Numerical Simulation of Two Phase Mathematical Model for Transportation of Mass and Drug from Drug Eluting Stents

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Abstract. A two phase coupled mathematical model for investigating the drug release in drug eluting stents is developed in this study. The release of drug in coating is modeled by the convection-diffusion equation while drug delivery in arterial wall is modeled by diffusion equation. This research explores the impact of non-dimensional parameters on drug release and mass concentrations from coating and arterial tissue having different dimensions and properties. Moreover, it is noted that the drug release speed and the timing of peak bound drug concentrations can be controlled by varying the values of ratio of available volume fraction to solid fraction $e_1$ and solid-liquid mass transfer parameter $\gamma$. The governing equations together with suitable initial and boundary conditions are numerically solved by finite element method. The obtained time dependent system of ordinary differential equations are solved by backward difference and Galerkin difference time marching schemes in order to calculate the results with desired degree of accuracy. This bilayer model is useful for providing better understanding of the mechanism of mass transfer in coating and tissue layers. Furthermore, for different times, the drug release profiles in both layers are presented graphically so as to verify the application of the considered model.

Keywords and phrases: Drug Release, Diffusion, Finite Element Method, Porous Medium, Drug-Eluting Stent, Convection-Diffusion-Reaction Equation, Mass Transport

Mathematics Subject Classification: 35Q53, 34B20, 35G31

1. Introduction

Organized drug delivery in drug eluting stents (DES) exerts an important influence in decreasing restenosis, ‘the re-narrowing of the arterial wall’, in intravascular stenting \cite{1, 2}. Drug eluting stents have an added benefit of a variable representing time delivery of a curative drug to the neighboring arterial tissue that treats the required injuries efficiently with negligible systemic drug interaction \cite{3, 4}. These devices are coated with drug in order to avoid restenosis, the re-narrowing of the arterial wall, which is associated with the original bare metal stents. One of the major advantages of DES over oral drug administration is

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the capability to transport a controlled amount of drug directly to the site where it is needed the most, while the damage that is resulted from the stent insertion is repairable. The release of drug is typically controlled by containing it inside the polymer coating which is on the surface of the stent. From the manufacturing and medical points of view, a careful consideration to the stent design is of great concern so that the required drug concentration is accomplished in the arterial wall over the entire healing duration. If too much drug is delivered too quickly, it may have a toxic or short term effect, and if the drug is delivered too slow or at sufficiently low concentration, then the arterial wall may not feel any therapeutic effect at all [5]. Hence the therapeutic success is dependent on many factors such as the rate of discharge, the extent of drug elution, amassing of drug and holding together of components within the tissue [6].

Furthermore, for manufacturers, this process is convenient to examine the value of the product along with the absence of variation in the discharge profiles. Manufacturers of stents primarily use scientifically based methods, which when joined with suitable modeling and the in vitro experiments may offer them insight into the mechanism of discharge, further making this a controversial issue in literature with dissolution, degradation, diffusion and polymer swelling; hence all of these issues are contextualized as possible discharge mechanisms. Many attempts have been made to design the drug transport from these devices. For instance, suggesting to polymer coated drug eluting stents, which is the nexus of this research [7], a critical answer is presented to a cylindrical diffusion model in order to designate the experimental drug transport of everolimus from a Dynalink-E stent while a mathematical model is designated by [8] that calculates the drug transport from a drug eluting stents coating, founded on two distinct means of transport. Many research models are in unanimous agreement that Fickian diffusion plays a significant part in the transport procedure. Noticeable objective consensus are that of modeling of diffusion controlled drug transport, the discharge of drug from reservoir, massive and constant drug transport systems and drug release from biodegradable polymers which have been the focus of many researchers. Many of their solutions are time approximated earlier or later, and in many other cases analytical and numerical solutions are discussed [9-12].

In reality, the mutual system of stent and the arterial wall have established much concern in the literature, as almost all of the models must be explained numerically because of the intricacy of the statement. For this purpose a drug release model based on diffusion together with convection and diffusion in the arterial wall is discussed by [13] in a research that also explains drug intake via a linear reaction. Separation of variables method is used to obtain analytical solutions and it is also used to display drug metabolism, amount of drug in the tissue and the effect of transmural velocity. Presently, a semi-experimental manifestation for the concentration of drug in all layers of the artery wall, where drug essentially dissolves in the polymer region before it may diffuse, is presented by [14]. Models that include more elegant binding reaction terms incorporate those of [15-18] and they all undertake an equilibrium reaction. While [16] has made some experimental development, the other authors exploit numerical methods to explain their equations. It is suggested that the most important model is that of [6], that presents a second order reversible binding model, which is explained not only statistically but also contains some parameters which are hard to measure analytically. There is an abundance of research work on drug release modeling from arterial stents, and consequently drug distribution within the arterial wall [19]. Hence most authors suppose that drug existing in the polymer coating in a form can immediately be available to be transferred to the arterial wall after implantation. Typically, independent of space, concentration and time, the drug in the coating is supposed to obey a diffusion equation with diffusion coefficient, while previous studies have combined modelling with experiments to demonstrate that this assumption is appropriate for a number of commercially available stents [7, 16].

