Journal of Pharmaceutical Sciences 105 (2016) 1934-1946

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Toward Understanding Drug Release From Biodegradable Polymer Microspheres of Different Erosion Kinetics Modes

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ARTICLE INFO

Article history:
Received 21 December 2015
Revised 1 April 2016
Accepted 1 April 2016

Keywords:
drug delivery
controlled release
erosion kinetics
polymer microspheres
sensitivity analysis
drug carrier design

ABSTRACT

Two generalized modes of erosion kinetics, that is, the power law mode and root type mode, respectively, were found to be able to better describe the reported weight loss data compared to the existing linear mode, for commonly used surface-eroding polymer microspheres. Based on the newly identified modes, a set of drug release models were developed by extending the existing model. Model validation was achieved by comparing the model predictions to the reported experimental data for surface-eroding polymer microspheres (poly(ortho esters) and polyanhydrides), and good consistency was found. Parameter investigation was conducted to reveal the effects of various important parameters (the dimensionless ratio between diffusion and erosion rates (Er), the dimensionless ratio between erosion and dissolution rates (p), the dimensionless drug loading concentration (q), and the fitting parameter of erosion kinetics (a)) on drug release behavior, which has rarely been examined previously. In general, the effects of these parameters were more significant for an earlier stage, and p, q, and a could effectively vary the drug release percentage. Design-of-experiments-based sensitivity analysis was further carried out and it was found that the most sensitive parameters were p (2.97%) and q (2.97%) for the cases of the power law mode, while it was a (−7.07%) for the cases of the root type mode. The information from the parameter investigation and sensitivity analysis could serve as a straightforward data bank for the practical designing of drug delivery processes. The proposed models are potential mathematical frameworks for the designing of drugs that are based on surface-eroding polymer microspheres in the future.

Introduction

The release of drugs from polymer scaffolds occurs either through the diffusion of the drug outward or the degradation of the polymer matrix itself. Polymers used in drug delivery can be classified into biodegradable or non-biodegradable, among which biodegradable polymers are gaining increased interest, as their degradation over time eliminates drug removal via surgery.[1-5] For biodegradable polymers, the hydrolytic cleavage of polymer chains leads to the erosion of matrix, and 2 major degradation mechanisms have been identified for biodegradable polymers, that is, bulk erosion and surface erosion, respectively.[6,7]

The relevant dominance of bulk erosion and surface erosion during a drug release process is dependent on the relative rates of water penetration and polymer backbone hydrolysis and thus is influenced by various factors such as the reactivity of polymer functional groups, the diffusivity of water, the size of device, and so on.[8] Bulk erosion occurs when the rate of water penetration is much higher than that of polymer hydrolysis, such that the degradation of polymer backbone spreads throughout the whole device due to the quick penetration of water before significant surface erosion occurs. In the case of surface erosion, the degradation of polymer matrix is significantly faster than the water diffusion process, such that the surface erosion occurs before the diffusion and penetration of water throughout the material.

Surface-eroding polymers have great potential for drug delivery applications, in view of their capability of achieving more controllable release patterns. Two surface-eroding polymers, polyanhydrides and poly(ortho esters), have been widely applied and studied for drug delivery. The hydrolysis of their chemical bonds (anhydride bonds for polyanhydrides and ortho esters for

Abbreviations used: BSA, bovine serum albumin; CDM, *trans*-cyclohexanedimethanol; CDM-mLT, cyclohexanedimethanol-monolactate; CPP, 1,3-bis(carboxyphenoxy)propane; DOE, design-of-experiments; SA, sebacic acid; TEG, tri(ethylene glycol); TMA-Tyr, trimellitylimido-l-tyrosine.

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http://dx.doi.org/10.1016/j.xphs.2016.04.002
0022-3549/

Nomenclature

a	parameter used in erosion modes 2 and 3
C_0	initial drug concentration (kg/m^3)
C_L	drug concentration in liquid phase (kg/m^3)
C_S	drug concentration in solid phase (kg/m^3)
C_{sat}	drug saturation concentration (kg/m^3)
C_{sat}	drug concentration in external medium (kg/m^3)
D_0	bulk diffusivity (m^2/s)
D	effective diffusivity (m^2/s)
Er	dimensionless parameter measuring relative rates of erosion and diffusion
k_{dis}	drug dissolution rate (s^{-1})
k_{ero}	erosion rate constant for surface erosion (s^{-1})
m_t	remaining amount of drug in polymer microspheres
m_∞	total amount of drug in polymer microspheres
p	dimensionless parameter measuring relative rates of dissolution and erosion
q	dimensionless parameter measuring initial drug loading
r	radial position in the sphere (m)
R_t	instantaneous radius of the sphere (m)
R_0	initial radius of the sphere (m)
s	dimensionless radial position
t	time (s)
u_L	dimensionless liquid phase concentration
u_S	dimensionless solid phase concentration
V_t	volume of sphere for surface erosion (m^3)
V_0	initial volume of sphere (m^3)
w	dimensionless time
ε	polymer porosity
εC_{sat}	effective drug saturation concentration (kg/m^3)
τ	polymer tortuosity

