

# A mechanistic model for drug release in PLGA biodegradable stent coatings coupled with polymer degradation and erosion

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**Abstract:** Biodegradable poly(D,L-lactic-co-glycolic acid) (PLGA) coating for applications in drug-eluting stents has been receiving increasing interest as a result of its unique properties compared with biodegradable polymers in delivering drug for reducing stents-related side effects. In this work, a mathematical model for describing the PLGA degradation and erosion and coupled drug release from PLGA stent coating is developed and validated. An analytical expression is derived for PLGA mass loss that predicts multiple experimental studies in the literature. An analytical model for the change of the number-average degree of polymerization [or molecular weight (MW)] is also derived. The drug transport model incorporates simultaneous drug diffusion through both the polymer solid and the liquid-filled pores in the coating, where an effective drug diffusivity model is derived

taking into account factors including polymer MW change, stent coating porosity change, and drug partitioning between solid and aqueous phases. The model is used to describe *in vitro* sirolimus release from PLGA stent coating, and demonstrates the significance of simultaneous sirolimus release via diffusion through both polymer solid and pore space. The proposed model is compared to existing drug transport models, and the impact of model parameters, limitations and possible extensions of the model are also discussed. © 2014 Wiley Periodicals, Inc. *J Biomed Mater Res Part A*: 103A: 2269–2279, 2015.

**Key Words:** mathematical modeling, drug-eluting stents, PLGA degradation and erosion, drug release, effective diffusivity

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## INTRODUCTION

Drug-eluting stents (DES) are predominantly used in coronary angioplasty procedures for reducing in-stent restenosis. Their distinguished therapeutic effect is attributed to the prolonged local release of anti-inflammatory or antiproliferative drugs from a polymeric stent coating into the arterial wall.<sup>1</sup> Biodegradable polymers are most commonly used for the stent coatings in DES, which release only part of the loaded drug and induce problems related to the intact polymer coating remaining in the arterial lumen after release (such as hypersensitivity reactions and late in-stent thrombosis).<sup>2,3</sup> The need of overcoming those problems has led to research on improving the DES techniques, and special attention has been paid on the evaluation of biodegradable polymers, in particular poly(D,L-lactic-co-glycolic acid) (PLGA), as alternative drug carriers.<sup>4,5</sup>

PLGA has been well recognized for its suitability in drug delivery due to its good biocompatibility and ability to achieve complete drug release as a result of degradation and erosion of the polymer matrix.<sup>6,7</sup> While degradation and erosion are intricately connected, they correspond to different processes. Degradation is a chemical process that involves scission of polymer backbones and formation of

monomers and oligomers, and erosion is a physical phenomenon designating the loss of material resulted from the monomers and oligomers leaving the matrix.<sup>8</sup> Polymer molecular weight (MW) change and mass loss are the two measures for quantifying degradation and erosion, respectively. Degradation and erosion are coupled to each other, and they collectively regulate the drug release rate in the PLGA stent coating.<sup>6</sup> Experimental studies have been carried out for studying and designing PLGA stent coatings,<sup>9–12</sup> which are based on the trial-and-error procedures. Complementarily, mathematical models could provide guidance in device design and optimization prior to or in concert with experimental procedures. While the literature is considerably rich in mathematical models for drug release from biodegradable stent coatings (to name just a few<sup>13–16</sup>), there is limited work in modeling biodegradable stent coatings for drug delivery.

Modeling the PLGA degradation and erosion is a prerequisite for drug release modeling, and mechanistic approaches are most commonly employed, as described in papers on PLGA-based drug delivery systems such as microspheres.<sup>17,18</sup> A simple and convenient approach for describing degradation, or the MW change, uses first-order

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degradation models.<sup>19–22</sup> Some other models generate a system of equations for all polymer chain lengths and compute the whole MW distribution.<sup>23,24</sup> Such approaches have high computational costs and require very detailed information for model initialization. As an alternative, a moments model adopts a “shrinking core” approach to significantly reduce the number of equations.<sup>25</sup> The moments model was extended by adding a monomer diffusion term for capturing the transition between reaction-controlled and diffusion-controlled states.<sup>26</sup> A limitation of the moments model is often the closure problem of second or higher order moments, which requires advanced treatment.<sup>27,28</sup> PLGA erosion, or mass loss, is important but yet limited modeling works are available in the literature. Among those works, a combined bulk random scission and end scission model was proposed for explaining the measured MW change and mass loss in PLGA microspheres.<sup>23</sup> A threshold of dissolvable oligomer size has been assumed in the calculation of the measured polymer MW and weight loss.<sup>24</sup>

The autocatalytic effect, which occurs due to accumulation of acidic monomers and small oligomers in the interior of the PLGA matrix and results in a heterogeneous degradation rate, is also included by adding an acid concentration dependency on the rate constants.<sup>29</sup> Assuming no mass loss and constant volume, a simple analytical expression for the number average MW in autocatalytic hydrolysis has been derived.<sup>29</sup> A mass balance model was also developed for three species (polymer PLA, oligomer, and monomer) where the monomer was considered to contribute to the autocatalytic effect.<sup>30</sup> Existing treatments of autocatalytic effect are summarized in a recent review.<sup>31</sup> Although interesting, the application of PLGA stent coating typically has a small characteristic length for which spatial nonuniformity of proton distribution disappears and the autocatalytic effect was not observed.<sup>10</sup>

Accompanied and facilitated by PLGA degradation and erosion, drug release undertakes significant impact from the changing properties of the polymer matrix (porosity and PLGA MW) and such factors need to be captured in the diffusion drug transport. For heparin release in PLGA microsphere, the pore size was modeled and an induction time for drug release was calculated.<sup>23</sup> The model, however, used constant drug diffusivity for its drug release calculation. While macromolecular hydrophilic drugs are limited by diffusion through the pore space, relatively smaller hydrophobic drugs could diffuse through both the PLGA matrix and the pore space. Several models have considered an effective drug diffusivity dependent on polymer MW change (summarized in Table I).<sup>6</sup> The diffusivity was considered as being inversely proportional to the polymer MW in an pseudo-steady state model for mifepristone release from PLGA films.<sup>21</sup> An inversely linear relationship between diffusivity and polymer MW was also used.<sup>19,22</sup> In a piroxicam release model, an empirical correlation was proposed by determining drug diffusivity in monodisperse PLGA microspheres with different MWs.<sup>20</sup> A similar approach was also used for determining a correlation between initial PLA MW and apparent drug diffusivity.<sup>32</sup> Exponential dependency of the

