A Mathematical Model for Predicting Controlled Release of Bioactive Agents from Composite Fiber Structures

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Abstract: A mathematical model for predicting bioactive agent release profiles from core/shell fiber structures was developed and studied. These new composite fibers, which combine good mechanical properties with desired protein release profiles, are designed for use in tissue regeneration and other biomedical applications. These fibers are composed of an inner dense polymeric core surrounded by a porous bioresorbable shell, which encapsulates the bioactive agent molecules. The model is based on Fick’s second law of diffusion, and on two major assumptions: (a) first-order degradation kinetics of the porous shell, and (b) a nonconstant diffusion coefficient for the bioactive agent, which increases with time because of degradation of the host polymer. Three factors are evaluated and included in this model: a porosity factor, a tortuosity factor, and a polymer concentration factor. Our study indicates that the model correlates well with in vitro release results, exhibiting a mean error of less than 2.2% for most studied cases. In this study, the model was used for predicting protein release profiles from fibers with shells of various initial molecular weights and for predicting the release of proteins with various molecular weights. This new model exhibits a potential for simulating fibrous systems for a wide variety of biomedical applications.

INTRODUCTION

Tissue regeneration involves the preparation of polymeric structures that serve as degradable scaffolds for bioactive agents or cells as well as the study of their structure and properties. However, the key problem of how to incorporate bioactive agent molecules into thin delicate structures that construct devices and scaffolds remains unresolved, since they must be incorporated into dense polymeric structures without adversely affecting either the scaffold’s properties or the agent’s activity. Two types of drug-loaded fibers have been reported previously. These are monolithic fibers in which the drug is dispersed throughout the fiber, and hollow reservoir fibers in which the drug is stored in the fiber’s internal cavity. However, most such systems suffer from poor mechanical properties (due to drug incorporation) and/or require destructively high melt-processing temperatures. Most drugs and all proteins cannot withstand high temperatures or endure many organic solvents.

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In one of our recent studies, we presented a new concept of core/shell fiber structures, which successfully meet these challenges. These composite fibers combine a dense poly(l-lactic acid) (PLLA) core fiber and a drug/protein-loaded porous shell structure, i.e., the drug or protein is located in a separate compartment (a “shell”) around a melt spun “core” fiber. A schematic representation of the composite fiber structure is presented in Figure 1. This results in good mechanical properties as well as in the desired drug release profile. Unlike conventional bulky multifiber structures that carry bioactive agent molecules in their pores, we incorporate these molecules directly into the shell (but not the core) of our composite fibers, rather than in the interstices between them. Better control over drug release can thus be achieved. In our initial studies, the shell was loaded with the model enzyme, horseradish peroxidase (HRP), which is very sensitive to both solvents and elevated temperatures and whose activity is a sensitive monitor of damage during processing. Our results indicated that HRP preserved 94–100% of its activity during the fiber preparation process.

In addition to tissue regeneration applications, our new fibers are ideal for forming thin, delicate, biomedically important structures for various applications, such as fiber-based endovascular stents that mechanically support blood vessels while delivering drugs for preventing restenosis directly to the blood
vessel wall, or bioresorbable wound and burn dressings loaded with antimicrobial agents.

Mathematical models for controlled release of bioactive agents from bioresorbable matrices are based on diffusion aspects, on the structural characteristics of the matrix polymer and its degradation and swelling, and on the micro-environmental pH changes inside polymer matrix pores that are due to the degradation products. Prediction of the drug release profile using a model is obviously very useful in the device’s design phase, since the model enables fast evaluation and tuning of the various parameters for achieving an optimal release profile, while reducing laboratory tasks to a minimum.9,10