poly(ortho esters)) is faster than the diffusion of water through the polymers,[9-11] leading to typical surface-eroding modes. Polyanhydrides have been used to encapsulate and deliver a wide variety of drugs of various morphologies.[12-15] For example, polyanhydride-based dosage forms with poly(1,3-bis(carboxyphenoxy)propane-co-sebacic acid) (20:80 CPP:SA) have been approved by the US Food and Drug Administration and applied to deliver the cancer treatment drug, BCNU. Poly(ortho esters) have been developed to the current version, POE IV, and applied for ocular delivery, protein release, post-operative pain treatment, and post-operative cancer treatment.[16] POE IV are easy to synthesize and very biocompatible. Especially, their versatility of synthesis allows the accurate control of erosion rates and mechanical properties.[17]

Various models have been proposed to explore polymer surface erosion processes.[8,9,18-27] For example, the study by Gopferich and Langer[21] applied Monte-Carlo simulation to model the erosion of polyanhydride matrices based on a Poisson process of first order. Boimvaser et al.[19] modeled the degradation of poly(lactic-co-glycolic acid) implants in the aqueous medium of physiological pH based on first-order erosion kinetics. von Burkersroda et al.[8] developed a theoretical model to determine the predominant erosion mechanism of polymer matrix, based on the ratio between water diffusion rate and polymer degradation rate. In the study by Zhang et al.,[25] the drug release process of polymer microspheres was modeled by combining the effects of drug diffusion, drug dissolution, and polymer surface erosion. Recently, Versypt et al.[24] derived an analytical solution to the reaction-diffusion model of polymer degradation and considered polymer erosion rate with a linear function. A more detailed review of existing mathematical models of polymer erosion is presented by Sackett and Narasimhan.[28]

Existing experimental studies[29-33] examined the weight loss of surface-eroding polymer microspheres with respect to time. Based on the weight loss information, the radius reduction profile of the microsphere could be estimated, by assuming that the volume of the microsphere is proportional to its weight. Ideally, if polymer erosion is confined at the surface and is uniformly dispersed over the surface of surface-eroding polymers, the drug release process would be fully controlled by surface erosion, and exhibits constant release kinetics.[34] In this case, the radius of the polymer microsphere could be assumed to decrease linearly with respect to time. However, actual drug release processes may deviate from the constant kinetics and depends on a variety of factors (e.g., the type, composition and porosity of polymer, crystallinity, molecular weight, glass transition temperature, monomer hydrophobicity, etc.). Based on the reported experimental data, it could be identified that the measured erosion kinetics (i.e. the reduction of microsphere radius) actually follows either a power law mode or root type mode, rather than the commonly assumed linear mode by existing studies (e.g., Zhang et al.[25]). Since the erosion kinetics of drug-laden polymer microspheres directly affects the release profile, material, conditions, dimensions, and geometries of drug,[28] it should be fully understood for developing precisely controlled drug delivery systems.[9,35,36] However, the existing models rarely account for the effects of erosion kinetics and there are still lacking of comprehensive models that explicitly differentiate the effects of erosion kinetics in terms of drug release. Such comprehensive models would help to effectively enhance the current capability of drug release modeling and achieve more accurate drug release designing.[37,38] Furthermore, the systemic comparison of different erosion kinetics would fill an existing knowledge gap and provide a straightforward data bank for practical drug design. Especially, the knowledge about the sensitivity of drug release to potential influential parameters would lay the groundwork for achieving controlled drug release.

Therefore, in this work, two generalized modes (i.e., power law and root type) of erosion kinetics from the existing experimental studies are first identified and summarized. A set of theoretical drug release models for biodegradable polymers covering potential erosion kinetics would be developed, by extending the existing model of Zhang et al.[25] Model validation would be conducted by comparing reported experimental data to model predictions in terms of drug release profiles. Second, parameter investigation and sensitivity analysis are performed to systematically investigate the influences of modeling parameters toward drug release processes, for the cases of different erosion kinetics modes, which sheds light onto the designing of drug release.

Model Development

Erosion Kinetics

Previous experiments[29-33] reported the variation of the weight loss of surface-eroding polymer microspheres with respect to time. Because the drug loading is generally low (e.g., <7% by weight), the volume of microsphere could be assumed to be proportional to the remaining weight. For spherical geometry, we have