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Modeling of Mass Dynamics in Arterial Drug-Eluting Stents

Giuseppe Pontrelli[1] **and Filippo de Monte**[2]

[1]Instituto per le Applicazioni del Calcolo — CNR Viale del Policlinico, 137, 00161 Roma, Italy

[2]Dipartimento di Ingegneria Meccanica, Energetica e Gestionale — University of L'Aquila, Località Monteluco, 67040 Roio Poggio (AQ), Italy

E-mail: pontrelli@iac.rm.cnr.it

ABSTRACT

A mathematical model describing the advection-diffusion reaction of a substance between two porous homogeneous media of different properties and dimensions is presented. A strong analogy with the one-dimensional transient heat conduction process across two layered slabs is evidenced and a similar methodology is proposed. The model incorporates not only drug diffusive effects, but also convection phenomena and metabolic processes in the wall. Transformation and separation of variables leads to a Sturm-Liouville problem with discontinuous coefficients and an exact analytical solution is given in the form of an infinite series expansion. The model points out the role of the nondimensional parameters, which control the complex transfer mechanism across the two layers. In particular, the drug diffusivity in the wall is shown to greatly influence the residence time. Drug concentration profiles at various times are given and discussed.

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1. INTRODUCTION

Application of a endovascular drug-eluting stent (DES) for prevention and cure of restenosis is an emerging technology that combines mechanical support of restricted lumen with local drug delivery (Maisel, 2007; Rogers, 2002). Although different configurations exist, a typical DES consists of one or more biocompatible polymeric layers coating the metallic strut and containing the therapeutic agent to be delivered. Drug release depends on many factors, such as the coating geometry and physico chemical properties, and drug characteristic, such as diffusivity and solubility (Delfour et al. 2005). Because only a limited amount of drug can be loaded onto an eluting stent, it is crucial to optimize the pharmacokinetics, in terms of concentration and residence time. In particular, the concentration should lie within a therapeutic range and its action prolonged (Hwang et al., 2001).

Because of the involvement of so many factors, prediction of drug release appears as a formidable task and mathematical models constitute a valuable tool used in designing coating and stent platforms for drug delivery. The first step in modeling is to identify all the relevant ingredients entering the mass transfer. Although diffusive process dominates the drug dynamics, in some circumstances other processes come into play and modify the release mechanism: a comprehensive model to guarantee generality is worth to be set up. For example, an important effect can be ascribed to the convective flow due to a pressure drop across the arterial wall (Hwang et al., 2001; Meyer et al., 1996). Moreover, when released into the arterial tissue, the drug is metabolized by living cells and its concentration decays in time. The fraction consumed with biochemical processes depends on the drug type, on the biological site and on individual factors (Ai and Vafai, 2006; Macheras and Iliadis, 2006).

In the last few years, some attempts to model and numerically simulate DES have been done, either from a mechanical point of view (Holzapfel et al., 2005; Migliavacca et al., 2007) or focusing drug release aspects (Migliavacca et al., 2007; Delfour et al., 2005; Zunino et al., 2004; Sakharov et al., 2002). In a recent study, a purely diffusive model has been presented and a strong analogy with the transient heat conduction process across two-layered slabs has been shown (de Monte, 2000). With such an approach, the concentration is expressed in a closed form as a finite sum of eigenfunctions (Pontrelli and de Monte, 2007 and 2008). The present work extends that model by adding drug convective motion and metabolism in the wall layer and provides a comprehensive model of mass release in vascular drug deliver. Through variable transformatio, the problem is amened to a pure diffusion problem and the concentration solution written in the form of a Fourier series.

Compared to a fully numerical method, the analytical approach provides a deeper insight into the physical sense of the drug delivery process. As a matter of fact, the present one-dimensional model is shown to catch most of the interplaying aspects of the drug dynamics. By showing relationships among the relevant variables and material parameters, it can be used to identify simple indexes or clinical indicators of biomechanical significance. Through a nondimensional analysis and a computational methodology, the role played by different physical and biochemical effects is highlighted. Results point out that the influence of the parameters, such as drug diffusivity, may be tuned to better design novel release mechanisms as well as to improve drug delivery protocols in therapy and diagnostics.