Early drug delivery models described either systems based on nondegradable matrices or surface-eroding systems.11 Several more recent models described bulk-eroding systems, in which the drug is physically immobilized. For example, Siepman and Gopferich12 quantified drug release from slab-shaped PLLA and poly(dl-lactic acid-co-glycolic acid) (PDLGA) matrices. Their model was based on Higuchi’s classical pseudo-steady-state equation for oversaturated, planar, nondegrading polymeric films, where the permeability of the drug within the polymer matrix was assumed to increase with time, due to cleavage of the polymer’s bonds. Another possibility for simulating the effect of erosion on the diffusion process is to use a diffusion coefficient, which increases with time. Various theories therefore related the drug diffusion coefficient inside a degradable polymer directly to its molecular weight, since short chains offer less restriction to drug diffusion than do long chains. This was one of the main assumptions in the models of Charlier et al.13 for predicting the release rate of Mifepristone from 50/50 PDLGA bulk-eroding films of various molecular weights, and Faisant et al.14 who examined the release rate of 5-fluorouracil from 50/50 PDLGA microspheres. Each of them used an additional assumption regarding the polymer’s first-order degradation kinetics, in order to calculate an appropriate time-dependent diffusion coefficient, which they used in Fick’s laws of diffusion. Zhang et al.15 addressed three mechanisms for drug release in a microspheric matrix, namely dissolution of the drug from the polymer matrix, diffusion of the dissolved drug, and erosion of the matrix.

It should be noted that most drug delivery systems are either in the form of films or microspheres, and so are the above-described models. Sagiv et al.,16 however, developed a specific model for predicting protein release from monolithic PLLA fibers. Since PLLA degrades relatively slowly, they assumed that polymer erosion is negligible during the release time; thus allowing them to use a constant diffusion coefficient so as to simplify the model. This model is therefore obviously not applicable to our core/shell fiber structures. However, our promising results raised the need for a suitable model that could facilitate and shorten the design process of the core/shell fiber structures. This need was the driving force for the current research, in which a mathematical model was developed for predicting protein release profiles from our composite fiber structures. The hypotheses of our study are: (1) A model based on Fick’s laws will be able to provide good prediction of protein release profile from our new core/shell fiber structures, and (2) the protein release profile from the fibers is affected by the molecular weights of the protein and the host polymer, and also by the emulsion’s formulation parameters.

**CASE DEFINITION AND MODEL ASSUMPTIONS**

A mathematical model for predicting drug/protein release from our novel core/shell fiber structures was developed in this study, using Matlab 6.1. The release profiles that were predicted using this model were compared with that of the experimental results for certain fiber types.

The experimental system

About 8-cm long fibers, composed of an inner PLLA core fiber, were coated with a porous 75/25 PDGLA shell. The porous shell was fabricated using the “freeze-drying” technique, where an organic solution (containing PDLGA and chloroform as solvent) and an aqueous solution (containing distilled water and HRP) were mixed together in a test tube. Each PLLA fiber was then dipped in the resulting emulsion and immediately frozen in liquid nitrogen. The water and the solvent were removed by sublimation, leaving the HRP molecules mechanically trapped in the porous PDLGA shell surrounding the PLLA fibers.8 The HRP load in the porous shell of all fibers was 5% (w/w; relative to the polymer weight). Various shell types were prepared and emulsions of organic:aqueous (o:a) phase ratios of 8:1 and 16:1 were obtained. Polymer contents

![Figure 1](https://example.com/figure1.png)
TABLE I  
Fiber Types Used for Obtaining the Experimental Data

<table>
<thead>
<tr>
<th>Fiber Type</th>
<th>Emulsion Organic Aqueous Phase Ratio (O:A)</th>
<th>Polymer Content in the Organic Phase (% w/v)</th>
<th>C_p</th>
<th>τ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8:1</td>
<td>15</td>
<td>0.29</td>
<td>3.3</td>
</tr>
<tr>
<td>2</td>
<td>8:1</td>
<td>19</td>
<td>0.58</td>
<td>7.0</td>
</tr>
<tr>
<td>3</td>
<td>16:1</td>
<td>13</td>
<td>0.54</td>
<td>8.0</td>
</tr>
<tr>
<td>4</td>
<td>16:1</td>
<td>15</td>
<td>0.8</td>
<td>11.0</td>
</tr>
<tr>
<td>5</td>
<td>16:1</td>
<td>19</td>
<td>1.4</td>
<td>21.0</td>
</tr>
</tbody>
</table>

of 13, 15, and 19% (w/v in the organic phase) were used for each o:a value. The types of fibers examined are presented in Table I.