However, the drugs that are commonly coated on DES are known to be highly lipophilic and poorly soluble [20] and so how the drug is able to leave the polymer coating and be transported into the arterial wall is ambiguous. The most common theory is that biological fluid that penetrates the polymer coating provides a means for the drug to diffuse after its dissolution as the drug typically exists in the coating in an encapsulated form. Therefore, a number of papers have been written on the dissolution of solid particles in liquids. Starting from the pioneering paper of Higuchi, [21] some authors have considered drug
dissolution from a polymer in a theoretical framework [22, 23] while others have adopted a computational approach [24]. Most of these works are based on the assumption of a substrate matrix fully wetted and hypothesize mono-dispersed finite-sized spherical-grained drug particles [25, 26]. Moreover, in this study we consider the role of convection on drug release as it has not been previously considered [27, 28]. It is supposed in this attempt that the drug initially resides wholly in the solid fraction of the porous medium and the solid region works as a drug container where the drug exists in its solid phase initially. Consequently, after stent insertion and deployment, the solid drug is first changed into fluid phase at rate dependent on the characteristics, the rate of flow and porosity of the drug before undergoing diffusion. In other words, solid drug must undergo a solid-liquid mass transfer process before it is biologically available to diffuse in and out of the coating.

In what follows, we have attempted to build upon the aforementioned works by devising a novel, two-layered, two-phased model of transportation of drug from drug-eluting stents and subsequent tissue absorption. Hence Partial differential equations system is employed which sketches out both solid and liquid mass transport and diffusion procedures in the polymer region along with convection, diffusion and reaction in the tissue phase. Numerical approach is adopted in this attempt in order to answer the specific question of what influences solid-liquid mass transfer and fraction of accessible void volume to the solid volume in the coating and arterial wall drug concentrations. Since these parameters may be adjusted at the manufacturing stage, we are trying to investigate the potential effect of increasing and decreasing the solid-liquid mass transfer rate and fraction of accessible void volume to solid volume on the coating and wall concentrations.

2. Material and Methods

A two-layer system, consisting of a polymeric platform that initially contains drugs, is examined in order to model DES along with the arterial wall where the drug is directed that also applies a therapeutic effect as shown in Figure 1.

First layer is mapped out as a thin planar block, with one side surrounded with a sealed backing (metallic strut) connected with second layer. A membrane that controls the rate and protects the polymer region may exist at the interface of two layers. The drug release significantly depends on the characteristics of coupled system. Mass dynamics takes place along normal direction to the surface of tissue, thus the modeling may sensibly be limited to a simplified unidimensional case. Let \( x = 0 \) be the interface, without the loss of generality and let \( L_1 \) and \( L_2 \) be the thicknesses of the layer (i) and layer (ii), respectively, as shown in Figure 1.

3. Dynamical Model of Drug Release in Tissue and Polymer

Primarily, the whole existence of drug enclosed inside the polymer region (e.g. in crystalline or nanoparticles form) \( (c_{solid}^1) \) can be delivered to the tissue in such a state. However, it is hypothesized, like in the in
vivo case, that polymer matrix becomes wet when it is exposed to biological fluid, starting a solid-liquid mass transfer (dissolution) process which transforms the solid drug to a biologically available free phase ($c_{1}^{fluid}$), providing a source for the drug to separate from the device. Compared to the other models of finite dissolution [25], we do not make any supposition on the shape of the solid particles, rather it is supposed that fluid phase ($c_{1}^{fluid}$) and solid ($c_{1}^{solid}$) exist contemporaneously and the transferring rate of the drug from the solid to fluid phase is proportional to the difference between $c_{1}^{solid}$ and $c_{1}^{fluid}$. It is also acknowledged that the solubility of drugs coated on stents is typically poor and the simultaneous dissolution and diffusion of dissolved drug through and beyond the coating and into the connected tissue layer ensure that we remain far from the solubility limit. This is in contrast to insulated systems where poor solubility becomes an important consideration.

Figure 2. Schematic of a finite polymeric matrix with a drug barrier.

Following the solid liquid mass transfer procedure, the available drug in coating diffusing through the first layer crosses the interface into the arterial wall. Inside the arterial tissue the unbound drug experiences diffusion as well as convection because of the difference in transmural pressure across the arterial wall. Furthermore, the drug may not be bound irreversibly to the particular tissue components; actually, the drug is generally directed to bind to specific receptors within smooth muscle cells. Therefore we are trying to model the unbinding and binding process as a first order reaction [17] and similar equations are used to examine the solid liquid mass transfer. On the other hand, different reaction rates between the reverse and forward reactions are considered, for example, $\beta_2$ and $\delta_2 \geq 0(s^{-1})$ which is defined as the opposite of the time scale of the reverse and forward reaction, respectively. They are joined with the equilibrium dissociation constant, $K_2 = \delta_2/\beta_2$, which is a parameter usually measured experimentally. Here we have employed the bound and free drug concentrations as $c_{1}^{b}$ and $c_{1}^{f}$, respectively. The dynamic equations of drug in terms of intrinsically averaged concentrations in layer (i) are [29].

\[
(1 - \epsilon_1) \frac{\partial c_{1}^{b}}{\partial t} = (1 - \epsilon_1)D_1 \frac{\partial^2 c_{1}^{b}}{\partial x^2} - \frac{hk_1 \epsilon_1}{r_h} (c_{1}^{s} - c_{1}^{f}) \quad in \quad (-L_1, 0)
\]

\[
k_1 \epsilon_1 \frac{\partial c_{1}^{f}}{\partial t} = k_1 \epsilon_1 D_1 \frac{\partial^2 c_{1}^{f}}{\partial x^2} + \frac{hk_1 \epsilon_1}{r_h} (c_{1}^{s} - c_{1}^{f}) \quad in \quad (-L_1, 0)
\]
where $h$ is the coefficient of mass transfer and $r_h$ is the hydraulic radius (free flow area over wetted perimeter). $D_s^2$ and $D_1$ are diffusion coefficients in solid and fluid phases. Thus, the drug dynamic in the artery wall is directed by the reaction-convection diffusion equation.