**TABLE I. Diffusivity Dependency on MW in Literature Models**

Model Expression	Reference
$D(M) = D_0 \frac{M_0}{M}$ (1)	Charlier et al. <sup>21</sup>
$D(M_w) = D_0 + \frac{k}{M_w}$ (2)	Siepmann and Peppas <sup>19</sup>
$\ln D = -0.347x^3 + 01.394x^2 - 104.950x + 316.950$ (3)	Raman et al. <sup>20</sup>
$x = \ln M_w$	
$D(M_n) = D_0 - k \ln M_w$ (4)	Wada et al. <sup>32</sup>

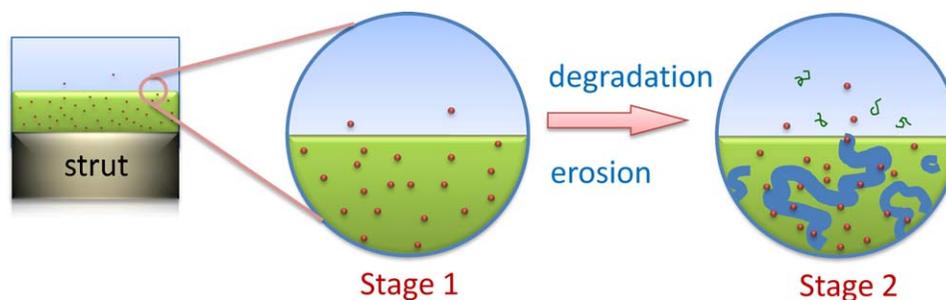
diffusivity on the concentration of nondegraded PLA was also seen.<sup>30</sup> The aforementioned models, however, have not considered the contribution in the enhanced drug diffusion through erosion and increasing porosity.

A mechanistic model should take into account the coupled aspects of PLGA degradation, erosion, and drug release while maintaining the mathematical form as simple as possible. In this work, a PLGA degradation-erosion model is proposed based on the method of moments, from which an analytical solution for the PLGA mass loss (erosion) rate is derived. The degradation-erosion model predicts the MW change and mass loss reported in different experiments. Drug transport in the PLGA coating is modeled by utilizing a varying effective diffusivity that incorporates the effects of PLGA MW change, porosity change, and drug partitioning in the solid and liquid-filled pores to describe simultaneous transport through the polymer solid and the pore space. The coupled degradation-erosion model and the drug release model is solved and validated for *in vitro* sirolimus release data using model parameter values reported in the literature. The release model is also formulated as a parameter estimation problem and solved via optimization to obtain the parameters with the best fit. Parameter exploration in the model is also performed to investigate the impact on changing the release profiles.

## THEORY AND METHODS

Drug release from a PLGA stent coating is a joint outcome of drug diffusion and the coating degradation and erosion. Both biphasic and triphasic release profiles are observed, with the latter having an additional phase of initial burst release. Burst release is typically found in large devices, which has been attributed to nonencapsulated drug or drug on the surface. The burst effect is conveniently removed through adjusting the fabrication technique and is not considered in this model.<sup>31</sup>

Our mathematical model focuses on the two releasing stages that are characteristic to PLGA drug release systems, involving an initial slow release and an enhanced release (Fig. 1). The slow release (stage 1 in Fig. 1) is contributed by drug diffusion through the PLGA polymer solid phase at early times. For macromolecular drug, the diffusion release can be negligible due to small drug diffusivity. As polymer degradation continues and erosion start to occur with smaller products diffusing out of the matrix, pores are



**FIGURE 1.** Two-stage scheme of the drug release coupled to PLGA degradation and erosion. Stage 1: slow release by diffusion through the matrix; stage 2: enhanced release contributed by diffusion through both matrix and micro-porous structured formed by polymer matrix degradation and erosion. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

formed and opened up within the coating. Drug diffusion is accelerated by partitioning into and passing through the liquid-filled pores. Meanwhile, the MW of PLGA polymers also decreases as a result of the degradation. Less molecular entanglement is present in the shorter PLGA chains, and drug diffusion through the PLGA polymer phase is also enhanced. Combining the drug diffusion enhancement from both pores and reduced PLGA chain length, a faster release (stage 2 in Fig. 1) is observed.

Heterogeneous degradation and erosion could occur in stage 2 when the diffusion distance is relatively large and diffusion for small degradation products is slower than the generation rates. The accumulation of the acidic degradation products (in particular monomers) can increase towards the interior of the PLGA device, to further catalyze degradation. This phenomenon, known as the size-dependent autocatalytic effect, leads to spatial nonuniformity and increases the complexity of drug release modeling. In the context of a stent coating, the coating thickness is on the order of 10  $\mu$ , which is small enough that the autocatalytic effect does not need to be considered.<sup>10</sup>

Two key components in modeling drug release from PLGA stent coating include: (1) capture of the PLGA matrix change, that is, PLGA MW change due to polymer degradation and porosity change as a result of erosion; and (2) description of the effective drug diffusivity varying with the matrix evolution. Increasing porosity and decreasing MW change the drug diffusion rate, and collectively contribute to simultaneous drug diffusion through the solid and porous phases. These aspects are modeled in the next two subsections, respectively.

### PLGA degradation and erosion model

The degradation reaction of PLGA polymer  $P_n$  of length  $n$  (number of monomer units) is described by



where  $k$  is the reaction rate constant. The reaction assumes that the breakage of chemical bonds is random. Each polymer  $P_n$  can be generated via degradation of longer chains and consumed by breaking down into smaller chains.