Assumptions used while deriving the model’s equations

i. The bulk-eroding PDLGA porous structure exhibits first-order degradation kinetics, i.e. the cleavage of its chains occurs at a constant rate.\(^\text{17-19}\)

ii. The protein’s diffusion coefficient within the porous structure is only time-dependent and is assumed to increase with time proportional to the polymer’s normalized molecular weight loss (\(M_{\text{w,n}}\)).

iii. The internal PLLA core exhibits minimal degradation, if any, within the considered protein release time-frame. This assumption is based on one of our previous studies.\(^\text{20}\)

iv. There is no protein flux towards the internal PLLA core.

v. The external environment provides perfect sink conditions for the released proteins. When conducting the experiments the aqueous release medium was replaced at each sampling point.

vi. The proteins within the porous PDLGA structure are released only when they find a continuous path to the surface, and their release occurs solely by diffusing through water. This assumption is based on other reports of drug delivery systems based on porous matrices.\(^\text{10}\)

MODEL EQUATIONS

In this model, the protein concentration within the fiber obviously changes with time. Fick’s second law of diffusion in cylindrical coordinates (\(r, \theta, z\))\(^\text{12}\) was therefore used, as follows:

\[
\frac{\partial C}{\partial t} = \frac{1}{r} \left( \frac{\partial}{\partial r} \left( r D \frac{\partial C}{\partial r} \right) \right) + \frac{\partial}{\partial \theta} \left( \frac{D}{r} \frac{\partial C}{\partial \theta} \right) + \frac{\partial}{\partial z} \left( r D \frac{\partial C}{\partial z} \right)
\]

(1)

where \(C\) is the HRP concentration and \(D\) is its diffusion coefficient within the porous PDLGA structure.

Because of circular symmetry, the HRP concentration along \(\theta\) is constant, therefore

\[
\frac{\partial C}{\partial \theta} = 0
\]

(2)

Furthermore, in the case of a fiber whose radius is significantly smaller than its length, the end effects are negligible, yielding

\[
\frac{\partial C}{\partial z} = 0
\]

(3)

In conclusion, it may be stated that the diffusion of proteins from a fiber is limited to the radial axis, i.e. \(C = f(r, t)\), thus simplifying equation (1) to

\[
\frac{\partial C}{\partial t} = \frac{1}{r} \left( \frac{\partial}{\partial r} \left( r D \frac{\partial C}{\partial r} \right) \right) + \frac{\partial}{\partial r} \left( D \frac{\partial C}{\partial r} + r D \frac{\partial^2 C}{\partial r^2} \right)
\]

(4)

Assuming that the diffusion coefficient is only a function of time simplifies it even further, and the following equation can be used:

\[
\frac{\partial C}{\partial t} = \frac{1}{r} \left( \frac{\partial}{\partial r} \left( r D \frac{\partial C}{\partial r} \right) \right) = \frac{1}{r} \left( D \frac{\partial C}{\partial r} + r D \frac{\partial^2 C}{\partial r^2} \right)
\]

(5)

Thus, the final diffusion equation is

\[
\frac{\partial C}{\partial t} = D \left( \frac{1}{r} \frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial r^2} \right)
\]

(6)

Appropriate initial and boundary conditions should be used in order to solve the diffusion equation (6). Assuming an initial uniform HRP concentration (\(C_0\)) leads to the following initial condition:

\[
C = C_0 \quad \text{at} \quad t = 0, \quad r_1 < r < r_2
\]