\[
\frac{\partial c_f^2}{\partial t} = \frac{\partial}{\partial x} \left( D_2 \frac{\partial c_f^2}{\partial x} - uc_f^2 \right) - \beta_2 c_f^2 - \delta_2 c_s^2 \quad \text{in} \quad (0, L_2) \quad (3.3)
\]

\[
\frac{\partial c_s^2}{\partial t} = k_2 c_f^2 \left( \beta_2 c_f^2 - \delta_2 c_s^2 \right) \quad \text{in} \quad (0, L_2) \quad (3.4)
\]

where $D_2$ is the diffusivity of free drug and $u$ is the magnitude of the convection, which acts in the positive $x$ direction. A supposition is made that the drug is unable to diffuse within the bound components. In the continuum process, a permeable medium may be indicated as an identical material by defining averaged variables over a large enough volume, the representative volume $V_{rve}$, since the medium is porous and has a uniform material. Let us define porosity $\epsilon = \frac{\text{pore volume}}{\text{total volume}}$, the total volume is $V_{rve} = V_{rve}^{\text{fluid}} + V_{rve}^{\text{solid}}$, the subscript rve stands for representative volume element. In addition, if all the penetrable and passing pores are not accessible to the drug, a partition coefficient $k$ is used in such situation, such that $k\epsilon$ is the available void volume. The fraction of accessible void volume to the solid volume is denoted by $e$ and is defined as:

\[
e = \frac{V_v}{V_s} = \frac{V_v}{V_T - V_v} = \frac{k\epsilon}{1 - \epsilon} \quad (3.5)
\]

There are two different methods that define average concentration over a volume. First method is established on volume of every phase containing rve, for the accessible fluid phase it is $kV_{rve}^{\text{fluid}}$ and $V_{rve}^{\text{solid}}$ for the solid-phase. The second method is established to average over the entire volume ($V_{rve} = V_{rve}^{\text{fluid}} + V_{rve}^{\text{solid}}$), [29]. The volume-averaged drug concentrations $c^f$ and $c^b$ are associated with intrinsic volume averaged concentration of drug in solid phases and accessible fluid $c_s^{\text{solid}}$ and $c_s^{\text{fluid}}$ as:

\[
c^f = k\epsilon c^{\text{fluid}}, c^b = (1 - \epsilon) c^{\text{solid}}
\]

Thus, drug dynamics equations in coating and arterial wall in terms of intrinsically volume averaged concentrations are Equation (3.6)

\[
\frac{\partial c_1^b}{\partial t} = -\gamma_1 (e_1 c_1^b - c_1^f) \quad \text{in} \quad (-L_1, 0) \quad (3.7)
\]

\[
\frac{\partial c_1^f}{\partial t} = D_1 \frac{\partial^2 c_1^f}{\partial x^2} + \gamma_1 (e_1 c_1^b - c_1^f) \quad \text{in} \quad (-L_1, 0) \quad (3.8)
\]

\[
\frac{\partial c_2^f}{\partial t} = \frac{\partial}{\partial x} \left( D_2 c_2^f - uc_2 \right) - \beta_2 \left( \frac{c_2^f}{K_1} - e_2 c_2^b \right) \quad \text{in} \quad (0, L_2) \quad (3.9)
\]

\[
\frac{\partial c_2^b}{\partial t} = \delta_2 \left( \frac{c_2^f}{K_1} - e_2 c_2^b \right) \quad \text{in} \quad (0, L_2) \quad (3.10)
\]

where $\gamma_1$ is the ratio of solid-liquid mass transfer coefficient and the hydraulic radius.

### 3.1. Initial and boundary conditions

The initial conditions are:

\[
c_1^b(x, 0) = C_1, c_1^f(x, 0) = c_2^f(x, 0) = c_2^b(x, 0) = 0
\]

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where $C_1$ is the release of drug in the coating initially. The flux continuity condition is considered at the interface of both layers.

$$-D_1 \frac{\partial c_1^f}{\partial x} = -D_2 \frac{\partial c_2^f}{\partial x} + uc_2^f \quad \text{at} \quad x = 0$$

In order to decelerate the rate of drug, a permeable membrane with permeability $P$ is founded at the interface between the wall and coating. A uniform mass flux moves through it orthogonally to the coating film with a large concentration jump owing to the very dissimilar physical properties between coating and arterial walls. The mass transporting from the topcoat can be defined using the following equation [30],

$$-D_2 \frac{\partial c_2^f}{\partial x} = P\left(\frac{c_1^f}{k_1 \epsilon_1} - \frac{c_2^f}{k_2 \epsilon_2}\right) \quad \text{at} \quad x = 0$$

The impermeable backing does not allow mass flux to pass to the outer surrounding therefore applying no-flux boundary condition:

$$D_1 \frac{\partial c_1^f}{\partial x} = 0 \quad \text{at} \quad x = -L_1$$

Further, we assume vanishing of concentration at the outer boundary $L_2$.

$$c_2^f = 0 \quad \text{at} \quad x = L_2$$

4. Non-Dimensionalization

For Non-dimensionalization the scale of variables and resulting parameters are as under:

$$\xi = \frac{x}{L_2}, \quad \tilde{t} = \frac{D_1 t}{L_2^2}, \quad \tilde{c}_1^f = \frac{c^f}{C_1}, \quad \tilde{c}_1 = \frac{c_i}{C_1} \quad (4.1)$$

Hence, the terms reaction and convection are governed by the dimensionless groups,

$$D = \frac{D_1}{D_2}, \quad L = \frac{L_1}{L_2}, \quad \gamma = \frac{\gamma_1 L_1^2}{L_2^2}, \quad \sigma = \frac{k_2 \epsilon_2}{k_1 \epsilon_1}, \quad \phi = \frac{P L_2}{D_2 k_1 \epsilon_1}, \quad Pe = \frac{u L_2}{D_2}, \quad Da = \frac{\beta_2 L_2^2}{D_2}$$