In a PLGA stent coating, the change of polymer of length  $i$  is described by the diffusion-reaction Eq. (6),

$$\frac{\partial P_i}{\partial t} = \frac{\partial}{\partial x} \left( D_i(M_w, \phi) \frac{\partial P_i}{\partial x} \right) + k(x) \left( -(i-1)P_i + 2 \sum_{j=i+1}^{\infty} P_j \right) \quad (6)$$

where  $P_i$  is the concentration of polymer of length  $i$ ,  $D_i$  is the effective diffusivity, and  $x$  is the coating thickness. The diffusivity of each polymer,  $D_i$ , is distinguished for different  $i$ , and is dependent on the average PLGA molecular weight  $M_w$  and matrix porosity  $\phi$ . The reaction term describes all possible generation/consumption of polymer chains. In general the rate constant  $k$  can vary with position. For example, in the autocatalytic scenario, rate constant  $k(x)$  is an explicit function of local proton concentration. Equation (6) is the general model form for describing the PLGA degradation and erosion process.

Modeling the stent coating using the full complexity of model Eq. (6) for all polymer lengths is unrealistic, due to the complicated imperfectly known dependencies of diffusivity and rate constants on other factors, and computationally expensive, as a result of the huge number of partial differential equations. Existing models all utilize simplifications by adopting various assumptions. The two main assumptions of our model are:

1. The diffusion of monomers (or neutralizing ions from the release buffer, if any) is fast at the length scale of the stent coating and therefore the pH gradient within the coating is negligible. As a result, the degradation reaction occurs homogeneously throughout the coating. This assumption eliminates the spatial dependency of rate constant  $k$ .
2. Because of their smaller size, the monomers diffuse through the coating much faster than the oligomers, and contributes to majority of the mass loss (erosion) in early times. Based on this fact, the second assumption considers that all monomers, and only monomers, contribute to mass loss at early times before disintegration of the coating matrix occurs.

Under the second assumption, the diffusion terms in Eq. (6) for all polymer lengths can be separated from the

degradation reaction. Leaving only the reaction terms in the equation, the model reduces to a set of ordinary differential equations (ODE) that can be conveniently transformed utilizing the method of moments (see Appendix A for detailed description). With  $\mu_n$  defined as the  $n$ th moment, the moments model is

$$\frac{d\mu_0}{dt} = k(\mu_1 - \mu_0) \quad (7)$$

$$\frac{d\mu_1}{dt} = 0 \quad (8)$$

$$\frac{dP_1}{dt} = 2k(\mu_0 - P_1) \quad (9)$$

where  $\mu_0$  stands for the total concentration (number) of polymer chains,  $\mu_1$  is the total mass (or total number of polymeric units) without consideration of mass loss, and  $P_1$  is the concentration of monomers. Observe that  $\mu_1$  is a constant in Eq. (8).

The moment model can be analytically solved to obtain (see Appendix A for the derivation),

$$\mu_0 = \mu_1 + \mu_1 \left( \frac{1}{X_{n,0}} - 1 \right) e^{-kt} \quad (10)$$

$$P_1 = \mu_1 + \mu_1 \left( 1 - \frac{2}{X_{n,0}} \right) e^{-2kt} + 2\mu_1 \left( \frac{1}{X_{n,0}} - 1 \right) e^{-kt} \quad (11)$$

where  $X_{n,0}$  is the initial number-average degree of polymerization. From assumption 2 and the assumption that the weight change induced by the addition of water molecules is negligible compared to the weight of polymer, the fraction of mass loss, or erosion rate, is calculated by

$$r_{ML} = \frac{P_1}{\mu_1} = 1 + \left( 1 - \frac{2}{X_{n,0}} \right) e^{-2kt} + 2 \left( \frac{1}{X_{n,0}} - 1 \right) e^{-kt} \quad (12)$$

By definition, the number-average degree of polymerization is given as the total number of monomer units divided by the total number of chains,

$$X_n = \frac{\mu_1}{\mu_0} = \frac{1}{1 + \left( \frac{1}{X_{n,0}} - 1 \right) e^{-kt}} \quad (13)$$

As time  $t$  approaches infinity, Eq. (13) indicates that the number-average degree of polymerization approaches one, which corresponds to complete degradation into monomers. Equation (13) is easily converted to the number-average MW by multiplying with the monomer molecular weight (e.g., 83 for PLGA 50/50). Considering the loss of monomers, the modified number-average degree of polymerization is

$$X_n = \frac{\mu_1 - P_1}{\mu_0 - P_1} = 1 + \frac{1}{1 - \frac{X_{n,0} - 2}{X_{n,0} - 1} e^{-kt}} \quad (14)$$

The weight-average degree of polymerization (or MW) is, however, not solved by the moments model because of

the closure problem encountered on the second moment (illustrated in Appendix A). Alternatively, the commonly used first-order degradation model is adopted for modeling the weight-average MW change,

$$M_w = M_{w,0} e^{-k_w t} \quad (15)$$

where  $M_{w,0}$  is the initial weight-average MW.

### Drug transport model

The drug transport in the coating proceeds by diffusion mechanism. Assuming that the drug is uniformly dispersed in the coating, the drug release is described by

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x} \left( D_e(M_w, \phi) \frac{\partial C}{\partial x} \right) \quad (16)$$

where  $D_e$  is the effective drug diffusivity that is dependent on the evolving MW and porosity.

