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Mathematical Model for Estimating the Diffusion Coefficients of Protein Release from Bacterial Cellulose-based Hydrogel

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ABSTRACT

To evaluate the oral protein delivery potential of pH-responsive bacterial cellulose-based hydrogels, a model protein drug was efficiently loaded into the hydrogels and the release profile was investigated in a simulated gastric fluid (SGF) and a simulated intestinal fluid (SIF). In this study, we will propose a mathematical approach to evaluating the performance of the hydrogels in the simulated gastrointestinal fluids. We start by using the power law to determine the type of the release in each fluid. Then, the swelling behaviour of the hydrogel will be studied and the least squares method will be developed to find a suitable mathematical function to represent the growth. Mathematical models for the release will be developed and solved to be used to find the concentration of the protein at a given time. The mathematical procedures for diffusion coefficient determination in SIF and SGF will be concluded in an algorithm at the end of this paper.

Keywords**:** Controlled drug delivery, swelling, hydrogel, effective diffusion coefficient.

1. Introduction

Peppas's power law has been extensively used for studying the release mechanism of drug delivery. Despite the simplicity of the method, it has been proven to successfully fit various drug release data (Siepmann and Peppas, 2001). However, the method is only suitable to fit experimental data for a fractional release rate of less than 0.6 and the information gained from the method is limited to the type of the release mechanism. The parameter that

could characterize the developed drug delivery device is not explicitly stated in the method. The exponent n and the prefactor k in equation (1) are both dependent on dosage form geometry, the relative importance of relaxation and diffusion, and structural factors governing diffusion and relaxation rates (Siepmann and Siepmann, 2012).

Mathematical models for diffusion-controlled drug release have been developed in various studies (Doumenc et al., 2001, Lu et al., 1998). The analytical solutions for the diffusion-controlled drug release models for regular geometries (Wang and Xia, 2009, Wang et al., 2009, Mohd-Mahali et al., 2011) in some ideal conditions have been derived. Numerical solutions, such as finite difference, finite volume and many more methods, have been used for more general geometries and many complicated models (Mohd-Mahali et al., 2012 and 2014). Most of the mathematical solutions have been tested using laboratory data and the usefulness has been shown in the respective papers. Although the numerical methods are able to solve a more flexible model, the huge computational time consumed for the simulation is sometimes not worth it. The diffusion-controlled model with a simplified geometry that has been analytically solved proved to be comparable with the numerical solution of the same model with a real three-dimensional geometry.

While the analytical solutions for diffusion-controlled drug delivery in various conditions are available, the analytical solution for drug delivery involving swelling effect is as yet restricted. Due to the model complexity, many researchers turn to numerical methods for such drug delivery (Siepmann et al., 1999). Different mathematical theories have been proposed in developing models for drug deliveries involving swelling devices (Siepmann and Siepmann, 2008, Bierbrauer, 2005).

In the meantime, swelling is one of the important characteristics for hydrogel devices. In the recent research by Ahmad et al. (2014), the in vitro controlled release of protein was investigated in SGF and SIF. Assuming that the release is diffusion-controlled after the fractional release reaches 0.6, the effective diffusion coefficients for the hydrogel devices have been estimated.

In the present research, we propose a mathematical algorithm that can be used to fit all protein release profiles from the same hydrogel devices in two different pH fluids. The algorithm combines the mathematical solutions for diffusion-controlled (Wang and Lou, 2009) and swelling-controlled (Bierbrauer, 2005) drug deliveries. The mathematical approach to determine the swelling behavior of the devices is also proposed in this work.

2. Problem Formulation

The Release Experiments

The studied bacterial cellulose-based hydrogels were first loaded with the model protein. Then, in order to measure the protein release from the loaded hydrogel disks, the disks were first immersed in 25 mL of SGF for 2 hour and then transferred to SIF until maximum release. At fixed intervals, the concentration of protein in the external fluid was measured. The observations showed that the hydrogels underwent a small amount of swelling in SGF and rapid swelling in SIF.

The Mathematical Model

In this section, we will introduce two different models to represent the protein release in SGF and SIF. In practice, the power law is usually used to determine the type of the release, i.e., whether it is diffusion-controlled or swelling-controlled. In the power law, the fractional drug release is represented by the following equation

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t is the amount of protein released until sampling time t, M_∞ is the total amount of protein released, k is the geometric constant characteristic of the drug delivery system, and n is the release exponent, indicating the release kinetic mechanism. Table 1 shows the release kinetic mechanism based on the value of n for the cylindrical drug device as concluded in Siepmann and Siepmann (2012).