The resulting non dimensional equations become

$$\frac{\partial \tilde{c}_1^f}{\partial \tilde{t}} = -\gamma (e_1 \tilde{c}_1^b - \tilde{c}_1^f) \quad \text{in} \quad (-L, 0) \quad (4.2)$$

$$\frac{\partial \tilde{c}_1^f}{\partial \tilde{t}} = D \frac{\partial^2 \tilde{c}_1^f}{\partial \tilde{x}^2} + \gamma (e_1 \tilde{c}_1^b - \tilde{c}_1^f) \quad \text{in} \quad (-L, 0) \quad (4.3)$$

$$\frac{\partial \tilde{c}_2^f}{\partial \tilde{t}} = \frac{\partial^2 \tilde{c}_2^f}{\partial \tilde{x}^2} - Pe \frac{\partial \tilde{c}_2^f}{\partial \tilde{x}} + Da(c_2^f - K_2 e_2 \tilde{c}_2^b) \quad \text{in} \quad (0, 1) \quad (4.4)$$

$$\frac{\partial \tilde{c}_2^b}{\partial \tilde{t}} = Da(c_2^f - K_2 e_2 \tilde{c}_2^b) \quad \text{in} \quad (0, 1) \quad (4.5)$$

where $Pe$ and $Da$ are the Peclet and Damkohler numbers, respectively. An important feature of drugs that are commonly coated on stents (e.g., sirolimus, paclitaxel and other limus compounds) is their tenacious binding properties; such properties ensure that the drug is strongly retained within tissue and thus exerts the desired effect for long time. In practice, this means that the time scale for binding is significantly lesser than that of convection and diffusion. Whilst there is a large degree of variation in
the literature relating to the magnitude of convection, diffusion and binding parameters, it is usual for the Peclet number to be less than 1 and the Damkohler number to be much greater than 1, that shows reaction dominates over diffusion which in turn is more important than convection [6]. In addition, [31] has compared the variation in total amount of drug with and without convection and has found that the results are barely distinguishable. In this way the initial and boundary conditions become:

\[
\begin{align*}
\frac{\partial c_1^f}{\partial x} &= 0 \quad \text{at} \quad x = -L \\
-D \frac{\partial c_1^f}{\partial x} &= \frac{\partial c_2^f}{\partial x} \quad \text{at} \quad x = 0 \\
\frac{\partial c_2^f}{\partial x} &= \phi (\sigma c_1^f - c_2^f) \quad \text{at} \quad x = 0 \\
0 &= \quad \text{at} \quad x = 1 \\
c_1^b = 0, c_1^f = c_2^f = c_2^b = 0 \quad \text{at} \quad t = 0
\end{align*}
\]

(4.6)

Table 1. Values of dimensional parameters are chosen from the extensive literature which is used for simulation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion coefficient in coating</td>
<td>(D_1)</td>
<td>(10^{-10} \text{cm}^2\text{s}^{-1})</td>
</tr>
<tr>
<td>Effective diffusivity of free drug</td>
<td>(D_2)</td>
<td>(7.10^{-8} \text{cm}^2\text{s}^{-1})</td>
</tr>
<tr>
<td>Permeability of topcoat</td>
<td>(P)</td>
<td>(10^{-6} \text{cm}^2\text{s}^{-1})</td>
</tr>
<tr>
<td>Thicknesses of coating</td>
<td>(L_1)</td>
<td>(5.10^{-3} \text{cm})</td>
</tr>
<tr>
<td>Unbinding rate constants</td>
<td>(\delta_2)</td>
<td>(10^{-4} \text{s}^{-1})</td>
</tr>
<tr>
<td>Partition coefficient in coating</td>
<td>(k_1)</td>
<td>1</td>
</tr>
<tr>
<td>Partition coefficient in tissue</td>
<td>(k_2)</td>
<td>1</td>
</tr>
<tr>
<td>Equilibrium dissociation constant</td>
<td>(K_2)</td>
<td>(\frac{\delta_2}{\beta_2})</td>
</tr>
<tr>
<td>Porosity coefficient in coating</td>
<td>(\epsilon_1)</td>
<td>0.1, 0.5, 0.9</td>
</tr>
<tr>
<td>Porosity coefficient in tissue</td>
<td>(\epsilon_2)</td>
<td>0.61</td>
</tr>
<tr>
<td>Thicknesses of tissue</td>
<td>(L_2)</td>
<td>(5.10^{-2} \text{cm})</td>
</tr>
<tr>
<td>Transmural velocity</td>
<td>(u)</td>
<td>(5.8 \times 10^{-2} \text{cm}^2\text{s}^{-1})</td>
</tr>
<tr>
<td>Binding rate constants</td>
<td>(\beta_2)</td>
<td>(10^{-3} \text{s}^{-1})</td>
</tr>
<tr>
<td>Ratio of accessible void volume to</td>
<td>(e_2)</td>
<td>(\frac{k_2 \epsilon_2}{1 - \epsilon_2})</td>
</tr>
<tr>
<td>solid volume in tissue layer</td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>Ratio of accessible void volume to</td>
<td>(e_1)</td>
<td>(\frac{k_1 \epsilon_1}{1 - \epsilon_1})</td>
</tr>
<tr>
<td>solid volume in coating layer</td>
<td></td>
<td>0.111, 1.9</td>
</tr>
</tbody>
</table>