As a consequence of the degradation and erosion, the key in predicting the drug release is finding a good description of the evolving effective diffusivity. As mentioned in the introduction, existing models typically consider only part of the affecting factors empirically (e.g., influence of MW change, Table I). In this model, an effective drug diffusivity is derived that incorporates the diffusivity in the polymer phase ( $D_s$ ), the diffusivity in the liquid-filled pores ( $D_l$ ), porosity ( $\phi$ ), and drug partitioning between the liquid-filled pores and solid PLGA phase ( $\kappa$ ):

$$D_e = \frac{(1 - \phi)D_s + \kappa\phi D_l}{1 - \phi + \kappa\phi} \quad (17)$$

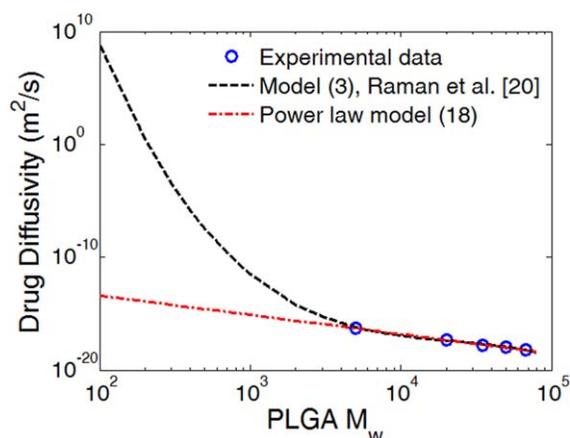
where the derivation is in Appendix B. The diffusivity in the polymer phase ( $D_s$ ) further depends on the changing MW. The various models summarized in Table I all correspond to this particular aspect. According to reptation theory in polymer physics, this diffusivity correlates with the average MW (e.g., weight-average MW) through the scaling law,<sup>33</sup>

$$D_s = D_{s0} \left( \frac{M_w}{M_{w,0}} \right)^{-\alpha} \quad (18)$$

with a theoretical value of power  $\alpha$  equal to 2.

A comparison of the power law model (18) with the literature fit in model (3) is illustrated in Figure 2 for initial diffusivities measured in piroxiam-releasing monodisperse PLGA microspheres. The power law model (18) matches the experimental data with  $\alpha = 1.714$  and  $R^2 = 0.9999$ . Extending the models to the low MW region, the predicted diffusivity is much more reasonable for the power law model (18) and stays within the physical range. Based on the analysis, the power law model (18) is adopted for modeling  $D_s$ .

Equation (17) can be verified with two simple scenarios. When no pores exist, or  $\phi = 0$ , the expression reduces to  $D_s$ , which is the drug diffusivity in the polymer solid. At the



**FIGURE 2.** Estimation of the dependency of drug diffusivity in the polymer phase on the PLGA average MW. The power law model gives a more physically reasonable prediction at low MWs than model (3) in the literature. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

other extreme with the porosity of one, or  $\phi = 1$ , the expression reduces to the aqueous drug diffusivity  $D_i$ .

A quick note is that in Eq. (17), the effect of geometric factors was not included. Such factors include the tortuosity, which describes how tortuous the pore connections are, and constrictivity, which is a hindering effect if the pore size is comparable to the drug molecule size.<sup>34,35</sup> Parameters for such factors are typically empirical, and could be incorporated with existing formulas.<sup>36</sup> In this work, the factors of tortuosity and constrictivity are assumed constant. According to the knowledge of the authors, this is the first time in the literature that such an effective diffusivity formula is developed to describe simultaneous drug transport through degrading polymers and eroding pores in a stent coating, while taking into account the key controlling factors.

## RESULTS

In this section, the degradation and erosion model as well as the drug release model are validated by comparing with experimental data reported in the literature. Three distinguished experiments independently done in different groups are utilized for model validation. The information of the three sets of experiments are labeled and summarized in Table II. For the three studies in Table II, dataset 1 is for a PLGA microsphere (20  $\mu\text{m}$  radius), dataset 2 is for a PLGA coating layer (loaded with sirolimus) on top of a ultra-high MW poly(L-lactide) (PLLA) layer with no drug (therefore, effectively a PLGA coating), and dataset 3 is a regular PLGA stent coating. Based on the two assumptions proposed for PLGA coating (or matrices) at small length scales that the

proton gradient within the PLGA matrix is negligible and monomers contribute solely to the mass loss, the degradation and erosion occur homogeneously. Under such circumstances, the particular geometry of the PLGA matrix shall have little impact on the degradation and erosion rates and utilization of the three experimental studies are reasonable.

### Predicting PLGA erosion

The erosion model as derived in Eq. (12) describes the mass loss as a function of time and initial number-average MW. The model parameter, degradation rate constant  $k$ , is determined from the half-time of the number-average MW decay. A reported value in the literature is used, with  $k = 2.5 \times 10^{-7} \text{s}^{-1}$  (half-time is 35 days).<sup>23</sup> The measured mass loss in all the three datasets falls on the model prediction (Fig. 3).

It is interesting to note that, even though the initial PLGA number-average MW is different in all three data sets, their model predictions overlap. The explanation lies in the insignificance of the term  $1/X_{n,0}$  compared with 1 in Eq. (12), due to the typical large initial number-average MW in PLGA polymers. Consequently, Eq. (12) is further simplified as

$$r_{\text{ML}} = 1 + e^{-2kt} - 2e^{-kt} \quad (19)$$

To the knowledge of the authors, it is the first time in the literature that an analytical model is proposed for describing mass loss in PLGA polymer thin films.

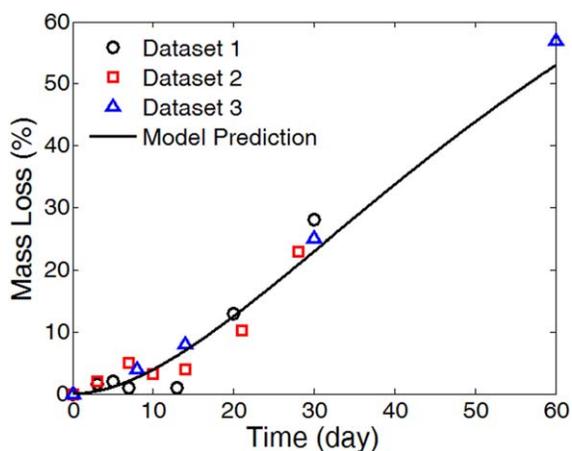
### Predicting PLGA degradation

In theory either the number-average MW or weight-average MW can be used for characterizing the degradation. Compared with weight-average MW, the number-average MW is significantly affected by the presence of low MW polymers such as monomers and oligomers. The low MW polymers are, however, difficult to be detected due to the resolution limitation of equipments. As a result, the number-average MW measurements in PLGA degradation only represents contributions from polymers with size larger than the lower detection limit.<sup>23</sup> The limit for PLGA is suggested to be oligomers with nine polymeric units. As a result, the comparison of the model for number-average MW (Eqs. (13) and (14)) with experiments becomes difficult. As expected, model equations would predict much faster decay in number-average MW than what would be observed in experimental measurements.