TABLE 1: The Release Mechanism for Cylindrical Device Indicated by the Value of n in the Power Law

n	Release Kinetic Mechanism
$n = 0.45$	Fickian diffusion
$0.45 < n < 0.89$	Anomalous transport; combination of swelling-controlled and diffusion
$n = 0.89$	Polymer swelling

Thus, before deciding the appropriate mathematical model for the release profiles in SGF and SIF, the power law is used to calculate the release exponent. However, this law is only applicable for fractional release profiles

less than 0.6. It is expected for the pH-responsive bacterial-based cellulose hydrogel that the swelling effect will only occur for release in SIF.

The Diffusion Model

If the value of n shows the release mechanism is Fickian diffusion, the mathematical model can be written as

$$\frac{\partial C(x,t)}{\partial t} = D\nabla^2 C(x,t), x \in \Omega_c, t > 0, \tag{2a}$$

$$\frac{\partial C(x_c,t)}{\partial x} = 0, t > 0 \tag{2b}$$

$$C(x,0) = \begin{cases} \frac{M_0}{V_d}, & x \in \Omega_d \\ 0, & x \in \Omega_c \backslash \Omega_d \end{cases} \tag{2c}$$

where $C(x,t)$ is the concentration of the protein, D is a constant diffusion coefficient, Ω_c represents the whole region of the container containing the simulated gastrointestinal fluids and the hydrogel device and Ω_d represents the region for the hydrogel device only.

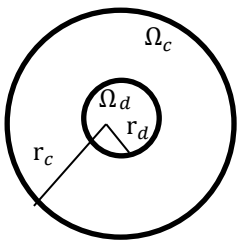

Figure 1: The 2D geometry of a disc device with radius r_d in a cylindrical container with radius r_c.

In two-dimensions, the simplified geometry of a hydrogel disc being position in a SGF/SIF full container is depicted in Figure 1. The device is assumed to be located at the centre of the container full with fluid. Based on this simplified geometry, the model can be rewritten in a cylindrical coordinate as suggested by Wang et al. (2009)

$$\frac{\partial C(r,t)}{\partial t} = D\left(\frac{\partial^2 C(r,t)}{\partial r^2} + \frac{1}{r}\frac{\partial C(r,t)}{\partial r}\right), \quad 0 < r < r_c, \quad t > 0, \tag{3a}$$

$$\frac{\partial C(r_c,t)}{\partial x} = 0, \quad t > 0, \tag{3b}$$

$$C(r,0) = \begin{cases} \frac{M_0}{V_d}, & 0 < r < r_d \\ 0, & r_d < r < r_c \end{cases} \tag{3c}$$

where r_d is the radius of the hydrogel disc and r_c is the radius of the cylindrical coordinate, considering both have the same height. The diffusion equation in this system had been solved using the separation of variable method and the formula for the total protein release until time *t* was derived as

$$M_t = \frac{M_0\sigma^2}{V_d}\left(V_c - V_d\right) - \frac{4M_0\sigma V_c}{V_d}\sum_{n=1}^{\infty}\frac{J_1^2\left(\sigma\alpha_n\right)}{\alpha_n^2 J_0^2\left(\alpha_n\right)}e^{-D\alpha_n^2 t/r_c^2} \tag{4}$$

where

$V_c = \pi r_c^2 h$ is the container volume,

$V_d = \pi r_d^2 h$ is the device volume (the height, *h* of the container and the device are assumed to be the same),

$\sigma = \frac{r_d}{r_c}$ is the ratio of the radius,

J_0 is the zeroth order Bessel function,

J_1 is the first order Bessel function and

α_n are the roots satisfying $J_0'(\alpha_n) = 0 = J_1(\alpha_n)$.

The fractional protein released is then obtained by dividing the formula for M_t with the initial drug loading, M_0 as follows

$$\frac{M_t}{M_0} = 1 - \sigma^2 - 4\sum_{n=1}^{\infty}\frac{J_1^2\left(\sigma\alpha_n\right)}{\alpha_n^2 J_0^2\left(\alpha_n\right)}e^{-D\alpha_n^2 t/r_c^2} \tag{5}$$

This formula has been used by Ahmad et al. (2014) to fit the experimental data of protein release from a swollen hydrogel disc in SIF for release beyond $\frac{M_t}{M_0} \geq 0.6$. The swelling effect had been neglected at that phase based on the assumption that the hydrogel disc had reach its fully swollen state, thus the release mechanism is assumed to be solely by diffusion. In the present research, we will use this formula when only limited swelling occurs, as it happened when the hydrogel disc was placed in SGF. However, for the release experiment in SIF which showed rapid swelling of the hydrogel, we

will consider the release mechanism to be a combination of diffusion and swelling mechanisms.