5. Numerical Simulations and Results

The non-dimensional Equations (4.2 - 4.5) with prescribed conditions in Equation (4.6) are explained by finite element method by splitting the interval \((-L, 0)\) into \(n + 1\) equispaced nodes \(x_i = (i - n)h_1, \ i = 0, 1, \ldots n\) and the interval \((0, 1)\) with \(n_1 + 1\) nodes points \(x_i = ih_2, \ i = 0, 1, \ldots n_1\). Here, \(h_1\) and \(h_2\) represent the spacing for tissue and coating layers, respectively. In order to solve Equations (4.2 - 4.5) that are subjected to the initial boundary conditions Equation (4.6), by using FEM, the domain is discretized into finite number of subdomains which are called finite element and then the weighted residual method [32, 33] is applied to Equations (4.2 - 4.5) over the element. Multiplying by weight function \(W_1\), these Equations take the form:
\[
\int_{\Omega_e} \left[ \frac{\partial c_b^f}{\partial t} - \frac{\partial c_b^f}{\partial x} - D \frac{\partial^2 c_b^f}{\partial x^2} + \gamma (e_1 c_b^f - c_b^f) \right] d\Omega_e = 0
\]  

(5.1)

where \( W_1 \) is the arbitrary weight function, \( c_b^f, c_1^f, c_2^f \) and \( c_b^b \) are the approximate solutions for the free and bound drug concentrations, respectively. Integrating above equations by parts along a typical element:

\[
\int_{\Omega_e} W_1 \left[ \frac{\partial c_b^f}{\partial t} + \gamma (e_1 c_b^f - c_b^f) \right] d\Omega_e = 0
\]  

(5.2)

\[
\int_{\Omega_e} W_1 \left[ \frac{\partial c_1^f}{\partial t} + \gamma (e_1 c_1^f - c_1^f) \right] d\Omega_e - D \int_{\Omega_e} \frac{\partial W_1}{\partial x} \frac{\partial c_b^f}{\partial x} d\Omega_e + D \int_{\Gamma_e} W_1 n_x \frac{\partial c_b^f}{\partial x} ds = 0
\]  

(5.3)

\[
\int_{\Omega_e} W_1 \left[ \frac{\partial c_2^f}{\partial t} + Pe \frac{\partial c_2^f}{\partial x} - Da (c_b^f - K_2 c_2^b) \right] d\Omega_e - \int_{\Omega_e} \frac{\partial W_1}{\partial x} \frac{\partial c_2^f}{\partial x} d\Omega_e + \int_{\Gamma_e} W_1 n_x \frac{\partial c_2^f}{\partial x} ds = 0
\]  

(5.4)

\[
\int_{\Omega_e} W_1 \left[ \frac{\partial c_b^b}{\partial t} - Da (c_b^f - K_2 c_2^b) \right] d\Omega_e = 0
\]  

(5.5)

The semi discrete FEM model of Equations (5.2 - 5.5) is obtained by substituting a finite element approximation for the dependent variables, \( c_1^f, c_1^b, c_b^f \) and \( c_2^b \). It is assumed that weight functions are approximated by \( N_i \). In selecting the approximation for \( c_b^f, c_1^f, c_b^f, c_2^b \) and \( t \), it is supposed that the dependence of time can be separated from the space variation.

\[
c_b^f(x) = \sum_{j=1}^{n} N_j(x) c_b^f; c_1^f(x) = \sum_{j=1}^{n} N_j(x) c_1^f; c_b^f(x) = \sum_{j=1}^{n} N_j(x) c_b^f; c_2^b(x) = \sum_{j=1}^{n} N_j(x) c_2^b
\]  

(5.6)

### 5.1. Special Discretization

The solutions of dependent variables which are under consideration are approximated by expressions of the form Equation (5.6), and the spatial finite element model is developed using the procedures of steady state problems while carrying all time dependent terms in the formulation. This step results in a set of time dependent ordinary differential equations. Using Equation (5.6) into Equations (5.2 - 5.5), we get

\[
\int_{\Omega_e} N_i [N_j \frac{\partial c_b^f}{\partial t} + \gamma (N_j e_1 c_b^f - N_j c_b^f)] d\Omega_e = 0
\]  

(5.7)

\[
\int_{\Omega_e} N_i [N_j N_j \frac{\partial c_1^f}{\partial t} + \gamma (N_j e_1 c_b^f - N_j c_b^f) - D \frac{\partial N_i}{\partial x} \frac{\partial c_1^f}{\partial x} c_b^f] d\Omega_e + D \int_{\Gamma_e} N_i n_x \frac{\partial N_i}{\partial x} c_b^f ds = 0
\]  

(5.8)

\[
\int_{\Omega_e} N_i [N_j \frac{\partial c_2^f}{\partial t} + Pe \frac{\partial N_i}{\partial x} c_2^f - Da N_j (c_b^f - K_2 c_2^b) - \frac{\partial N_i}{\partial x} \frac{\partial N_j}{\partial x} c_2^f] d\Omega_e + \int_{\Gamma_e} N_i n_x \frac{\partial N_i}{\partial x} c_2^f ds = 0
\]  

(5.9)

\[
\int_{\Omega_e} N_i [N_j \frac{\partial c_b^b}{\partial t} - Da N_j (c_b^f - K_2 c_2^b)] d\Omega_e = 0
\]  