(7)

where \(r_1\) is the radius of the internal PLLA fiber and \(r_2\) is the radius of the entire composite fiber (see Fig. 1). A “no flux” boundary condition was set on the internal wall of the porous structure, which is also the external wall of the inner PLLA fiber, \((r = r_1)\), indicating that the proteins within the porous structure are assumed to diffuse only toward the surface of the composite fiber and not toward its core:

\[
\frac{\partial C}{\partial r} = 0 \quad \text{at} \quad r = r_1, \quad t > 0
\]

(8)

The second boundary condition is a “perfect sink” at the external wall of the composite fiber, i.e.

\[
C = 0 \quad \text{at} \quad r = r_2, \quad t > 0
\]

(9)

Using the above initial and boundary conditions, the differential equation (6) was resolved via the “pdepe” Matlab function, and yielded \(C(r, t)\), the HRP concentration function inside the fiber. Thus, the total mass of proteins still trapped within the porous structure
Estimation of the diffusion coefficient

Previous reports on drug delivery systems based on porous matrices revealed that the drug is released much more slowly than that would be expected from the simplest consideration of aqueous diffusion. The porous structure apparently slows the progress of the diffusing agents, since they go through a tortuous path on their way to the matrix surface. The length of this path is unknown, but it is greater than $r_{r_{1}}$ by a tortuosity factor $\tau$, which was initially proposed by Higuchi.

Thus, the HRP diffusion coefficient within the porous PDLGA structure is assumed to initially have a certain low “effective” value, $D_{0}$, which is determined by the microstructure of the matrix, i.e. tortuosity $\tau$ and porosity $\varepsilon$ (the volume fraction accessible to the diffusing molecules). As degradation and finally erosion progress with time, the diffusion coefficient gradually increases, until it reaches HRP’s molecular diffusion coefficient, i.e. its diffusion coefficient in water, $D_{w}$. The above behavior can therefore be expressed using the following equations:

$$D_{0} = D_{w} \frac{\varepsilon}{\tau}$$
$$D(t) = D_{0} + (D_{w} - D_{0}) \times M_{w}(t)$$

where

$$M_{w}(t) = \frac{M_{w}(t = 0) - M_{w}(t)}{M_{w}(t = 0)}$$

Polson’s semiempirical equation was used for the protein molecular diffusion coefficient, $D_{w}$:

$$D_{w} = A \frac{T}{\mu M_{wp}^{1/3}}$$

where $M_{wp}$ is the protein’s molecular weight, $T$ is the absolute temperature, $\mu$ is the fluid viscosity, and $A$ is a constant that varies for each protein.

Tortuosity, $\tau$, is an empirical parameter whose value was determined by us. The stereology sampling technique was used in order to estimate the matrix porosity. This technique enables estimating a sample’s porosity using SEM (2D) images of sample cross-sections. Point-counting estimation was therefore used, where a grid of points is placed on the fiber’s cross-section image and the estimated porosity is the ratio between the number of points that fall on the pores themselves and the number of points that fall on the entire cross-section.

Adding the polymer concentration effect

As mentioned earlier, three polymer concentrations (w/v) were used in the organic phase while fabricating the different porous structures: 13, 15, and 19%. A higher polymer concentration results in a more viscous organic phase, thus creating a more stable emulsion. This higher viscosity, along with the obvious higher density, are expected to create the following hindering effects on the system: (1) slowing the matrix degradation rate due to a lower “readiness” to water penetration; (2) reducing the free volume available for protein diffusion, leading to a shorter initial burst effect in the release profile. An additional empirical parameter, $C_{p}$, was therefore introduced in order to add the variant polymer concentration to the model, as follows.

