Acta Biomaterialia 7 (2011) 1140–1149

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Mathematical modeling of degradation for bulk-erosive polymers: Applications in tissue engineering scaffolds and drug delivery systems

Yuhang Chen, Shiwei Zhou, Qing Li *

School of Aerospace, Mechanical and Mechatronic Engineering, University of Sydney, Sydney, NSW 2006, Australia

ARTICLE INFO

Article history:
Received 23 June 2010
Received in revised form 7 September 2010
Accepted 28 September 2010
Available online 16 October 2010

Keywords:
Biodegradation
Biodegradable polymers
Autocatalysis
Microparticle
Scaffold

ABSTRACT

The degradation of polymeric biomaterials, which are widely exploited in tissue engineering and drug delivery systems, has drawn significant attention in recent years. This paper aims to develop a mathematical model that combines stochastic hydrolysis and mass transport to simulate the polymeric degradation and erosion process. The hydrolysis reaction is modeled in a discrete fashion by a fundamental stochastic process and an additional autocatalytic effect induced by the local carboxylic acid concentration in terms of the continuous diffusion equation. Illustrative examples of microparticles and tissue scaffolds demonstrate the applicability of the model. It is found that diffusive transport plays a critical role in determining the degradation pathway, whilst autocatalysis makes the degradation size dependent. The modeling results show good agreement with experimental data in the literature, in which the hydrolysis rate, polymer architecture and matrix size actually work together to determine the characteristics of the degradation and erosion processes of bulk-erosive polymer devices. The proposed degradation model exhibits great potential for the design optimization of drug carriers and tissue scaffolds.

1. Introduction

Degradable biomaterials, such as polymers, have drawn significant attention recently for their extensive application in a range of new fields, e.g. scaffold tissue engineering and drug delivery systems [1–3]. In general, biodegradable polymers undergo a series of bioprocesses after being implanted in the human body which could dynamically affect the local biochemical and biophysical environment in a number of ways, including: (1) hydrolysis or other forms of chemical breakdown that produce oligomers and monomers in the polymeric matrix; (2) mass transport inside the polymer matrix and exchange of these products with the surroundings; (3) bioabsorption of the degraded biocompatible products. In this context, substantial experimental studies have been conducted to help better understand the mechanisms of biodegradation in such a complex process [4].

Although polymer degradation involves various complex chemical reactions, it is more often accompanied by multifaceted physical processes. Conceptually, degradation is defined as the molecular changes due to chain scission inside a polymer matrix, while erosion indicates the phenomenological and structural changes due to mass loss of degraded chains. Although detailed mechanisms have not yet been fully understood, extensive experimental studies have been conducted to explore the degradation and erosion pathways. Chain scission of the polymer matrix takes place when adjacent water molecules attack the chemical bonds, immediately after the surrounding solution starts to penetrate the matrix. As a result, both the speed of penetration and the hydrolysis rate can determine the degradation pattern. In essence, polymeric erosion has been categorized as following either 'bulk' or 'surface' pathways [5,6]. If the water penetration speed is considerably faster than the natural hydrolysis rate, e.g. as for polylactide (PLA) and polyglycolide (PGA) materials, degradation should take place over the entire polymer matrix, leading to a uniform mode of erosion, termed the 'bulk' pathway. On the other hand, if the diffusion of water molecules is relatively slow, hydrolysis will mostly happen in the form of surface erosion. Typically, such erosion is largely restricted to the exterior, while the interior remains almost unchanged, leading to an erosive front at the matrix surface which could proceed at a nearly constant velocity, termed 'surface' pathway. Nevertheless, these two extreme cases can happen concurrently for some materials with sophisticated configurations, which could greatly affect drug release and tissue regeneration within biodegradable synthetics. For this reason, the modeling of biodegradable devices is a crucial step towards regulating and controlling the degradation process.

For some commonly used biodegradable polymers, e.g. PLA and PGA, the hydrolytic products can result in a high concentration of carboxyl end groups that are specific catalysts of the hydrolysis reaction. If these products cannot be removed from the matrix within a certain period of time, acid catalyst in the polymer bulk

* Corresponding author. Tel.: +61 2 9351 8607; fax: +61 2 9351 7060.
E-mail address: Qing.Li@Sydney.edu.au (Q. Li).

1742-7061/$ - see front matter © 2010 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.actbio.2010.09.038