(5.10)
Suppose
\[ M_{ij}^{11} = \int_{\Omega} N_i N_j d\Omega, \quad k_{ij}^{11} = \gamma e_1 \int_{\Omega} N_i N_j d\Omega = k_{ij}^{21} \]
\[ k_{ij}^{22} = \int_{\Omega} [\gamma N_i N_j - \frac{\partial N_i}{\partial x} \frac{\partial N_j}{\partial x}] d\Omega, \quad k_{ij}^{12} = \gamma \int_{\Omega} N_i N_j d\Omega \]
\[ k_{ij}^{33} = \int_{\Omega} [PeN_i \frac{\partial N_j}{\partial x} - Da N_i \frac{\partial N_j}{\partial x} - \frac{\partial N_i}{\partial x} \frac{\partial N_j}{\partial x}] d\Omega, \quad k_{ij}^{34} = -DaK_2 \int_{\Omega} N_i N_j d\Omega \]
\[ k_{ij}^{44} = -DaK_2 \int_{\Omega} N_i N_j d\Omega, \quad k_{ij}^{43} = -Da \int_{\Omega} N_i N_j d\Omega \]
\[ q_1 = 0, \quad q_2 = D \int_{\Gamma_n} N_i n_x \frac{\partial N_j}{\partial x} ds, \quad q_3 = \int_{\Gamma_n} N_i n_x \frac{\partial N_j}{\partial x} ds, \quad q_4 = 0 \]

Equations (5.7 - 5.10) take the following form
\[ M_{ij}^{11} \frac{\partial c_j^b}{\partial t} + k_{ij}^{11} c_{1j}^b - k_{ij}^{12} c_{1j}^f = f_1 + q_1 \]  
(5.11)
\[ M_{ij}^{11} \frac{\partial c_j^f}{\partial t} + k_{ij}^{21} c_{1j}^b + k_{ij}^{22} c_{1j}^f = f_2 + q_2 \]  
(5.12)
\[ M_{ij}^{11} \frac{\partial c_j^e}{\partial t} + k_{ij}^{33} c_{2j}^f + k_{ij}^{34} c_{2j}^b = f_3 + q_3 \]  
(5.13)
\[ M_{ij}^{11} \frac{\partial c_j^b}{\partial t} - k_{ij}^{43} c_{2j}^f + k_{ij}^{44} c_{2j}^b = f_4 + q_4 \]  
(5.14)

The Matrix form of Equations (5.11 - 5.14) become:
\[
\begin{bmatrix}
M_{ij}^{11} & 0 & 0 & 0 \\
0 & M_{ij}^{11} & 0 & 0 \\
0 & 0 & M_{ij}^{11} & 0 \\
0 & 0 & 0 & M_{ij}^{11}
\end{bmatrix}
\begin{bmatrix}
\frac{\partial c_j^b}{\partial t} \\
\frac{\partial c_j^f}{\partial t} \\
\frac{\partial c_j^e}{\partial t} \\
\frac{\partial c_j^b}{\partial t}
\end{bmatrix}
+ 
\begin{bmatrix}
k_{ij}^{11} & k_{ij}^{12} & 0 & 0 \\
k_{ij}^{21} & k_{ij}^{22} & 0 & 0 \\
k_{ij}^{33} & k_{ij}^{34} & 0 & 0 \\
k_{ij}^{43} & k_{ij}^{44} & 0 & 0
\end{bmatrix}
\begin{bmatrix}
c_{1j}^b \\
c_{1j}^f \\
c_{2j}^f \\
c_{2j}^b
\end{bmatrix}
= 
\begin{bmatrix}
f_1 \\
f_2 \\
f_3 \\
f_4
\end{bmatrix}
+ 
\begin{bmatrix}
q_1 \\
q_2 \\
q_3 \\
q_4
\end{bmatrix}
\]  
(5.15)

Equation 5.15 is called the semi discrete form of finite element model. To obtain fully discretized model we have to discretize time derivatives of dependent variables.

5.2 Temporal discretization

The system of ordinary differential Equation (5.15) is further approximated in time by applying finite difference methods [34]. This system allows conversion of the system of ODEs into a system of algebraic equations among dependent variables at time \( t_{i+1} = (i + 1)\Delta t \) where \( \Delta t \) is the time increment and \( i \) is a non-negative integer. All time approximation schemes seek to find solutions using known values of previous times. The variation in velocity with respect to time domain between \( n \) and \( n + 1 \)th time levels can be calculated by using backward and Galerkin difference schemes. The system of equations by applying backward difference method becomes:
\[ [M_{ij}^{11} + \Delta tk_{ij}^{11}](c_j^b)^{n+1} = M_{ij}^{11}(c_{1j}^b)^n + \Delta tk_{ij}^{12}(c_{1j}^f)^n + \Delta tF_1 \]  
(5.16)
\[ [M_{ij}^{11} + \Delta tk_{ij}^{22}](c_j^b)^{n+1} = M_{ij}^{11}(c_{2j}^b)^n - \Delta tk_{ij}^{21}(c_{2j}^b)^n + \Delta tF_2 \]  
(5.17)
\[ [M_{ij}^{11} + \Delta t k_{ij}^{33}](c_2^f)^{n+1} = M_{ij}^{11}(c_2^f)^n + \Delta t k_{ij}^{34}(c_2^b)^n + \Delta t F_3 \]  
(5.18)

\[ [M_{ij}^{11} + \Delta t k_{ij}^{44}](c_2^b)^{n+1} = M_{ij}^{11}(c_2^b)^n + \Delta t k_{ij}^{43}(c_2^f)^n + \Delta t F_4 \]  
(5.19)