2. MATHEMATICAL MODEL

A stent consists of a tubular wire mesh (*strut*) inserted and then expanded in a stenosed artery (Fig. 1). A drug-eluting stent (DES) is a stent coated with a thin layer of biocompatible polymeric gel containing a therapeutic drug (*coating*). Such a drug is aimed at healing the vascular tissues or at preventing a possible restenosis by virtue of its antiproliferative action against smooth muscle cells. In the present work, we are interested in the mechanism of release into the arterial tissue. Such a phenomenon is not completely under-

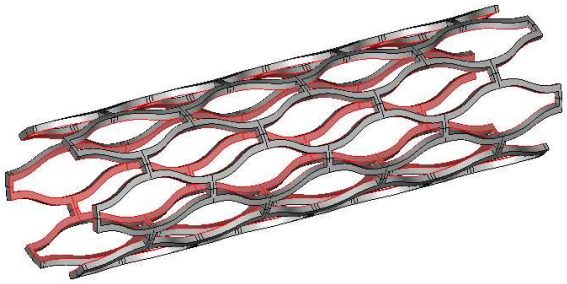

Figure 1. Typical strut of a bare-metal stent

stood and may be influenced by different concurrent physical processes.

Let us consider a stent coated by a thin layer (of thickness L_1) of gel containing a drug and embedded into the arterial wall (of thickness L_2). The complex multilayered structure of the arterial wall has been disregarded, and a homogeneous material with averaged properties has been considered for simplicity (*fluid-wall* model) as in Zunino (2004) and Prosi et al., (2005). Both the coating and the arterial wall are treated as porous media. Because most of the mass dynamics occurs along the direction normal to the two layers (radial direction), we restrict our study to a simplified one-dimensional (1D) model. In particular, we consider a radial line crossing the metallic strut, the coating, and the arterial wall and pointing outward, and being that the wall thickness is very small with respect to the arterial radius, a cartesian coordinate system x is used along it (Fig. 2).

At the initial time ($t = 0$), the drug is contained only in the coating and is distributed with maximum, possibly nonuniform, concentration $C_1 f(x)$ and subsequently released into the wall. Here, and throughout this paper, a mass volume-averaged concentration $c(x,t)$ (in milligrams per milliliter) is considered. Because the metallic strut is impermeable to the drug, no mass flux passes through the boundary surface $x = -L_1$. Moreover, it is assumed that the plasma does not penetrate the surface of the stent coating. Thus, the dynamics of the drug in the coating (first layer) is described by the following 1D averaged diffusion equation, and related boundary-initial conditions:

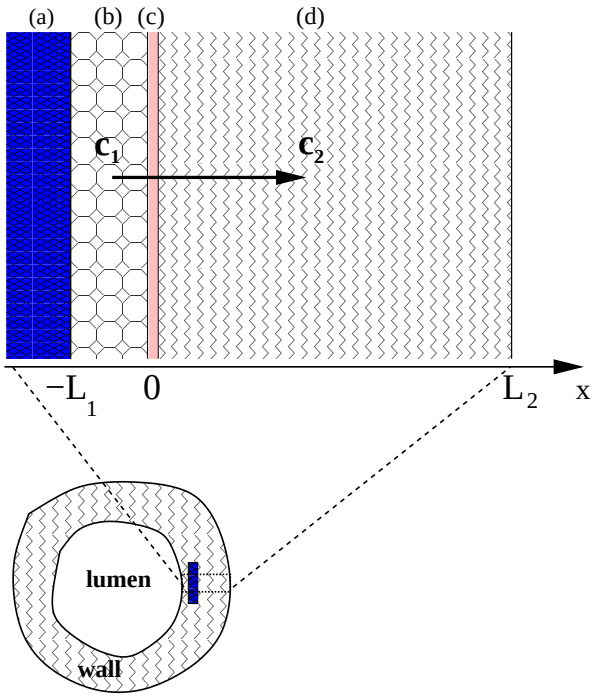

Figure 2. Cross-section of a stented artery with a zoomed area near the wall that shows the metallic mesh and the two-layer medium at the adventitial side described by the model (2.1) and (2.2): **(a)** stent strut, **(b)** coating, **(c)** topcoat, **(d)** arterial wall. Due to an initial difference of concentration, drug is released in the arterial wall from (b) to (d) through the permeable membrane (c). An analogous two-layer pattern is present on the opposite side of the strut, referring to the drug dynamics towards the lumen (lumenal side)

$$\begin{aligned} &\frac{\partial c_1}{\partial t} + \frac{\partial}{\partial x}\left(-D_1 \frac{\partial c_1}{\partial x}\right) = 0 \qquad \text{in} \qquad [-L_1, 0] \\ &-D_1 \frac{\partial c_1}{\partial x} = 0 \qquad \text{at} \qquad x = -L_1 \\ &c_1 = C_1 f(x) \qquad \text{at} \qquad t = 0 \end{aligned} \tag{2.1}$$

where D_1 (in centimeters squared per second) is the drug diffusivity in the porous coating and $0 \le f(x) \le 1$.

