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Adaptive Finite Element Solutions of a Diffusion Model for Drug Release in PLGA Microspheres

Hongyu Chen[1], Guanghui Hu[1,2,3,*] and Defang Ouyang[4,5,*]

[1] *Department of Mathematics, Faculty of Science and Technology, University of Macau, Macao SAR, China*
[2] *Zhuhai UM Science and Technology Research Institute, Guangdong, China*
[3] *Guangdong-Hong Kong-Macao Joint Laboratory for Data-Driven Fluid Mechanics and Engineering Applications, University of Macau, Macao SAR, China*
[4] *State Key Laboratory of Mechanism and Quality of Chinese Medicine, Institute of Chinese Medical Sciences (ICMS), University of Macau, Macao SAR, China*
[5] *Department of Public Health and Medicinal Administration, Faculty of Health Sciences (FHS), University of Macau, Macao SAR, China*

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Abstract. Poly (lactic-co-glycolic acid) copolymer (PLGA) microspheres are crucial in drug delivery due to their ability to provide controlled release of a wide range of therapeutic agents while minimizing side effects and enhancing biocompatibility. In this paper, a mathematical model is proposed and numerically studied for the drug release process in PLGA microspheres. A three-dimensional diffusion model is constructed based on Fick's law, being different from the traditional one-dimensional model in the past and fitting the configuration from the drug delivery system, while an h-adaptive finite element method is designed and realized using a C++ library AFEPack for numerical solutions of the proposed model. A notable feature is that the h-adaptivity makes the proposed model and numerical method a quality tool for studying concerned phenomena such as initial bursts in drug delivery. In numerical experiments, besides demonstrating the convergence of the numerical method, a case on progesterone release from PLGA is also studied using the proposed model, from which the potential of the model and the method towards the practical application is shown successfully.

AMS subject classifications: 65N30, 65N50, 92C45, 35K57

Key words: PLGA microspheres, drug delivery, diffusion model, *h*-adaptive finite element method.

*Corresponding author.
Emails: garyhu@um.edu.mo (G. Hu), defangouyang@um.edu.mo (D. Ouyang)

1 Introduction

Poly(lactic-co-glycolic acid) (PLGA) is the copolymer first approved by the FDA in January 1989 [1]. Because of its superb biodegradability and biocompatibility, it has been popularly researched as a biological material in drug delivery systems [2,3]. By slowly releasing drug molecules over an extensive period starting from a single administration, these systems can control the drug concentrations between the target scopes, decrease side effects caused by extraordinary concentrations and repeated administrations, and enhance patient compliance in contrast with traditional therapies [4,5]. Intending to obtain a required dosage depending on the type of medication, the degradation time of the polymer matrix can be controlled by modifying some parameter values, such as molecular weight of the polymer, drug concentration, and proportion of lactide to glycolide [6,7]. In spite of these benefits, the characterization and design of PLGA mainly rely on plenty of trial experiments and error modification, and it is still being explored that the interaction among complicated processes that influence the drug release [8].

With the development of drug delivery systems, it is critical to optimize therapeutic effects by accurately controlling the release rate of drugs. Mathematical modeling provides a powerful tool for predicting and optimizing drug release kinetics, as they can quantitatively demonstrate the complicated interactions between drug properties, design of the delivery system, and environmental factors [9]. By combining experimental data with mathematical models, a deeper understanding of the mechanisms will be gained by underlying drug release and more efficient and effective delivery systems [10]. Thus, the integration of mathematical modeling with drug release research is essential for advancing drug delivery technology and improving the prognosis of patients.

In order to reduce the multitudinous experiments predicting the unknown trial results, establishing a suitable mathematical model is a practical approach to address the problem. With the inspiration from heat conduction, Fick first founded the diffusion equation in 1855. The main idea of this equation is that the transition rate of diffusive material through per unit cross-sectional area proportionate to the concentration gradient with the measurement from perpendicular to the cross-section [11]. In 1975, Crank collected the previous mathematical theories of diffusion, including the discussion of the solution and the numerical experiments [12]. Since 2000, a common method has built a relevance between the effective drug diffusivity and molecular weight with exponential decline, which is on account of the pseudo-first-order degradation kinetics [13–15]. Ford et al. (2011) developed a reaction-diffusion model to generate quadratic autocatalytic degradation of the matrix of polymer and evolution in the pore structure [16]. Casalini et al. and Busatto et al. considered the acid-catalyzed hydrolysis mechanism to consist of the polymer degradation process as a system of partial differential equations(PDEs), the model also takes the autocatalytic influence into consideration [17–19]. Recently, the machine learning method has also been utilized for the estimation of effective diffusion coefficients in a one-dimensional diffusion-erosion model [20]. Notwithstanding the methodology of building the mathematical model has become increasingly