Experimental determination of the weight-average MW is more robust as it is less influenced by the exclusion of small degradation products in the measurement. In the

**TABLE II. Sources and Information of the Experimental Data Used for Model Validation**

Label	PLGA Composition (LA:GA)	PLGA weight-average MW	Reference
Dataset 1	50:50	37,954	Batycky et al. <sup>23</sup>
Dataset 2	53:47	$7.69 \times 10^4$	Wang et al. <sup>9</sup>
Dataset 3	Unreported	Unreported	Xi et al. <sup>10</sup>



**FIGURE 3.** Weight loss predicted by the analytical erosion model matched the three experimental datasets. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

weight-average MW model, as described in Eq. (15), the model parameter  $k_w$  is distinguished with parameter  $k$  used in the erosion model and the number-average MW change. While  $k$  corresponds to the reaction rate constant and is estimated via the half-time for the decay of the number-average MW,  $k_w$  is conveniently obtained through the half-time for weight-average MW decay. The  $k_w$  is acquired as  $k_w = 7.5 \times 10^{-7} \text{ s}^{-1}$  through the same experimental source for  $k$ .<sup>23</sup> Similar values are reported in other experimental studies.<sup>20,22</sup>

The degradation model predicting the weight-average MW is compared with the experimental datasets in Figure 4. Figure 4(a) plots the experimental measurements for two data sets. The model predictions are nearly perfect for data set 1, from which the model parameter  $k_w$  was determined. The model predictions for data set 2 are satisfactory except for day 20, where the particular data point is much lower than the model prediction. While the abrupt drop is proposed to be associated with the increase in mass loss at the same time point,<sup>9</sup> the occurrence is unclear as no measurement was available for later times. The normalized MW change is plotted for all three datasets in Figure 4(b). For data set 3, although the initial MW is unknown, the model predicts the MW change fairly well for the entire time course up to 60 days.

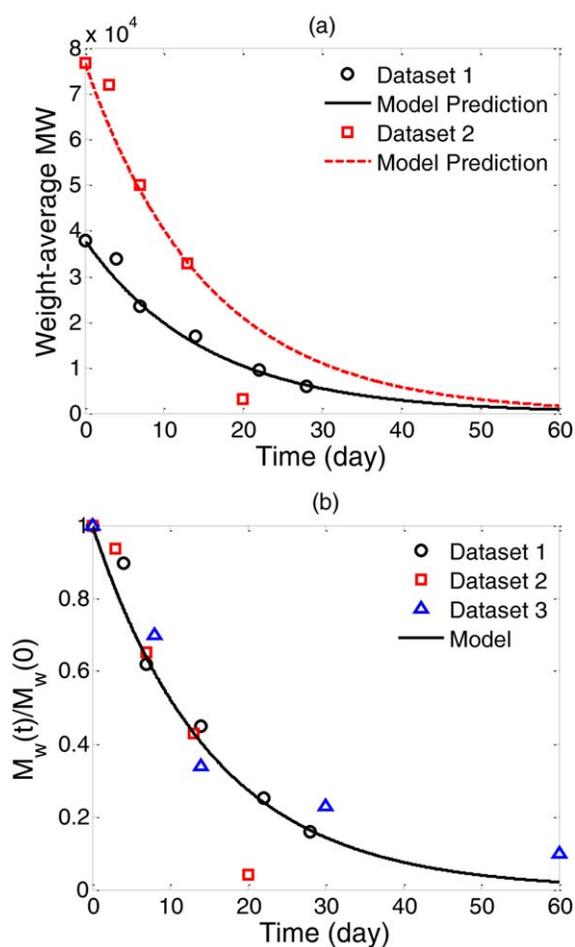
#### Simulations match sirolimus release data from PLGA coating

To model the drug release, the effective drug diffusivity (17) requires information input for average MW and porosity. The average MW can be directly obtained via incorporating the validated first-order degradation model in the previous section. By assuming constant volume of the coating matrix and the same density for PLGA polymers of different lengths, the porosity is related to the mass loss (19) via

$$\phi = \phi_0 + (1 - \phi_0)(1 + e^{-2kt} - 2e^{-kt}) \quad (20)$$

where  $\phi_0$  is the initial porosity in the PLGA coating.

The complete set of equations for describing the drug release is summarized in Table III for clarity. As a demonstration, the model is solved for simulating *in vitro* sirolimus release from PLGA stent coating to compare with experimental study.<sup>9</sup> In the experiment, the PLGA coating loaded with sirolimus was coated on top of an ultra-high MW PLLA layer that contained no drug. Compared with the PLGA coating layer, the PLLA undergoes much slower degradation and erosion because of its high MW and the chemical composition. As a result, even though the polymer matrix is fully biodegradable, the PLGA layer acts as if it is a coating layer on the PLLA layer. In the simulation, the wash out boundary condition is utilized on the external surface of the stent coating. While the initial porosity is a parameter dependent on the manufacturing procedures of the PLGA coating, an initial porosity of zero is used in the simulation as the micrographs of the PLGA coating morphology in the experiments indicated absence of microcavities in the beginning.<sup>9</sup> Because both sirolimus and piroxiam are hydrophobic drugs with small molecule size, the power law model (18) for  $D_s$