In the wall (second layer), the drug dynamics is described by the following advection-diffusion-reaction equation and related boundary-initial conditions:

$$\frac{\partial c_2}{\partial t}+\frac{\partial}{\partial x}\left(-D_2\frac{\partial c_2}{\partial x}+2\delta_2 c_2\right)+\beta_2 c_2=0$$
$$\text{in} \quad [0,L_2]$$
$$c_2=0 \quad \text{at} \quad x=L_2 \qquad (2.2)$$
$$c_2=0 \quad \text{at} \quad t=0$$

where D_2 (in centimeters squared per second) is the diffusivity of drug in the arterial wall and $2\delta_2$ (centimeters per second) accounts for a constant characteristic convection parameter, based on a filtration velocity u_2. Even not strictly realistic in a multidimensional model, for the 1D flow of an isothermal and incompressible fluid in a porous medium, the filtration velocity u_2 is a constant. In other words, in the present 1D approximation model, u_2 represents an *averaged* filtration velocity in the x direction, evaluable through the Darcy law (Pontrelli and de Monte, 2007). Moreover, $2\delta_2=\alpha_2 u_2/k_2\epsilon_2$, where α_2 [sieving coefficient or hindrance coefficient, see (Zunino, 2004)] accounts for the reduction of the convective term due to the collisions of large molecules of drug with the porous structure of the wall, k and ϵ are the partition coefficient and porosity, respectively [see Pontrelli and de Monte (2007) for a precise definition of the physical quantities].

The last term on the left-hand side of Eq. (2.2.1) represents the drug reaction on the surface of smooth muscle cells (SMCs) inside the media layer of the arterial wall. Here, it is approximated by a linear reaction having $\beta_2>0$ (in seconds to the minus 1) as an effective first-order consumption rate coefficient. Equation (2.2.2) accounts for a drug dispersion at relatively large distance ($L_2 \gg L_1$) and is justified for quite small values of δ_2.

To close the previous mass transfer system of Eqs. (2.1) and (2.2), the conditions at the interface $x=0$ have to be assigned. One of them is obtained by imposing continuity of the mass flux across the two layers,

$$D_1\frac{\partial c_1}{\partial x}=D_2\frac{\partial c_2}{\partial x}-2\delta_2 c_2 \qquad \text{at} \qquad x=0 \quad (2.3)$$

In addition to slow down the drug release rate, a permeable membrane (called *topcoat*) of permeability P (in centimeters per second) is located at the interface ($x=0$) between the coating and the arterial wall. A continuous mass flux passes through it orthogonally to the coating film with a large concentration jump due to the very different physical properties between arterial walls and coating. In the present case, the mass transfer through the topcoat can be described using the second Kedem-Katchalsky equation (Kargol et al., 1996), that is

$$-D_1\frac{\partial c_1}{\partial x}=P\left(\frac{c_1}{k_1\epsilon_1}-\frac{c_2}{k_2\epsilon_2}\right) \quad \text{at} \quad x=0 \qquad (2.4)$$

2.1. Variable Transformation

All the variables and the parameters are now scaled as follows:

$$\bar{x}=\frac{x}{L_2} \qquad \bar{t}=\frac{D_2}{L_2^2}t \qquad \bar{c}_1=\frac{c_1}{C_1} \qquad \bar{c}_2=\frac{c_2}{C_1}$$
$$\gamma=\frac{D_1}{D_2} \quad L=\frac{L_1}{L_2} \quad \phi=\frac{PL_2}{D_2k_2\epsilon_2} \quad \sigma=\frac{k_1\epsilon_1}{k_2\epsilon_2} \quad (2.5)$$

Thus, the convection and reaction terms are controlled by the dimensionless groups,

$$\text{Pe}=\frac{\delta_2 L_2}{D_2} \qquad \text{Da}=\frac{\beta_2 L_2^2}{D_2} \qquad (2.6)$$

termed as Péclet and Damkholer numbers, respectively (Baehr and Stephan, 1998). By means of the following change of variables:

$$\bar{x}\to x \qquad \bar{t}\to t \qquad \bar{c}_1\to c_1 \qquad \bar{c}_2\to c_2 \quad (2.7)$$

and, in the second layer, through the following transformation (Özişik, 1993):

$$c_2(x,t)=w_2(x,t)\exp\left[\text{Pe}\,x-\left(\text{Pe}^2+\text{Da}\right)t\right] \quad (2.8)$$

the problem [(2.1) and (2.2)] can be written in terms of c_1 and w_2 in dimensionless form as