The Swelling Model

In this section, a mathematical model for protein release from the hydrogel disc in SIF will be developed. The release mechanism is believed to be swelling-controlled. Swelling-controlled in this sense means that although the swelling step is of importance, the diffusion still significantly affects the release rate. The drug diffuses out of a device that swells as fluid is absorbed. The advection-diffusion equation for a growing domain may be used to represent such a release mechanism (Bierbrauer, 2005). If we consider that the diffusion coefficient is constant, the equation is written as

$$\frac{\partial C}{\partial t} = D\nabla^2 C - \nabla(Cu) \tag{6}$$

where u is the growth velocity of the region. By only considering the region within the device and assuming the concentration is uniform at the boundary (due to stirring), the model can be written as follows

$$\frac{\partial C(\mathrm{x},t)}{\partial t} = D\nabla^2 C(\mathrm{x},t) - \nabla\big(C(\mathrm{x},t)\cdot u(\mathrm{x},t)\big), \quad \mathrm{x}\in\Omega_d(t),\ \mathrm{t}>0 \tag{7a}$$

$$C(\partial\Omega_d(t),t) = \overline{C}(t), \quad t>0, \tag{7b}$$

$$C(\boldsymbol{x},0) = 1, \quad \boldsymbol{x}\in\Omega_d(0), \tag{7c}$$

where $\boldsymbol{x}$ denotes the point in space which has coordinate (x,y,z) if in three dimensions, $\Omega_d(t)$ is the region for the swelling hydrogel device with $\partial\Omega_d(t)$ as the moving boundary. This model is rather complicated to solve analytically. We can however simplify the model by only considering one-dimensional space and applying a sink condition to the boundary. The model is now reduced to the model proposed by Bierbrauer (2005)

$$\frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C(x,t)}{\partial x^2} - C(x,t)\frac{\partial u(x,t)}{\partial x} - u(x,t)\frac{\partial C(x,t)}{\partial x}, \tag{8a}$$

$$0<x<X(t),\ t>0$$

$$C(X(t),t) = 0,\ t>0, \tag{8b}$$

$$\frac{\partial C}{\partial x}(0,t) = 0,\ t>0 \tag{8c}$$

$$C(x,0)=1,\ 0<x<X(0), \tag{8d}$$

where $X(0)=L$ is the original length of the device region before it starts swelling, $X(t)$ is the moving front of the region, $C\dfrac{\partial u}{\partial x}$ is the dilution term due to local volume change and $u\dfrac{\partial C}{\partial x}$ is the advection of elemental volumes moving with the flow. For the current disc device, we denote x =0 as the centre of the device, $X(0)=L$ is the original radius of the device and $X(t)$ is the surface of the device that been in contact with SIF. The one-dimensional model had been solved in Bierbrauer (2005) for concentration as

$$C(x,t)=\frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)}\frac{L}{X(t)}\cos\left(\frac{(2n+1)\pi x}{2X(t)}\right)e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_0^t X(\tau)^{-2}d\tau}. \tag{9}$$

Thus, the total mass release formula can be gained by subtracting the integration of the initial concentration over the original region with the integration of the concentration at time *t* over the current region

$$M_t=\int_0^{X(0)}C(x,0)dx-\int_0^{X(t)}C(x,t)dx=L-\int_0^{X(t)}C(x,t)dx. \tag{10}$$

The fractional protein release is gained by dividing the total mass release (10) with the integration of the initial concentration as follows

$$\frac{M_t}{M_0}=\frac{L-\int_0^{X(t)}C(x,t)dx}{L} \tag{11}$$

which then can be written as

$$\frac{M_t}{M_0}=1-\sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_0^t X(\tau)^{-2}d\tau} \tag{12}$$

The Growing Boundary

The solution from the previous section requires information for the function of the growing boundary, $X(t)$. The growing boundary could follow various types of function depending on the device material properties such as linear function, exponential function, logistic function and many more. In the current work, it is known that the hydrogel disc will swell up to a certain size. Therefore, the logistic function seems to be the most appropriate function to be considered. The function is in the following form

$$X(t) = \frac{Le^{rt}}{1 + (\frac{1}{m})\left(e^{rt} - 1\right)}$$

where $m = \frac{\lim_{t\to\infty} X(t)}{X(0)} = \frac{\lim_{t\to\infty} X(t)}{L}$ and r is the growth factor that speeds up or slows down the growth to its final size, mL. In order to choose the right r for our hydrogel disc, the measurements of the radius at every time interval need to be taken. Then, the least squares method can be used to determine the parameter.