The system of equations by applying Galerkin finite difference Method

\[ [M_{ij}^{11} + \frac{3}{2} \Delta t k_{ij}^{11}](c_1^f)^{n+1} = M_{ij}^{11}(c_1^f)^n + \frac{3}{2} \Delta t k_{ij}^{21}(c_1^b)^n + \frac{3}{2} \Delta t F_1 \]  
(5.20)

\[ [M_{ij}^{11} + \frac{3}{2} \Delta t k_{ij}^{22}](c_1^b)^{n+1} = M_{ij}^{11}(c_1^b)^n - \frac{3}{2} \Delta t k_{ij}^{21}(c_1^b)^n + \frac{3}{2} \Delta t F_2 \]  
(5.21)

\[ [M_{ij}^{11} + \frac{3}{2} \Delta t k_{ij}^{33}](c_2^f)^{n+1} = M_{ij}^{11}(c_2^f)^n - \frac{3}{2} \Delta t k_{ij}^{34}(c_2^b)^n + \frac{3}{2} \Delta t F_3 \]  
(5.22)

\[ [M_{ij}^{11} + \frac{3}{2} \Delta t k_{ij}^{44}](c_2^b)^{n+1} = M_{ij}^{11}(c_2^b)^n + \frac{3}{2} \Delta t k_{ij}^{33}(c_2^f)^n + \frac{3}{2} \Delta t F_4 \]  
(5.23)

Interpolation functions, known data, and secondary variables are used to calculate the matrices given in all above equations. Equations (5.16 - 5.19) and (5.20 - 5.23) provide a system of equations and we can solve them by any suitable iterative method. The PDEs system is reduced to an ordinary differential equations system after spatial discretization and can be written in matrix form as [35]:

\[ \frac{dX}{dt} = A(X) \]  
(5.24)

where \( X = (c_1^{(b,0)}, c_1^{(b,1)}, \ldots, c_1^{(b,n)}, c_1^{(f,0)}, c_1^{(f,1)}, \ldots, c_1^{(f,n)}, c_2^{(f,0)}, c_2^{(f,1)}, \ldots, c_2^{(f,m)}, c_2^{(b,0)}, c_2^{(b,1)}, \ldots, c_2^{(b,m)})^T \) and \( A(X) \) contains \( 2(n + n_1) \) discretized equations. To confirm the correctness of the numerical solution, the system (5.24) is solved by two different time marching schemes, backward finite difference (BD) and Galerkin finite difference schemes (GD). Moreover, zero flux conditions are applied at \( x = L \) and \( x = 1 \) and calculate the total mass of drug in the system with time to ensure mass conservation. The mass of drug in each layer is simply calculated by using the following concentration integral (5.25).

\[ M_j(t) = \int j(x,t)dt \quad j = c_b^1, c_f^1, c_f^2 \]  
(5.25)

Thus the purpose of this study is to investigate the effect of solid liquid mass transport in the coating on the drug concentrations that are achieved within the arterial wall. Hence we are struggling to investigate the varying effect on solid liquid mass transfer rate parameter \( \gamma_1 \) and fraction of accessible void volume to solid volume \( \epsilon_1 \), and on the resulting drug concentration profiles and drug mass profiles within each layer in the coating and in the tissue. The concentration profiles are obtained by using values of parameters given in Table 1 with the variation of only three parameters \( \gamma_1, \epsilon_1 \) and \( \epsilon_1 \). The results obtained have a good agreement with the results calculated by [13, 28].

In Figure 3, we plot free and bound drug concentration profiles in each layer for different non-dimensional times. In the coating we observe decreasing drug concentration profiles with time for each of the two phases. At each of the considered times, the concentrations in the encapsulated phase \( c_b^1 \) are higher than the corresponding concentrations in the free phase \( c_f^1 \). Within the tissue, the free drug concentration levels \( c_f^2 \) rise from zero to some maximum value before decreasing with time. A similar effect is observed for bound drug concentrations \( c_b^2 \), although higher values of \( c_b^2 \) are achieved, in line with the selected \( K_1 \) (modelling a lipophilic drug).

In Figure 4, we plot the nondimensional time histories of the drug mass contained within each phase. The free drug mass \( M_f^1 \) rises to its maximum value quickly and decreases after that monotonically. The mass of encapsulated drug \( M_f^1 \) is also decreasing monotonically with function of time, the solid-liquid
Figure 3. Normalized concentration profiles for different times in coating and in the wall when $\gamma_1 = 10^{-3}, \epsilon_1 = 1, \epsilon_1 = 0.5$.

Figure 4. Variation in normalized mass of drug in each phase of the coating and in the wall with normalized time $\gamma_1 = 10^{-2}, \epsilon_1 = 1, \epsilon_1 = 0.5$.

Mass transfer is a one way process since dissolved drug is immediately cleared by diffusion. Within the tissue, the free drug mass $M_f^2$ rises from zero to a maximum value and then slowly decays with time. The maximum $M_f^2$ occurs later than the maximum $M_f^1$. We observe that, for this set of parameter values, a considerable amount of drug can be transferred to the bound phase, and furthermore, can be retained. It is also worth pointing out that the two maxima are not in phase: the maximum $M_b^2$ occurs later than the maximum $M_f^2$. It is also observed that the discontinuity of drug concentration across the interface and steep gradients has developed close to the boundary between the coating and tissue layers.
In Figure 5 and Figure 6, we plot the corresponding profiles for the case of $\gamma_1$ one order of magnitude higher. Comparing Figure 3 with Figure 5, it was expected and is also observed that the higher the results of $\gamma_1$, the quicker the drug being transferred from the encapsulated to the free phase. The result is that $c_1^b$ reduces more quickly and consequently, higher $c_1^f$ and $c_2^f$ values are observed in the initial stages. However, for higher drug concentrations in the initial stages, the effect on the observed tissue bound drug concentrations is minimal. This is further demonstrated by comparison of Figure 4 with Figure 6. The maximum $M_1^f$ is higher when $\gamma_1$ is higher but the time taken for $M_1^f$ to reduce to negligible values is
essentially unchanged. The maximum $M_f^j$ is slightly greater and occurs sooner. Whilst the uptake rate of drug to the bound tissue phase is higher initially, the drug mass contained inside the bound tissue phase is largely unaffected.