$$
\begin{aligned}
&\frac{\partial c_1}{\partial t} = \gamma \frac{\partial^2 c_1}{\partial x^2} \qquad \text{in} \qquad [-L, 0] \\
&\frac{\partial c_1}{\partial x} = 0 \qquad \text{at} \qquad x = -L \\
&\gamma \frac{\partial c_1}{\partial x} = \left(\frac{\partial w_2}{\partial x} - \mathrm{Pe}\, w_2 \right) \exp\left[-\left(\mathrm{Pe}^2 + \mathrm{Da} \right) t \right] \\
&\qquad\qquad \text{at} \qquad x = 0 \\
&c_1 = f(x) \qquad \text{at} \qquad t = 0
\end{aligned} \tag{2.9}
$$

$$
\begin{aligned}
&\frac{\partial w_2}{\partial t} = \frac{\partial^2 w_2}{\partial x^2} \qquad \text{in} \qquad [0, 1] \\
&-\gamma \frac{\partial c_1}{\partial x} = \phi \left\{ \frac{c_1}{\sigma} - w_2 \exp\left[-\left(\mathrm{Pe}^2 + \mathrm{Da} \right) t \right] \right\} \\
&\qquad\qquad \text{at} \qquad x = 0 \\
&w_2 = 0 \qquad \text{at} \qquad x = 1 \\
&w_2 = 0 \qquad \text{at} \qquad t = 0
\end{aligned} \tag{2.10}
$$

3. EIGENVALUE PROBLEM

By separation of variables,

$$
\begin{aligned}
c_1(x,t) &= X_1(x) G_1(t) \\
w_2(x,t) &= X_2(x) G_2(t)
\end{aligned} \tag{3.1}
$$

Equations (2.9) and (2.10) yield the ODEs,

$$
\frac{1}{\gamma} \frac{G_1'}{G_1} = -\lambda_1^2 \qquad \frac{G_2'}{G_2} = -\lambda_2^2 \tag{3.2}
$$

having as solution,

$$
G_1(t) = e^{-\gamma \lambda_1^2 t} \qquad G_2(t) = e^{-\lambda_2^2 t} \tag{3.3}
$$

By imposing $G_1 = G_2 \exp\left[-\left(\mathrm{Pe}^2 + \mathrm{Da} \right) t \right]$, we have the following relationship:

$$
\lambda_1 = \sqrt{\frac{\lambda_2^2 + \mathrm{Pe}^2 + \mathrm{Da}}{\gamma}} \tag{3.4}
$$

The spatial part leads to the Sturm-Liouville eigenvalue system,

$$
\begin{aligned}
&X_1'' = -\lambda_1^2 X_1 \qquad \text{in} \qquad [-L, 0] \qquad (3.5) \\
&X_1' = 0 \qquad \text{at} \qquad x = -L \qquad (3.6) \\
&\gamma X_1' = X_2' - \mathrm{Pe} X_2 \qquad \text{at} \qquad x = 0 \qquad (3.7) \\
&X_2'' = -\lambda_2^2 X_2 \qquad \text{in} \qquad [0, 1] \qquad (3.8) \\
&X_2 = 0 \qquad \text{at} \qquad x = 1 \qquad (3.9) \\
&\gamma X_1' + \frac{\phi}{\sigma} X_1 = \phi X_2 \qquad \text{at} \quad x = 0 \qquad (3.10)
\end{aligned}
$$

The general solution of the ordinary differential Eqs. (3.5) and (3.8) is

$$
\begin{aligned}
X_1(x) &= a_1 \cos(\lambda_1 x) + b_1 \sin(\lambda_1 x) \\
X_2(x) &= a_2 \cos(\lambda_2 x) + b_2 \sin(\lambda_2 x)
\end{aligned} \tag{3.11}
$$

where the eigenvalues λ_i and the unknown coefficients a_i and b_i may be computed by imposing the outer and inner boundary conditions as follows. From Eqs. (3.6) and (3.9), we have

$$
\sin(\lambda_1 L) a_1 + \cos(\lambda_1 L) b_1 = 0 \tag{3.12}
$$

$$
a_2 \cos(\lambda_2) - b_2 \sin(\lambda_2) = 0 \tag{3.13}
$$

From the interface conditions (3.7) and (3.10), it follows:

$$
\gamma \lambda_1 b_1 + \mathrm{Pe} a_2 - \lambda_2 b_2 = 0 \tag{3.14}
$$

$$
\frac{\phi}{\sigma} a_1 + \gamma \lambda_1 b_1 - \phi a_2 = 0 \tag{3.15}
$$

Equations (3.12)–(3.15) form a system of four homogeneous linear algebraic equations with unknowns a_1, b_1, a_2, and b_2. To get a solution different from the *trivial* one $(0, 0, 0, 0)$, it is needed that the determinant of the coefficient matrix associated with the above system be equal to zero; that is,

$$
\begin{aligned}
&\varphi(\lambda_2) = \sigma \gamma \lambda_1 \tan(\lambda_1 L) \left[(\phi + \mathrm{Pe}) \tan \lambda_2 + \lambda_2 \right] \\
&- \phi(\lambda_2 + \mathrm{Pe} \tan \lambda_2) = 0
\end{aligned} \tag{3.16}
$$

where λ_1 is related to λ_2 by virtue of Eq. (3.4). Note that, in general, Eq. (3.16) admits an infinite number of real and possible imaginary roots. These may appear

when Pe > 0 or Da > 0, their number being finite and proportional to the magnitude of Pe and Da.

