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Review

Mathematical modeling of drug delivery from autocatalytically degradable PLGA microspheres — A review☆

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ABSTRACT

PLGA microspheres are widely studied for controlled release drug delivery applications, and many models have been proposed to describe PLGA degradation and erosion and drug release from the bulk polymer. Autocatalysis is known to have a complex role in the dynamics of PLGA erosion and drug transport and can lead to size-dependent heterogeneities in otherwise uniformly bulk-eroding polymer microspheres. The aim of this review is to highlight mechanistic, mathematical models for drug release from PLGA microspheres that specifically address interactions between phenomena generally attributed to autocatalytic hydrolysis and mass transfer limitation effects. Predictions of drug release profiles by mechanistic models are useful for understanding mechanisms and designing drug release particles.

Contents

1. Introduction

Poly(lactic-co-glycolic acid) (PLGA) microspheres are controlled-release drug delivery alternatives to conventional drug therapy regimens. By releasing drug molecules in a controlled manner over extended periods of time from a single administration, controlled-release systems have the potential to maintain drug concentrations within target ranges, diminish side effects caused by concentration extremes and repeated

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administrations, and improve patient compliance as compared to conventional regimens. PLGA microspheres have been extensively studied for controlled-release drug delivery [1–4] mainly because of the biodegradable and bioabsorbable qualities that allow for the passive degradation of the polymer in aqueous environments such as living tissues and for the resorption of degradation products into the surrounding media [5–7]. Despite these advantages, the implementation of controlled-release drug delivery devices composed of PLGA microspheres for human patients has been gradual; the characterization and design of the microspheres depends heavily on trial-and-error experiments, and the interplay between complex phenomena that contribute to the drug release is still being deciphered.

Several processes contribute to the overall kinetics of drug release from PLGA microspheres including chemical degradation of the polymer by autocatalytic ester hydrolysis, polymer erosion, evolution of pore structure as a result of mass erosion, and diffusive transport of the drug through the polymer matrix and the aqueous pore structure [8]. In the present work, the term *degradation* refers to the process through which the polymer chain bonds are hydrolyzed to form oligomers and monomers. The term *erosion* refers to the loss of mass due to diffusion of water-soluble, small oligomers and monomers out of the polymer matrix. The definitions of degradation and erosion are the same as those given by Göpferich [5] and have been widely adopted in the literature.

Three main phenomena—PLGA degradation, PLGA erosion, and drug transport—are discussed in Section 2, and mathematical models that mechanistically address these phenomena and the interactions between them are described in Section 3. The coupling between the three phenomena is important for understanding how one of the three may dominate or work in conjunction with the others under different conditions. The autocatalytic degradation mechanism may accelerate the degradation and erosion in the center of microspheres and enhance size-dependent drug transport. The complex effects of autocatalysis are difficult to predict without understanding of the relative strengths of the phenomena and their dynamics.

Mathematical models can reduce the number of experiments needed to probe different conditions and designs and to deepen the understanding of the physical and chemical mechanisms of drug release, particularly when the effects of different phenomena are coupled. Empirical or correlative mathematical models, which are commonly applied in the drug delivery field, have very limited predictive capability outside of the specific experimental conditions used to fit parameters in the models [9]. In contrast, mechanistic mathematical models aim to account for the physical and chemical phenomena that contribute to the overall drug release kinetics [10] and are applicable over a wide range of conditions to be used in the model-based design of microspheres to produce desired release profiles (e.g., constant rate of release for uniform therapeutic dosage). Here, only mechanistic models and hybrid empirical and mechanistic models are addressed.

2. Background concepts

Polymeric drug delivery can be categorized based on the mechanisms of drug release [11–13]: diffusion-controlled systems (diffusion from non-degrading polymers), swelling-controlled systems (enhanced diffusion from polymers that swell in aqueous media), and erosion-controlled systems (release as a result of degradation and erosion of polymers). For biodegradable polyesters such as PLGA, drug release occurs through a combination of degradation and erosion of polymer and transport of drug and is classified as being erosion-controlled. In this section we overview the mechanisms of each of these processes for erosion-controlled drug release from PLGA microspheres and how their effects interact.

2.1. PLGA degradation

PLGA is a poly(α-hydroxy-ester) (see Fig. 1) that is depolymerized in the presence of water. The hydrolysis reaction cleaves the ester bonds of polymer chains. The reaction can be catalyzed by acids or bases, but experimental data on the acidic local pH within PLGA particles [14–18] suggest that only the reaction mechanism catalyzed by acid is relevant. The acid-catalyzed ester hydrolysis proceeds by the bimolecular, acyl-oxygen cleavage $A_{AC}2$ mechanism [19,20] summarized by

$$P_n + H_2O + H^+ \rightarrow P_m + P_{n-m} + H^+, \quad n = 2,3,\ldots \text{ and } m = 1,2,\ldots,n-1, \tag{1.1}$$

where P_n, P_m, and P_{n-m} denote polymer chains having degrees of polymerization n, m, and $n-m$, respectively, and H^+ is the acid catalyst.

The source of the acid catalyst can be external from strong acid in the medium (non-autocatalytic reaction) or internal from the carboxylic acid end groups of the polymer chains (autocatalytic reaction) [21]. In autocatalysis, the reaction product catalyzes further hydrolysis in the manner

$$A + B \rightarrow 2B, \tag{1.2}$$

where A is water and B is acidic polymer chains in the context of PLGA degradation.

2.2. PLGA erosion

Polymer erosion is classified as surface-eroding or bulk-eroding [4,5,22,23]. For surface-eroding polymers such as polyanhydrides, the rate of polymer degradation at the surface is faster than the rate of penetration of water from bodily fluids in vivo or from the buffer medium in vitro into the polymer bulk. Surface-eroding polymers react from the surface inward. Bulk-eroding polymers exhibit a faster rate of water penetration than the rate of polymer degradation. The degradation and erosion in bulk-eroding polymers occurs throughout the polymer bulk. PLGA is a bulk-eroding polymer at the length scales used in drug delivery microspheres (10s to 100s of microns) as the hydration time scale is on the order of a few minutes compared to weeks or months for degradation [24–26].

Erosion depends on the degradation, dissolution, and diffusion processes [27]. For PLGA, the dissolution of water-soluble oligomers up to nonamers [28–30] and of drug molecules is often assumed to occur faster than diffusion and polymer degradation in many mathematical models and is neglected. A few models propose that dissolution is rate-limiting for PLGA oligomers [31].

2.3. Drug transport

An "initial burst" of drug release often occurs wherein a significant percentage of the drug is released during the early stage of the release process. This effect has been reported for many formulations of PLGA microspheres. The initial burst can be diminished or eliminated by adjusting the fabrication technique [32–34].

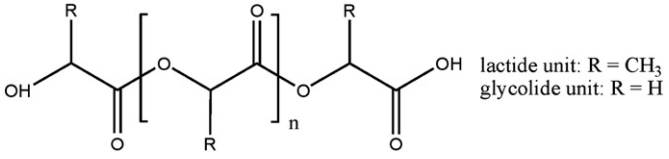

Fig. 1. Structure of poly(α-hydroxy-esters). PLGA has a fraction of functional groups with lactide units and the remaining fraction with glycolide units. n is the number of interior lactide and/or glycolide monomeric units.