By having a logistic function to represent the growth of the hydrogel, the fractional protein release formula (12) can be further reduced to

$$\frac{M_t}{M_0} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} e^{-\frac{D}{2r}\left(\frac{(2n+1)\pi}{2mL}\right)^2 \left[(m-1)^2\left(1-e^{-2rt}\right)+4(m-1)\left(1-e^{-rt}\right)+2rt\right]} \tag{13}$$

3. Determination of the Effective Diffusion Coefficient

The laboratory data for fractional protein release from the hydrogel discs are denoted as

$$\frac{M^e_{t_1}}{M_0}, \frac{M^e_{t_2}}{M_0}, \cdots, \frac{M^e_{t_G}}{M_0}$$

for protein release in SGF where t_G denotes the end time point in the release experiment in SGF and

$$\frac{M^e_{t_{G+1}}}{\tilde{M}_0}, \frac{M^e_{t_{G+2}}}{\tilde{M}_0}, \cdots, \frac{M^e_{t_K}}{\tilde{M}_0}$$

for protein release in SIF where t_K denotes the final time of the experiment and

$$\tilde{M}_0 = M_0 - M^e_{t_G}$$

is the value considered as the initial drug loading for release in SIF. Since the hydrogel acts differently in each fluid, it is important to determine the effective diffusion coefficients for the hydrogel devices separately so as to have a clear picture of the device characteristics. Effective diffusion coefficient in this research refers to a constant approximation of the real diffusion coefficient which in general can be a function of space, time and much more. The following algorithm list the steps for this estimation. The computation for the release in SGF and SIF is propose to be done separately using the following index:

$$ini = \begin{cases} 1, \text{for } t_k \le t_G \\ G+1, \text{for } t_k > t_G \end{cases} \text{ and } final = \begin{cases} G, \text{for } t_k \le t_G \\ K, \text{for } t_k > t_G \end{cases}.$$

Algorithm (perform separately for release at time $t_k \le t_G$ and $t_k > t_G$)

1. Find the optimal *n* by minimizing the following least squares function

$$E(\mathrm{k}, n) = \sum_{k=ini}^{final} \left(\frac{M^e_{t_k}}{M_0} - \mathrm{k} t_k{}^n \right)^2 w_k .$$

2. If $n \le 0.45$ calculate the fractional protein release using formula (5)

$$R(t_k, D) = \frac{M_{t_k}}{M_0} = 1 - \sigma^2 - 4\sum_{n=1}^{\infty} \frac{J_1^2(\sigma\alpha_n)}{\alpha_n^2 J_0^2(\alpha_n)} e^{-D\alpha_n^2 t_k / r_c^2}$$

else

- Find the growth factor *r* by minimizing the following least squares function

$$E(r)=\sum_{k=ini}^{final}\left(X^{e}(t_k)-\frac{Le^{rt_k}}{1+(\frac{1}{m})\left(e^{rt_k}-1\right)}\right)^2 w_k.$$

- calculate the fractional protein release using formula (13)

$$R(t_k,D)=\frac{M_{t_k}}{M_0}=1-\sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}e^{-\frac{D}{2r}\left(\frac{(2n+1)\pi}{2mL}\right)^2\left[(m-1)^2\left(1-e^{-2rt_k}\right)+4(m-1)\left(1-e^{-rt_k}\right)+2rt_k\right]}.$$

3. Find the optimal D by minimizing the following least squares function

$$E(D)=\sum_{k=ini}^{final}\left(\frac{M^{e}_{t_k}}{M_0}-R(t_k,D)\right)^2 w_k.$$

4. Conclusions

The protein release experiments from a PH-responsive bacterial cellulose-based hydrogel have been done in SIF and SGF (Ahmad, 2014). It is important to determine the effective diffusion coefficients of the developed devices in both fluids in order to predict the behaviour of the devices in the gastrointestinal track. In this study, we proposed an algorithm to determine the parameters. The algorithm is a combination of an analytical solution of diffusion-controlled drug delivery from a disc device (Wang and Lou, 2009) and a one-dimensional analytical solution from a swelling-controlled drug delivery device (Bierbrauer, 2005).

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