Solving Eq. (3.16), the coefficients are evaluated in cascade as

$$a_2 = -\tan(\lambda_2)\, b_2 = \tilde{a}_2\, b_2 \tag{3.17}$$

$$b_1 = \left(\frac{\lambda_2 - \mathrm{Pe}\,\tilde{a}_2}{\gamma\lambda_1}\right) b_2 = \tilde{b}_1 b_2 \tag{3.18}$$

$$a_1 = \left(-\frac{\tilde{b}_1}{\tan(\lambda_1 L)}\right) b_2 = \tilde{a}_1 b_2 \tag{3.19}$$

where the multiplicative constant b_2 will be determined through the initial condition (see Section 3.1).

The nonlinear system of Eqs. (3.4) and (3.16) admits as solution an infinite number of couples $(\lambda_{1m}, \lambda_{2m}, m = 1, 2, ...)$. Subsequently, the constants $\tilde{a}_{1m}$, $\tilde{b}_{1m}$, and $\tilde{a}_{2m}$ are obtained from (3.19), (3.18), and (3.17), respectively, and thus the eigenfunctions X_{1m} and X_{2m} defined in Eq. (3.11) have the form

$$\begin{aligned} X_{1m} &= b_{2m}\left[\tilde{a}_{1m}\cos(\lambda_{1m}x) + \tilde{b}_{1m}\sin(\lambda_{1m}x)\right] \\ &= b_{2m}\tilde{X}_{1m} \end{aligned} \tag{3.20}$$

$$\begin{aligned} X_{2m} &= b_{2m}\left[\tilde{a}_{2m}\cos(\lambda_{2m}x) + \sin(\lambda_{2m}x)\right] \\ &= b_{2m}\tilde{X}_{2m} \end{aligned} \tag{3.21}$$

3.1. Concentration Solution

Once the eigenvalues λ_{1m} and λ_{2m} are computed, the corresponding time-variable functions G_{1m} and G_{2m} defined by Eqs. (3.3) are obtained as

$$G_{1m} = e^{-\gamma\lambda_{1m}^2 t} \qquad G_{2m} = e^{-\lambda_{2m}^2 t} \tag{3.22}$$

Thus, the general solution of the problem [(2.9) and (2.10)] is given by a linear superposition of the fundamental solutions [(3.20) and (3.21)] in the form

$$\begin{aligned} c_1(x,t) &= \sum_{m=1}^{\infty} A_m \tilde{X}_{1m}(x)\, e^{-\gamma\lambda_{1m}^2 t} \\ w_2(x,t) &= \sum_{m=1}^{\infty} A_m \tilde{X}_{2m}(x)\, e^{-\lambda_{2m}^2 t} \end{aligned} \tag{3.23}$$

where the Fourier coefficients $A_m := b_{2m}$ are computed in accordance with the initial condition. By evaluating Eq. (3.23.1) at $t = 0$ and multiplying it by $\tilde{X}_{1n}$, after integration we get

$$\int_{-L}^{0} \sum A_m \tilde{X}_{1m}\tilde{X}_{1n}dx = \int_{-L}^{0} f(x)\tilde{X}_{1n}dx \tag{3.24}$$
$$n = 1, 2, ...$$

Similarly in the interval $[0, 1]$, we have

$$\int_{0}^{1} \sum A_m \tilde{X}_{2m}\tilde{X}_{2n}dx = 0 \qquad n = 1, 2, ... \tag{3.25}$$

By combining Eqs. (3.24) and (3.25) and by using the orthogonality property (Pontrelli and de Monte, 2007), we have

$$A_m\left(\int_{-L}^{0}\tilde{X}_{1m}^2 dx + \sigma\int_{0}^{1}\tilde{X}_{2m}^2 dx\right) = \int_{-L}^{0} f(x)\tilde{X}_{1m}dx \tag{3.26}$$

where the term in brackets on the left-hand side is the norm $\tilde{N}_m = N_m/b_{2m}^2$ and N_m obtained by straightforward computations (Pontrelli and de Monte, 2007). We get

$$A_m = \frac{\int_{-L}^{0} f(x)\tilde{X}_{1m}dx}{\tilde{N}_m} \qquad m = 1, 2, ... \tag{3.27}$$