Nomenclature

x	status variable for degradation cells. 'Hydrolysable' ($x_H = 1$), 'hydrolyzed' ($x_h = 0.001$) and 'void' ($x_v = 0$)	C_m	concentration profile of released monomers
M_a	average molecular weight	n	number of nodes for a degradation element
λ	experimental degradation rate constant	D_m^0	diffusivity of released monomers before degradation
λ_0	autocatalysis-free degradation rate constant	D_m	diffusivity of released monomers during degradation
p	hydrolysis probability density function	R_m	material constant for the diffusivity change after hydrolysis
α	initial architectural porosity	β	parameter that regulates the autocatalysis effect for matching the modeling results to known experimental data
t_{add}	hysteretic degradation time for a polymer matrix with initial architectural porosity α		
V	volume fraction of polymer matrix during degradation		

will greatly accelerate the local hydrolytic process and consequently produce a hull-like distribution of molecular weight. Thus, autocatalysis plays an important role in the degradation rate and erosion pathway, thereby making the design of synthetic biodegradable matrices size dependent [7–12]. If the thickness of the polymer wall (i.e. the diffusion path) is sufficiently small and the hydrolysis products diffuse quickly, the acid catalysts can be rapidly removed by mass diffusion. Thus autocatalysis would be largely suppressed [13]. It should be noted that, due to the mechanism of erosion, the autocatalytic effect becomes more significant in bulk-erosive polymer devices [6]. Agrawal et al. [14] examined the effects of fluid flow on the degradation characteristics of biodegradable scaffolds *in vitro* and found that the degradation rate can be greatly decreased by fluid flow, suggesting that the autocatalytic effect plays an important role in altering the scaffold degradation process. Nevertheless, the impact of autocatalysis on polymer degradation and erosion lacks quantitative characterization to date, often leading to an imprecise prediction to the performance of biodegradable devices.

In terms of the better design of biodegradable devices, mathematical modeling has proved effective by extending the knowledge obtained from degradation experiments [15]. The literature shows that there are two main categories of mathematical models available to date, namely discrete and continuous schemes, which allow the simulation of polymeric degradation and erosion in different scenarios. On the one hand, discrete element-based models, as in Zygourakis [16] and Zygourakis and Markenscoff [17], are widely accepted as taking into account both the degradation and erosion processes. In this respect, Gopferich and co-workers [18–20] considered hydrolysis to be a stochastic process using a percolation-based erosion model, where both the 'bulk' and 'surface' pathways were phenomenologically simulated. Later, Bertrand et al. [21] modeled drug release from bioerodible microspheres using a cellular automaton method in which the polymer matrix was represented by elements in different states. Barat et al. [22] further proposed a cellular automata (CA) agent-based Monto Carlo (MC) model to simulate protein release from PLGA nano- and micro-particles. All these discrete models exploited the individual cells or elements to deal with complicated degradation and erosion processes.

Continuous models governed by partial differential equations have also been widely adopted to model the degradation process [23]. In this respect, Thombre and Himmelstein [24] proposed a diffusion–reaction model to describe controlled drug release that took into account the unsteady-state mass equilibrium for all components within bioerodible polymers. More recently, Wang et al. [25] developed a phenomenological model to simulate the degradation process based on the diffusion–reaction equation, and further investigated the interplay between crystallization and degradation [26]. In addition, Rothstein et al. [27] derived a mathematical model for predicting drug release from polymer matrices by both the surface and bulk pathways, in which the transition from surface to bulk erosion characteristics was explored. Soares and Zunino [28] also proposed a mixed model that can quantify the water-dependent degradation and erosion of drug delivery systems. More details of the mathematical methods used to characterize the degradation and erosion of biodegradable polymers can be found in recent review articles [15,23].

The development of scaffold tissue engineering and advanced drug delivery systems often necessitates consideration of other issues, such as the oxygen concentration and mechanical stimulation, rather than only the degradation itself. Although the continuous model involving a diffusion equilibrium and hydrolysis products appears straightforward in characterizing complicated degradation scenarios, the finite element-based design of biomedical devices shows certain benefits, along with the rapidly developing technology of solid free-form fabrication (SFF) [1,29,30], through which physical, mechanical and fluidic analyses can be readily conducted for sophisticated scaffold structures and other synthetic porous constructs. To facilitate such multi-fold analyses, it appears essential to integrate the continuous mass diffusion process into the discrete model.

In this paper we propose a hybrid mathematical model that combines stochastic hydrolysis and diffusion-governed autocatalysis to simulate polymer degradation and erosion for bulk-erosive biodegradable devices. Specifically, a reduced degradation rate constant that eliminates size-dependent effect of hydrolysis and a regulating parameter that takes into account autocatalysis are both considered. The examples, including drug delivery microparticles and tissue scaffolds, illustrate the degradation and erosion processes for polymeric devices of different sizes and with different architectures, thus addressing the size-effect and the need for design of biodegradable devices.

2. Methods

2.1. Basic assumptions

Consider a biodegradable polymer with an arbitrary configuration in a regular design domain that is uniformly discretized into a finite number of degradation elements (cells). Variable x is assigned for each element, indicating three different states of degradation, "hydrolysable" ($x_H = 1$), "hydrolyzed" ($x_h = 0.001$) and "void" ($x_v = 0$), respectively. For the sake of simplicity, the size distribution of polymer chains and initial density are assumed to be uniform throughout the polymer matrix. Therefore, it is assumed that variable x represents the local average molecular weight, provided that the number of degradation elements is sufficiently large (e.g. 140×140 in the two-dimensional (2D) model, as suggested by Gopferich [19]). For bulk-erosive polymers such as PLA, PGA and their co-polymers, since the speed of water penetration is significantly higher than the rate of hydrolysis, it is assumed that the polymer matrix is fully saturated with water in the initial state