**FIGURE 4.** MW change predictions using the degradation model. (a) Model prediction for weight-average MW in data set 1 and data set 2. (b) Normalized weight-average MW in all three data sets compared with model prediction. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

**TABLE III. Summary of Complete Set of Equations for the Drug Release Model**

Drug Transport	$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x} (D_e(M_w, \phi) \frac{\partial C}{\partial x})$	(16)
Effective diffusivity	$D_e = \frac{(1-\phi)D_s + \kappa\phi D_l}{1-\phi + \kappa\phi}$	(17)
Diffusivity in polymer solid	$D_s = D_{s0} \left(\frac{M_w}{M_{w,0}}\right)^{-\alpha}$	(18)
PLGA average MW	$M_w = M_{w,0} e^{-k_w t}$	(15)
Porosity change	$\phi = \phi_0 + (1 - \phi_0)(1 + e^{-2kt} - 2e^{-kt})$	(20)

and  $\alpha=1.714$  are adopted for modeling sirolimus from Section PLGA degradation and erosion model.

The model is solved using the numerical method of lines. The spatial dimension ( $x$ ) is discretized, which results in a system of ODE. The system of ODEs is conveniently solved using a standard ODE solver in Matlab (ode15s). The numerical procedure is straightforward and details are not included here.<sup>37</sup>

Sirolimus release of two loadings (1 and 2% loadings, both from dataset 2 in Table II) was compared for the experimental measurements and model simulations (Fig. 5). The simulated sirolimus release in the model matches the experimental data quite closely. Because the loadings are relatively low, the drug could be considered as in a dissolved state. As a result, the percentage release profiles overlap for the two loadings both experimentally and in the model. Only three parameters are used in the drug release model: the drug diffusivity in the initial PLGA solid ( $D_{s0}$ ), aqueous drug diffusivity ( $D_{l0}$ ), and drug partitioning coefficient ( $\kappa$ ). The values of the parameters are directly obtained from ranges reported in the literature (summarized in Table IV). The model predictions capture the biphasic release behavior, and describe the process of simultaneous diffusion through polymer solids and the liquid-filled pores.

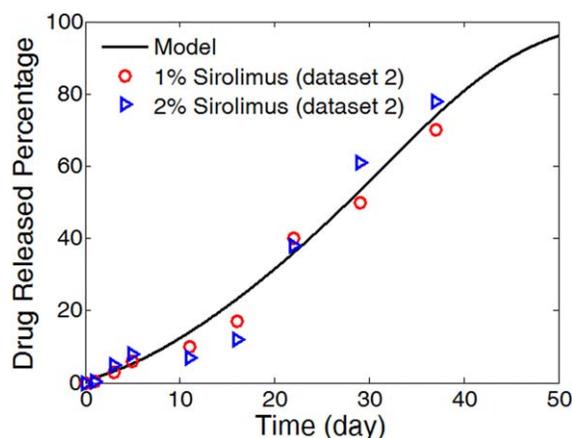
## DISCUSSION

### Model parameters

To obtain the parameters that best fit the experimental data, the model is also formulated as a parameter estimation problem. The parameter estimation defines an objective function that minimizes the summed square error (SSE) between values of model predictions and experimental data,

$$SSE = \min \left\{ \sum (\text{Model Prediction} - \text{Data})^2 \right\} \quad (21)$$

and is conveniently solved using the optimization toolbox (fmincon) in Matlab. The parameter values obtained via optimization are very close to the initial values used in the



**FIGURE 5.** Model simulation matches experimental data of sirolimus release from PLGA coating. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

model (Table IV). The small difference indicates that the parameter values are optimal and further supports the validity of the model.

The drug release model in this work is also compared with existing models (Fig. 6). Using a constant diffusivity in the polymer coating results in a very limited release. Including the MW dependency in the diffusivity results in significant enhancement in the drug release. However, the discrepancy between that model and our model indicates that the contribution from diffusion through the pores described in our model is significant. As the comparison suggests, the simultaneous diffusion through the polymer solid and the pore space is the most appropriate mechanism for describing sirolimus release in PLGA stent coating, and is only captured in our proposed model.

### Analysis of the hydrophobicity parameter on release rate

The partitioning coefficient ( $\kappa$ ) reflects the hydrophobicity of the drug. The smaller the partition coefficient, the less water-soluble the drug is and the higher the tendency that the drug prefers to stay within the polymer solid. For sirolimus, the partitioning coefficient is very low because of its high hydrophobicity.<sup>38,39</sup> The effect of the partitioning coefficient is illustrated in Figure 7 by fixing the other parameters (e.g., drug diffusivities in the polymer solids and aqueous phase). With higher partitioning coefficient value, faster release is predicted. The release profiles all exhibit biphasic characteristics. For all release profiles, the release profiles have a lower bound by the curve corresponding to  $\kappa = 0$ .

**TABLE IV. Model Parameters and Estimated Values via Optimization**

Model Parameters	Initial Values	Estimation via Optimization	Reference Range
Partition coefficient $\kappa$	$10^{-4}$	$1.0035 \times 10^{-4}$	$10^{-6} \sim 10^{-338,39}$
Initial diffusivity in PLGA polymer $D_{s0} (\mu\text{m}^2/\text{s})$	$10^{-5}$	$9.9826 \times 10^{-6}$	$10^{-6} \sim 10^{-420,22}$
Diffusivity in aqueous phase $D_{l0} (\mu\text{m}^2/\text{s})$	50	49.6386	$10 \sim 10^{333}$
MW change model parameter $a$	1.714	1.7179	$\sim 2^{33}$

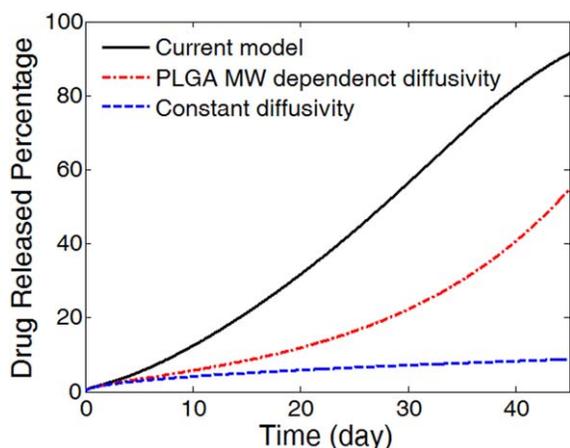
### Limitations and possible extensions of the model

The model developed in this work considers the various important factors that collectively regulate the drug release in PLGA stent coatings. While demonstrating successful matching between model simulation and experimental studies, the model does have limitations and it is worthwhile for further research in several aspects that could produce even better predictability and extended applicability.