In particular, if $f(x) = 1$, bearing in mind Eq. (3.20) and integrating from $-L$ to 0, we have

$$\begin{aligned} A_m &= \frac{\tilde{a}_{1m}\sin(\lambda_{1m}L) + \tilde{b}_{1m}\left[\cos(\lambda_{1m}L) - 1\right]}{\tilde{N}_m\lambda_{1m}} \\ &= -\frac{\tilde{b}_{1m}}{\tilde{N}_m\lambda_{1m}} \qquad m = 1, 2, ... \end{aligned} \tag{3.28}$$

Finally, using the inverse of the transformation (2.8), the complete solution for concentration reads

$$c_1(x,t) = \sum_{m=1}^{\infty} A_m \tilde{X}_{1m}(x)\, e^{-\gamma\lambda_{1m}^2 t}$$
$$c_2(x,t) = \sum_{m=1}^{\infty} A_m \tilde{X}_{2m}(x)\, e^{\mathrm{Pe}x} e^{-\gamma\lambda_{1m}^2 t} \qquad (3.29)$$

The analytical form of Eq. (3.29) allows an easy computation of the dimensionless drug mass (per unit of area) in both coating and wall layers as function of time as

$$M_1(t) = \int_{-L}^{0} c_1(x,t)dx$$
$$M_2(t) = \int_{0}^{1} c_2(x,t)dx$$

obtaining,

$$M_1(t) = -\sum_{m=1}^{\infty} A_m \frac{\tilde{b}_{1m}}{\lambda_{1m}} e^{-\gamma\lambda_{1m}^2 t} \qquad (3.30)$$

$$M_2(t) = \sum_{m=1}^{\infty} A_m \Big(\big(e^{\mathrm{Pe}} \big[(\mathrm{Pe} + \lambda_{2m}\tilde{a}_{2m}) \sin(\lambda_{2m}) + (\mathrm{Pe}\,\tilde{a}_{2m} - \lambda_{2m}) \cos(\lambda_{2m}) \big] + \lambda_{2m} - \mathrm{Pe}\,\tilde{a}_{2m} \big) / \big(\mathrm{Pe}^2 + \lambda_{2m}^2 \big) \Big) e^{-\gamma\lambda_{1m}^2 t} \qquad (3.31)$$

In particular, $M_1(0) = \int_{-L}^{0} f(x)dx$ and $M_2(0) = 0$. When $f(x) = 1$, we have $M_1(0) = L$. A relevant quantity is the normalized mass

$$\hat{M}_2(t) = \frac{M_2(t)}{M_1(0) + M_2(0)} \qquad (3.32)$$

which indicates the drug fraction left in the wall at time t (compared to the initial total mass).

4. NUMERICAL RESULTS AND DISCUSSION

The physical problem depends on a large number of variables, each of them may vary in a finite range, and there is a variety of different limiting cases. As a matter of fact, they cannot be chosen independently from each other, but they are related by some compatibility condition to give rise to a realistic model. The following parameters are considered for computational experiments:

$$L_1 = 5\times10^{-4}\,\mathrm{cm} \quad L_2 = 10^{-2}\,\mathrm{cm} \quad P = 10^{-6}\,\mathrm{cm/s}$$
$$D_1 = 10^{-10}\,\mathrm{cm^2/s} \quad D_2 = 7\times10^{-8}\,\mathrm{cm^2/s}$$
$$k_1 = 1 \quad k_2 = 1 \quad \epsilon_1 = 0.1 \quad \epsilon_2 = 0.61 \qquad (4.1)$$

These parameters have been chosen according to a physical basis or to the experimental evidence, and in agreement with the typical scales in DES and data in literature for the arterial wall and heparin drug in the coating layer (Hwang et al., 2001; Sakharov et al., 2002; Creel et al., 2000). Actually, it has been shown that the problem depends only on the six independent groups defined by Eqs. (2.5.2) and (2.6). According to Eq. (4.1) the four ratios ϕ, σ, L, γ are fixed as

$$\phi = 0.234 \quad \sigma = 0.164 \quad L = 0.05 \quad \gamma = 0.0014 \qquad (4.2)$$

The effect and the sensitivity of the solution on them have been analyzed in a recent work (Pontrelli and de Monte, 2007), and for the time being, their values are left unchanged as reference parameters. However here, we are interested to systematically investigate the dependence on Pe and Da only, aimed to understand the relative influence of convection and reaction inside the wall, compared to the diffusive terms.