A function describing the decrease in molecular weight with time (degradation profile) for the relevant polymer (in this case the initial molecular weight = 100 kDa) had to be used. Data taken from a research by Wu and Wang were used and interpolation was performed in order to obtain a good estimation for the degradation profile of 75/25 PDLGA with an initial molecular weight of 100 kDa. The estimated degradation profiles of the 100 kDa PDLGA and two other polymers, which will be used in this model, are presented in Figure 2.
The normalized molecular weight curves apparently fit a function of the type:

\[ M_w(t) = \exp\left(\frac{-t}{C_0 B}\right) \]

Since the polymer concentration was hypothesized to alter the degradation rate, it was added to the model as follows:

\[ M_{wl}(t) = 1 - M_w(t) = 1 - \exp\left(\frac{-t}{C_0 B}\right) \]

\[ = 1 - \exp\left(\frac{-C_p t}{B}\right) \] (15)

According to theory, the degradation of bulk-eroding polymers follows first-order kinetics, i.e. plotting the natural logarithm of the molecular weight vs. the hydrolyzing time yields a nearly linear curve.17–19 The B coefficient was thus found using the “least squares” algorithm.

**RESULTS AND DISCUSSION**

As mentioned earlier, the experimental data used to validate this model were taken from one of our recent studies.8 The chosen core/shell fiber types and their semiempirical \(C_p\) and \(\tau\) values are presented in Table I. The predicted HRP release profile was compared with that of the experimental release profile for each type of composite fiber structures, and the results are presented in Figure 3. A very good fit was...
obtained for all studied fibers, except for the fiber with an o:a of 8:1 and 15% (w/v) polymer, where the predicted HRP release during the first week is lower than the experimental HRP release (Fig. 2a). Hence, these results support our first hypothesis about good predictability of a model based on Fick’s laws.

As explained above, two main emulsion types were created by using a constant organic phase volume with two different aqueous phase volumes: o:a of 8:1 and 16:1. The fibers fabricated with a higher o:a (16:1) exhibit a more tortuous diffusion path, leading to higher values of the tortuosity factor (Table 1). Furthermore, the tortuosity factor within both 8:1 and 16:1 “groups” increases with the increase in polymer content. Therefore, either increasing the emulsion’s o:a ratio (i.e., decreasing the aqueous phase volume) or increasing the polymer content, results in a decrease in the free space available for diffusion, leading to a higher tortuosity factor, which in turn leads to a lower release rate of the bioactive agent from the fiber’s shell. These results are in agreement with our second hypothesis, saying that the emulsion formulation parameters affect the release profile.

Since a higher polymer content leads to an emulsion with a more viscous and dense organic phase, we assumed that the resulting solid porous structure will tend to absorb less water, resulting in slower hydrolysis and hence degradation, leading to a shorter and

Figure 4. The effect of the polymer’s initial molecular weight on the predicted HRP release profile from various core/shell fiber structures containing 5% w/w HRP. Molecular weight: upper curve (red line) 40 kDa, center curve (blue line) 100 kDa, lower curve (green line) 160 kDa; (a) o:a = 8:1, 15% w/v polymer, (b) o:a = 8:1, 19% w/v polymer, (c) o:a = 16:1, 13% w/v polymer, (d) o:a = 16:1, 15% w/v polymer, (e) o:a = 16:1, 19% w/v polymer. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
more moderate burst effect. Following this hypothesis, $C_p$ was introduced into the model in a way that alters the porous structure’s degradation rate. This is also supported by the experimental results, which demonstrate that as the polymer content increases, the matrix degradation decreases, leading to a smaller initial burst release.

It is interesting to compare the $C_p$ and $\tau$ values of different composite fiber types and elucidate the effect of processing conditions on these parameters (through microstructure). For example, the $C_p$ value of the 16:1 sample of fibers fabricated with the same polymer content of 15% (w/v) is 2.8 times higher than that of the 8:1 sample, and for 19% (w/v) polymer fibers the $C_p$ value of the 16:1 sample is 2.4 times higher than that of the 8:1 sample. A similar trend was obtained for $\tau$: the $\tau$ value of the 16:1 sample of fibers fabricated with a polymer content of 15% (w/v) is 3.3 times higher than that of the 8:1 sample, and for 19% (w/v) polymer fibers the $\tau$ value of the 16:1 sample is 3.0 times higher than that of the 8:1 sample (Table 1). This consistent behavior of both parameters as a function of the polymer concentration can simplify the model. Although it cannot be demonstrated without additional experiments, it seems that certain calibration curves and/or functions may be developed in order to simplify the model.