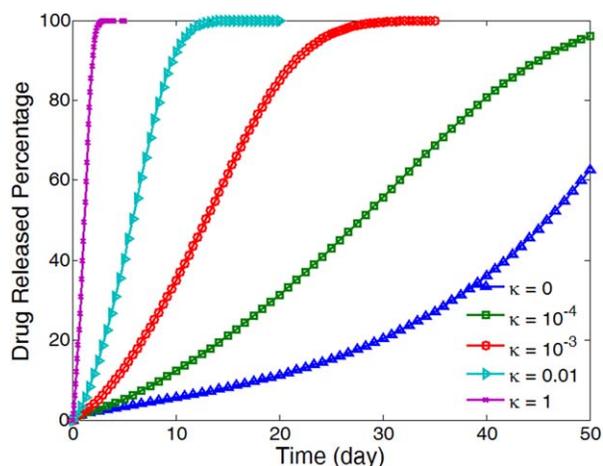
The first limitation lies in the simplifications adopted in the development of the effective drug diffusivity. As pores are formed randomly throughout the polymer matrix, the path through the pores could zigzag and the tortuosity effect may be significant. Correspondingly, the diffusivity contribution corresponding to the pores would be reduced. This modification would correct the higher predicted release than measured data at times around 10 to 20 days in Figure 5. Usually included as an empirical factor, the tortuosity effect could be potentially incorporated if sufficient information was available.

While this work focuses on hydrophobic drug with relatively small size, which are typically used in drug-eluting stent applications (i.e., sirolimus, with MW of less than 1 kDa), the model application could be extended to the release of macromolecular hydrophilic drugs (such as proteins or genes). In such situations, another factor besides the tortuosity effect, called *constrictivity*, would become important. The constrictivity describes the delay and hindrance in diffusion through pores when the pore size is comparable to the drug molecule size, and expressions for describing the factor are available. As a result, utilization of the constrictivity effect would require knowledge of the pore sizes in the coating.

In the erosion model, only monomers were included as the source for weight loss so that simple analytical expression could be derived. In reality, dimers, trimers, and other oligomers may all contribute to the weight loss to varying extents. Even though treated with simplification in this work, the autocatalytic effect could have some influence in



**FIGURE 6.** Sirolimus release profiles predicted in different models. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]



**FIGURE 7.** Impact of drug hydrophobicity on the drug release behaviors in PLGA stent coating. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

PLGA stent coating systems. Capture of those details in the degradation and erosion model may offer extra benefits in improving the drug release prediction.

A further limitation of the model developed here is the consideration of dissolved (well-dispersed) drug state. While the mechanistic model is verified with release of sirolimus at relatively low loadings, much higher drug loadings in the stent coating (10% or even higher) are not uncommon in the application of DES.<sup>40</sup> The latter could lead to both initial burst and aggregation of drug (for example, crystal formation), for which the current model will need to be extended to consider the drug dissolution mechanism.<sup>41</sup>

### CONCLUSIONS

This article develops a complete model set for describing the PLGA degradation and erosion and coupled drug release from PLGA stent coating. An analytical and simple expression for the PLGA mass loss was derived for the first time in the literature, together with an analytical expression for the number-average degree of polymerization (or MW) change. The mass loss model and the first-order degradation model are validated with experimental data from the literature.

Simultaneous drug diffusion through polymer solid with changing average MW and liquid-filled pores was modeled, and an effective drug diffusivity model was derived taking into account various factors including polymer MW change, diffusivity in the polymer, diffusivity in the liquid-filled pores, and drug partitioning between solid and liquid phases. The model was demonstrated for sirolimus release from PLGA stent coating and matched well with the experimental data in the literature. Comparison of the proposed model with existing models revealed the significance of simultaneous sirolimus diffusion through polymer solid and pore space. The impact of drug hydrophobicity was also demonstrated using the model.

The mechanistic model developed here has potential for applications to the design of PLGA coatings for DES. The model can also be extended for applications to other PLGA-

based drug delivery systems. The limitations are also discussed that provides guidance in possible model improvements.

## APPENDIX A

### Derivation of the differential moment equations

Under the assumptions in Section Theory and Methods, the partial-differential equations are reduced to ODE. The change of polymers of different length is given by,

$$\frac{dP_1}{dt} = 2k_n \sum_{j=2}^N P_j \quad (A1)$$

$$\frac{dP_2}{dt} = -k_n P_2 + 2k_n \sum_{j=3}^N P_j \quad (A2)$$

$$\frac{dP_3}{dt} = -2k_n P_3 + 2k_n \sum_{j=4}^N P_j \quad (A3)$$

⋮

$$\frac{dP_i}{dt} = -(i-1)k_n P_i + 2k_n \sum_{j=i+1}^N P_j \quad (A4)$$

⋮

$$\frac{dP_{N-2}}{dt} = -(N-3)k_n P_{N-2} + 2k_n \sum_{j=N-1}^N P_j \quad (A5)$$

$$\frac{dP_{N-1}}{dt} = -(N-2)k_n P_{N-1} + 2k_n P_N \quad (A6)$$

$$\frac{dP_N}{dt} = -(N-1)k_n P_N \quad (A7)$$

Define the  $n$ th moment of the polymers as

$$\mu_n = \sum_{i=1}^N i^n P_i \quad (A8)$$

Physically, the zeroth moment corresponds to the total number of polymers in the system, while the first moment stands for conservation of polymer units.