Being that the problem diffusion dominated ($\mathrm{Pe} \simeq 10^{-1}$ and $\mathrm{Da} \simeq 10^{-1}$ in typical regimes), we first consider

$$\mathrm{Pe} = \mathrm{Da} = 0 \qquad (4.3)$$

as starting values and let them raise separately in a convenient range consistent with the other quantities.

Because of the character of the series, Eq. (3.29) a relatively small number of terms in the series (typically $m \leq 50$) is required to achieve an acceptable accuracy. Computational results show that drug is eluting from coating to the wall, with the wall concentration decaying in time. Figure 3 shows the concentration profiles in the two layers at three instants.

4.1. Effect of Filtration Velocity

To show the influence of filtration velocity on the drug release, a value $\delta_2 \simeq 10^{-6}$ cm/s is considered, in agreement with measurements (Meyer et al., 1996; Migliavacca et al., 2007). Simulations for four values of Pe in a compatible range are carried out to show the trend of the solution. It turns out that a relatively small advection lowers the concentration curves at all times (Fig. 4). This can be explained because the convection velocity sweeps the drug away from the wall, where it is dispersed. At intermediate and later instants, the profiles may appear bulged and therefore a more uniform concentration is guaranteed. A critical value of Pe exists; beyond it the solution becomes unphysical.

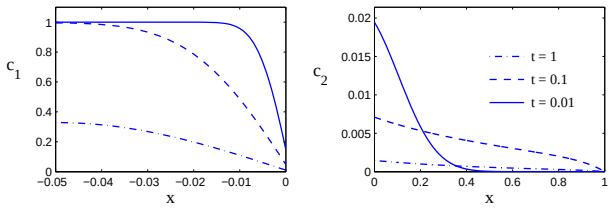

Figure 3. Concentration profiles in the coating (left) and in the wall (right) with Pe $= 4$ and Da $= 20$ (note the different scales)

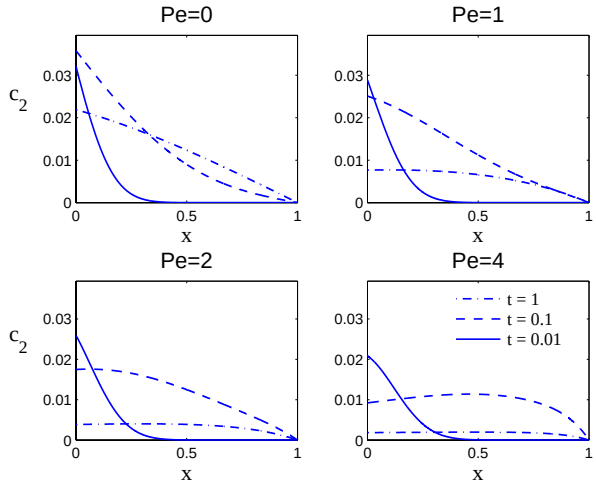

Figure 4. Wall concentration decay profiles at varying Pe (with Da $= 0$)

4.2. Effect of Drug Metabolism

The importance of the reaction term depends on the drug used, on the specific tissue and on individual factors. However, the presence of a reactive term acts as a sink for concentration. A typical value for the consumption rate is $\beta_2 \simeq 10^{-4}$ s^{-1} (Ai and Vafai, 2006). Consequently, $\mathrm{Da} \simeq 0.15$ and the trend of the concentration at three increasing values of Da is depicted in Fig. 5. Raising of Da accelerates the drug consumption and diminishes the concentration, but preserves the shapes at fixed times. A negligible variation with Da is reported at early times. At later instants, the concentration profiles flatten and decrease linearly. In conclusion, the effect on varying Pe is similar, though more sensitive, to that on Da, and they combine when both coexist.

Drug mass $\hat{M}_2$ is first raising up to a peak value and then falls down asymptotically to zero (Fig. 6). The M_2 peak lowers and anticipates with Pe (with a sharper drop) and Da.