**Figure 7.** Normalized concentration profiles for different times in coating and in the wall when $\gamma_1 = 10^{-4}, \epsilon_1 = 1, \epsilon_1 = 0.5$.

**Figure 8.** Variation in normalized mass of drug in each phase of the coating and in the wall with normalized time $\gamma_1 = 10^{-4}, \epsilon_1 = 9, \epsilon_1 = 0.9$.
In Figure 7 and Figure 8, we plot the corresponding profiles for the case of $\gamma_1$ where one order of magnitude is lower. In this situation the timescale for solid-liquid mass transfer is slower than that for diffusion in the coating. Thus drug transport is limited by the rate at which drug is transferred from the solid to liquid phases. Comparing Figure 3 with Figure 7, we observe that the values of $c^f_1$ are higher due to the slower rate of transfer between the phases. Consequently, the values of $c^b_1$ are lower. The tissue drug concentrations, both $c^f_2$ and $c^b_2$, are lower at the interface due to this slow rate of transfer. By comparing Figure 4 with Figure 8, we see further evidence of the slower rate of decrease of $M^b_1$ coupled with the smaller observed maximum $M^f_1$, when $\gamma_1$ is reduced. The parameter $M^f_2$ also notices a slight delay in reaching its maximum value, which is now lower. However, perhaps surprisingly, the $M^b_2$ profile is very similar, with the maximum value only slightly reduced and delayed.

Now we are trying to investigate the impact of the ratio of the accessible void to solid volume, $e_1$. This is a parameter which potentially can be manipulated at the manufacturing stage. In addition to $e_1 = 1$ which we have considered above, we now keep $\gamma_1$ fixed at $10^{-2}$, and by varying $e_1$ for different values corresponding to the two extreme cases. The first case represents a coating with extremely low porosity and is mainly solid. The second case describes a coating which is extremely porous and is almost entirely empty space.

![Normalized concentration profiles](image)

**Figure 9.** Normalized concentration profiles for different times in coating and in the wall when $\gamma_1 = 10^{-2}, e_1 = 0.111, e_1 = 0.1$.

In Figure 9 and Figure 10, we find that with a lower value of $e_1$, $c^f_1$ takes much longer to reduce and consequently the values of $c^f_1$ are considerably smaller. Whereas the values of $c^f_2$ and $c^b_2$ are also reduced, the observed concentrations are also less uniform across the thickness of the arterial wall. When compared with the mass of drug, it is found that it takes significantly longer for $M^b_1$ to decay to negligible levels and $M^f_1$ is markedly reduced. Whereas the $M^b_2$ maxima is only slightly reduced, it takes long time
to reach this maximum. The value of $M_1^f$, however, is fairly uniform across the duration studied. Now, when we increase $e_1 = 0.111$ to $e_1 = 9$,

In Figure 11 and Figure 12, we find that drug is rapidly converted from encapsulated form to free form in the coating, resulting in initially higher values of $c_{f1}^1$, $c_{f2}^1$ and $c_{b2}^1$. Consequently, the values of $M_1^b$ and
M_1^f (after rapidly reaching their maximum) decay very quickly to zero. Perhaps most importantly, while the maximum c_2^f value increases only slightly, this value is attained more readily.

6. Conclusion

Mathematical modeling paves the way for a deeper perception of the drug transport mechanisms in the arterial wall and coating, especially in the drug eluting stents case. In this way, it has turned into an effective means to catalyze drug release processes. Although cardiovascular drug transportation shows a very complicated physiological and biochemical phenomena, an improved release model may give a better understanding of the release mechanism of the drug from arterial wall tissue to drug coating. Therefore it is our sincere intention to discuss the transportation of drug from drug eluting stent and the subsequent drug distribution in the arterial wall. In particular, we assume that the drug coated on the DES must undergo a solid-liquid mass transfer process before it becomes biologically available and can freely diffuse into the tissue. We have applied finite element method with two finite difference schemes to solve the proposed model equations for drug concentration profiles of coating and tissue. It is found that the fraction of accessible void volume to solid volume e_1 and rate of solid-liquid mass transfer parameter γ have indeed an impact on the drug concentrations and drug mass that is achieved in the tissue. Although we have considered values of the solid-liquid mass transfer parameter across three orders of magnitude, the resulting tissue bound drug concentrations and bound drug mass profiles are very similar, suggesting that the rate of solid-liquid mass transfer does not appear to have a large influence on the bound drug concentrations. However, we have also varied the fraction of accessible void volume to solid volume e_1 and have found that this parameter may have a significant influence on drug concentration profiles and drug mass profiles in the arterial wall. In particular, drug release speed and the timing of peak bound drug concentrations can be controlled by varying the value of e_1. Thus it is concluded that solid-liquid mass transfer is controlled not only by the parameter γ, but also by the ratio of available volume fraction to solid fraction, e_1. It is identified that the system key parameters can be altered during manufacturing time to attain the preferred drug release profiles and it is also demonstrated that a two phase system can give further flexibility in altering the release profiles. The other parameters, the Peclet number and Damkohler number, can be used to find specific release profiles. In this way, two distinctive drug release phases can be achieved, with distinctive duration and consequently, the delivery rate of drug at every phase may be varied by regulating the model parameters. Future directions related to this effort may also consider the multi layers of the arterial wall together with their different biomechanical properties. Moreover, an additional effort is required to enhance this model as two dimensional model together with convection diffusion and reversible bindings in artery wall. The impacts of ratios of binding rate constants of the arterial wall may not be discounted for additional investigation.
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