Summing all equations (A1)–(A7) gives an equation for the zeroth moment,

$$\begin{aligned} \frac{d\mu_0}{dt} &= \frac{d \sum_{i=1}^N P_i}{dt} = k_n \sum_{j=2}^N (j-1) P_j \\ &= k_n \left( \sum_{j=1}^N j P_j - \sum_{j=1}^N P_j \right) = k_n (\mu_1 - \mu_0) \end{aligned} \quad (A9)$$

Similarly, the first moment is given by

$$\frac{d\mu_1}{dt} = \frac{d \sum_{i=1}^N i P_i}{dt} = -k_n \sum_{j=2}^N j(j-1) P_j + 2k_n \sum_{j=2}^N [1 + \dots + (j-1)] P_j = 0 \quad (A10)$$

which implies that  $\mu_1$  is a constant.

The change of monomer is described by

$$\frac{dP_1}{dt} = 2k_n (\mu_0 - P_1) \quad (A11)$$

The second moment can be derived as

$$\frac{d\mu_2}{dt} = k_n \left( \frac{1}{3} \mu_1 - \frac{1}{3} \mu_3 \right) \quad (A12)$$

However, it is clear that the equations for the higher order moments do not have closure (that is, the differential equations for the  $i$ th moment are algebraic functions of higher order moments).

With initial condition  $\mu_0(t=0) = \mu_1/X_{n,0}$ , where  $X_{n,0}$  is the initial number-average degree of polymerization, and  $P_1(t=0) = 0$ , Eqs. (A9) and (A11) are analytically solved to give

$$\mu_0 = \mu_1 + \mu_1 \left( \frac{1}{X_{n,0}} - 1 \right) e^{-kt} \quad (A13)$$

$$P_1 = \mu_1 + \mu_1 \left( 1 - \frac{2}{X_{n,0}} \right) e^{-2kt} + 2\mu_1 \left( \frac{1}{X_{n,0}} - 1 \right) e^{-kt} \quad (A14)$$

## APPENDIX B

### Derivation of the effective diffusivity in the coating

Consider one-dimensional transport in a small control volume consisting of polymer matrix and pore space (Fig. B1). The drug transport is contributed by both diffusion through the pore space and diffusion through the polymer solid.

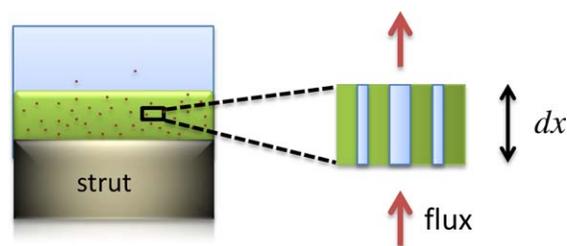
The drug transport through the polymer solid is given by

$$\frac{\partial((1-\phi)VC_S)}{\partial t} = (1-\phi)AD_S \nabla C_S \Big|_{x=x}^{x=x+\Delta x} - A'J_{SL} \quad (B1)$$

and the drug transport through the pore space is given by

$$\frac{\partial(\phi VC_L)}{\partial t} = \phi AD_L \nabla C_L \Big|_{x=x}^{x=x+\Delta x} + A'J_{SL} \quad (B2)$$

where  $A'$  is the interface area between the solid and pore space within the micro control volume,  $J_{SL}$  is the flux



**FIGURE B1.** Illustration of one-dimensional drug diffusion through pores and polymer solid in a small control volume. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

through the solid and liquid interface, and  $C_S$  and  $C_L$  denotes the concentration within the polymer solid and the liquid filled pores, respectively.

Summing Eqs. (B1) and (B2) gives an expression for the total drug diffusion,

$$V\left(\frac{\partial((1-\phi)C_S)}{\partial t} + \frac{\partial(\phi C_L)}{\partial t}\right) = A((1-\phi)D_S \nabla C_S|_{x=x}^{x=x+\Delta x} + \phi D_L \nabla C_L|_{x=x}^{x=x+\Delta x}) \quad (B3)$$

Note that the interfacial diffusion terms cancel due to the opposite signs. Assuming that the drug is in partitioning equilibrium between the pore phase and solid polymer phase gives

$$C_L = \kappa C_S \quad (B4)$$

where  $\kappa$  is the partition coefficient.

Substituting Eq. (B4) into (B3) gives

$$V\left(\frac{\partial((1-\phi)C_S + \phi C_L)}{\partial t}\right) = A((1-\phi)D_S + \kappa\phi D_L) \nabla C_S|_{x=x}^{x=x+\Delta x} \quad (B5)$$

The average drug concentration over the entire control volume is given by

$$C_{ave} = (1-\phi)C_S + \phi C_L \quad (B6)$$

As  $\phi$  is only a function of time (uniform degradation throughout the coating),

$$\nabla C_{ave} = (1-\phi + \phi\kappa) \nabla C_S \quad (B7)$$

Substituting (B6) and (B7) into (B5) gives

$$V \frac{\partial C_{ave}}{\partial t} = A \left( \frac{(1-\phi)D_S + \kappa\phi D_L}{1-\phi + \kappa\phi} \right) \nabla C_{ave}|_{x=x}^{x=x+\Delta x} \quad (B8)$$

For infinitesimal  $\Delta x$ ,

$$\frac{\partial C_{ave}}{\partial t} = \left( \frac{(1-\phi)D_S + \kappa\phi D_L}{1-\phi + \kappa\phi} \right) \nabla^2 C_{ave} \quad (B9)$$

Correspondingly, the average concentration in the coating is described by

$$\frac{\partial C_{ave}}{\partial t} = D_e \nabla^2 C_{ave} \quad (B10)$$

where  $D_e$  is the effective diffusivity defined as

$$D_e = \frac{(1-\phi)D_S + \kappa\phi D_L}{1-\phi + \kappa\phi} \quad (B11)$$

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