The advantage of building a model for drug/protein delivery systems is the ability to elucidate the effect of the system’s parameters on the release profile of the bioactive agent. In this regard, the effect of the molecular weight of both components, PDLGA and HRP, was studied. The effect of the PDLGA molecular weight on the release rate was examined using the degradation profiles of polymers with initial molecular weights of 40 and 160 kDa, in addition to that of the standard 100 kDa used in our experiments. These degradation profiles were obtained using interpolations based on the experimental results of Wu and Wang and are presented in Figure 2. Our predicted HRP release profiles for the series of 75/25 PDLGA with three molecular weights are presented in Figure 4 for each of the studied fiber types. The decrease in initial molecular weight always resulted in an increased HRP release rate. This prediction is logical, since a lower initial molecular weight polymer will result in shorter polymer chains as degradation proceeds, giving rise to an enhanced drug release rate. It should be mentioned that the predicted release profiles are not accurate, and that the burst release values almost do not change with the initial molecular weight. This occurs mainly because the only parameter that was changed while making these predictions is the matrix degradation profile, leaving the same tortuosity factor that was calculated for the 100 kDa fiber type. However, the tortuosity factor is supposed to increase with an increase in the molecular weight. Our future work will focus on an additional minimodel that predicts the effect of various parameters on the tortuosity of the polymer and therefore enables more accurate prediction of release profiles.

The effect of HRP’s molecular weight (i.e., size) on its release profile from the various fibers was also studied using our model. The results for fiber structures with a shell prepared from an emulsion of 5% (w/w) HRP and 19% (w/v) polymer are presented in Figure 5. The predicted profiles demonstrate that the HRP release rate decreases with the increase in its molecular weight, i.e. higher molecular weight proteins exhibit a lower diffusion coefficient, which results in lower mobility in water. Since protein release occurs by means of diffusion in water, this lower diffusion coefficient should result in a lower release rate. These results support our second hypothesis, saying that the release profile is affected by the sizes of the system’s components, the bioactive agent, and the host polymer. We discovered that the effect of HRP’s size on its

![Figure 5](https://www.interscience.wiley.com)
release profile is apparently higher than that of the host polymer’s initial molecular weight.

SUMMARY AND CONCLUSIONS

The aim of this study was to develop a mathematical model for predicting protein release profiles from novel bioresorbable core/shell fiber structures designed to be used in tissue regeneration and other biomedical applications. These novel composite structures are composed of a dense polymeric core fiber coated with a porous protein-loaded PDLGA shell, and combine desired mechanical properties with versatile release profiles of the active agent. Use of the suggested model affords a good and rapid evaluation of the release profile, enabling further economical in vitro/in vivo release studies.

The model is based on Fick’s second law of diffusion and on two major assumptions: (a) first-order degradation kinetics of the porous shell, and (b) a time-dependent bioactive agent diffusion coefficient, which increases with time because of the degradation of the host polymer. The model also uses three empirical parameters that address the matrix microgeometry: porosity factor, tortuosity factor, and a polymer concentration factor that relates to the polymer concentration in the emulsion from which the matrix was fabricated.

The model correlates well with in vitro release results, exhibiting a mean error of less than 2.2% for most studied cases. The behavior (values and tendencies) of the empirical tortuosity and polymer concentration factors in the model correlated well with theory. Furthermore, the model predicts an increased polymer concentration factor for higher polymer contents, resulting in a smaller burst release and a more moderate release profile.

In this study, the model was used for predicting protein release profiles from fibers with shells of various initial molecular weights and for predicting the release of proteins with various molecular weights (sizes). This new model exhibits a potential for simulating fibrous systems for a wide variety of biomedical applications.

References