32–34] is modified to separate the different hydrolysis mechanisms, including noncatalytic random scission, autocatalytic random scission, noncatalytic end scission and autocatalytic end scission. The polymer is assumed to consist of amorphous polymer chains, oligomers, monomers and a crystalline phase. It is assumed that the crystalline phase, characterized by the degree of crystallinity X_c (no units) strongly resists hydrolysis such that only the amorphous polymer chains suffer from hydrolysis chain scission. The rate of chain scission is determined by the concentrations of the reactants and catalyst. For random scission, the reactant is the ester bonds in amorphous chains, which are characterized by the concentration C_e (mol m^{-3}). For end scission, the reactant is the amorphous chain ends characterized by C_{end} (mol m^{-3}). It is assumed that water is always abundant [40] and its concentration does not affect the hydrolysis rate. The hydrolysis reaction can be catalysed by H$^+$ disassociated from the carboxylic acid end groups. Using C_{acid} (mol m^{-3}) to represent the concentration of the carboxylic end groups, the concentration of H^+ can be calculated as $C_{H^+} = (K_a C_{acid})^n$ [34], where K_a is the acid disassociation constant and n (no units) is usually taken to be 0.5, as suggested by Siparsky et al. [37]. We use R_{rs} (mol m^{-3}) and R_{es} (mol m^{-3}) to represent the molar concentrations for random and end scissions, respectively. Following Han et al. [34], the rate of random scission is given by

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

and the rate of end scission is given by

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

Here k_{r1} and k_{e1} (day^{-1}) are the noncatalytic reaction constants and k_{r2} and k_{e2} ([mol^{-1} m^3]$^{0.5}$ day^{-1}) are the autocatalytic reaction constants, where subscripts r and e indicate random and end scission, respectively. The acid disassociation constant K_a has been merged into k_{r2} and k_{e2}. The single rate equation for chain scission proposed by Han et al. [34] has been split into two equations so that the random and end scissions can be evaluated separately. The total scission concentration R_s (mol m^{-3}) is then given by

$$R_s = R_{rs} + R_{es} \tag{3}$$

In end scission, a monomer is produced by each scission and the production of monomers per unit volume R_m (mol m^{-3}) is simply given by

$$R_m = R_{es} \tag{4}$$

In random scission, an oligomer may be produced by chance if an ester bond near a chain end is cleaved. Following the statistical analysis by Flory [41], the production of ester units of oligomers per unit volume, R_{ol} (mol m^{-3}), can be related to the concentration of random scissions R_{rs} through

$$\frac{R_{ol}}{C_{e0}} = \alpha\left(\frac{R_{rs}}{C_{e0}}\right)^\beta \tag{5}$$

in which C_{e0} (mol m^{-3}) is the concentration of ester bonds in all phases at time $t = 0$. The values $\alpha = 28$ (no units) and $\beta = 2$ (no units) apply if the oligomers are defined as short chains of less than eight units [38], as assumed in this work.

Assuming Fick's law of diffusion, the oligomer and monomer concentrations, C_{ol} and C_m (mol m^{-3}), are governed by

$$\frac{dC_a}{dt} = \frac{dR_a}{dt} + \underset{x_i}{div}\left(D\underset{x_i}{grad}(C_a)\right) \tag{6}$$

in which the nomenclature of vector analysis is used and the subscript a is either m, to represent monomer diffusion, or ol, to represent oligomer diffusion. The terms R_{ol} and R_m represent the concentrations of oligomers and monomers that have been produced due to chain scission, whereas C_{ol} and C_m (mol m^{-3}) represent the current concentrations due to both production and diffusion. A finite difference scheme is implemented for the spatial discretization of the second term on the right hand side in Eq. (6). The diffusion coefficient D (m^2 day^{-1}) depends on the porosity and crystallinity of the polymer. It is calculated based on the diffusion coefficient of the polymer D_0 (m^2 day^{-1}) and of pores D_{pore} (m^2 day^{-1}), as discussed in the work of Han and Pan [33].

Pan and co-workers [32–34] further assumed that only the oligomers and monomers can catalyse the hydrolysis reaction because the carboxylic end groups of the long chains could be initially capped and the chains are not mobile. C_{acid} in Eqs. 1 and 2 can then be calculated as

$$C_{acid} = C_m + (C_{ol}/m) \tag{7}$$

in which m (no units) is the average degree of polymerization of the oligomers. In this study we have set $m = 4$ because oligomers are assumed to have less than eight units of degree of polymerization. The molar concentration of polymer chains N_{chain} (mol m^{-3}) is given by

$$N_{chain} = N_{chain0} + (R_{rs} - (R_{ol}/m)) \tag{8}$$

in which N_{chain0} (mol m^{-3}) is the initial molar concentration of chains and $C_{end} = 2N_{chain}$ in Eq. (2).

According to Avrami [42–44], the degree of crystallinity X_c can be calculated through the extended degree of crystallinity X_{ext} (no units) by