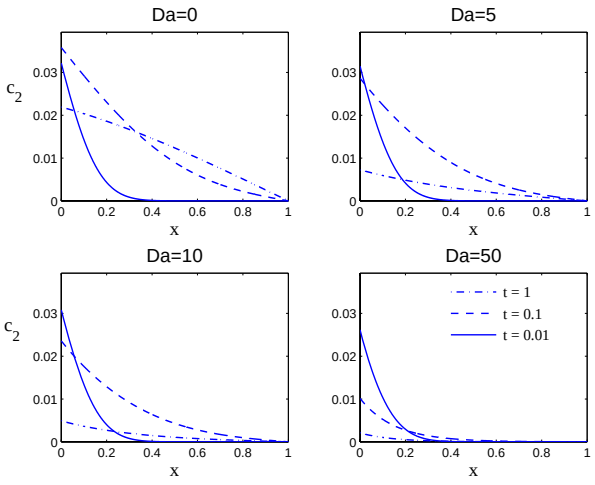

Figure 5. Wall concentration decay profiles at varying Da (with Pe $= 0$)

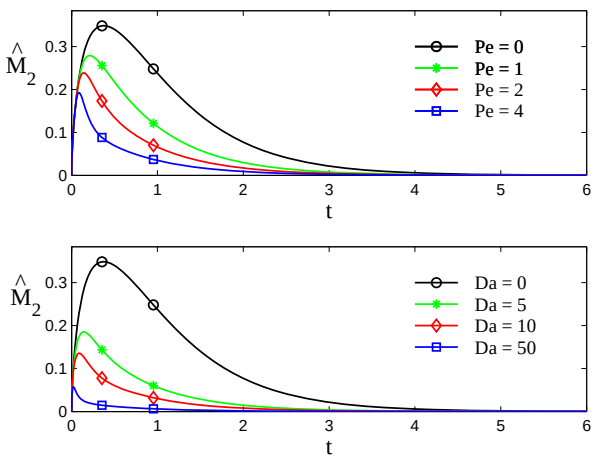

Figure 6. Normalized mass $\hat{M}_2$ in the wall as a function of the nondimensional time at varying Pe (above) and Da (below)

4.3. Drug Elution Indicator

In the pharmacokinetic characterization of drugs, it is of interest to evaluate to what extent the drug is distributed and retained in a tissue. This parameter is generally known as mean residence time (MRT) and provides a useful insight into the kinetics of a substance released in a medium (Macheras and Iliadis, 2006).

Roughly speaking, the mean residence time measures the capability of a drug to reside in a tissue and for the present application, can be defined as the time that mass (or mean concentration) in the wall reaches a given percentage of its maximum value, say

$$\mathrm{MRT}_n = \max\left\{ t \,\middle|\, \int_0^1 c_2(x,t)dx \geq \frac{n}{100}\int_{-L}^{0} c_1(x,0)dx \right\} \tag{4.4}$$

In other words: $\hat{M}_2(\mathrm{MRT}_n) = M_2(\mathrm{MRT}_n)/M_1(0) \simeq \frac{n}{100}$ [see Eq. (3.32)]. For example, MRT_{10} indicates the time elapsed until the mass in the wall stays above 10% of the initial maximum value.

MRT constitutes a useful quantitative indicator of drug elution and can be used for comparative purposes and for designing novel coating technologies in DES. Actually, for a prolonged therapeutic efficacy, it is important to maximize MRT as a function of some physical quantity. Whereas the effect of Pe and Da has been examined with drug diffusivity held fixed, with a second set of numerical experiments we now turn about the case and the influence of varying D_2 only is investigated.

It is found that a decrease of D_2 augments simultaneously the parameters γ, ϕ, Pe, and Da, but also reduces the nondimensional time [see Eqs. (2.5) and (2.6)]. As a consequence, a sensible rising of MRT is reported, as shown in Table 1.

5. CONCLUSIONS

Many physical phenomena, from biology to geophysics, from hydraulics to chemical engineering are described by convection-diffusion-reaction models, even at different time scales. A biomedical application provided the source of inspiration for the present work: mass transport, diffusion phenomena and metabolism of a drug in the vascular wall are of great importance in delivery processes and, in particular, in coating stent technology. Although drug-eluting stents represent an important advance in the management of coronary arterial diseases, much remains uncertain about their long-term benefits and safety: much effort in modeling is currently addressed to a deeper understanding of the complex drug elution mechanism.

The study presents a one-dimensional approximation model, which, as an idealized case, provides a useful tool to predict the fundamental physics of mass transfer and to assess the efficacy of the DES technology. The analytical form of the solution and some numerical experiments evidence the role played by the convective and reaction processes when compared to the diffusive ones. Lastly, the mean residence time is deemed a valuable indicator for a desired tissue concentration and results greatly controlled by the drug diffusion.

Table 1

Mean residence times (in seconds) relative to 1%, 5%, 10%, at increasing D_2. Simulations run with the parameters in Eq. (4.1) and $\delta_2 = 10^{-6}$ cm/s and $\beta_2 = 10^{-4}$ s

D_2	MRT_1	MRT_5	MRT_{10}
5×10^{-9}	11152	8160	6832
1×10^{-8}	9876	7088	5840
5×10^{-8}	3999	3628	2812
1×10^{-7}	1999	1999	1765

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