XXV Congresso Nazionale UIT sulla Trasmissione del Calore
Trieste, 18-20 Giugno 2007

MODELLING OF MASS CONVECTION-DIFFUSION IN STENT-BASED DRUG DELIVERY

Giuseppe Pontrelli*, Filippo de Monte**

*IAC-CNR, Viale del Policlinico 137, 00161 Roma, E-mail: g.pontrelli@iac.cnr.it
**DIMEG, Università dell'Aquila, 67040 Roio Poggio (AQ), E-mail: demonte@ing.univaq.it

ABSTRACT

A mathematical model describing delivery of therapeutic agents from polymeric coatings into coronary arteries after stenting procedures is developed. A metabolic term denoting a drug consumption and a volume-averaged filtration velocity of the plasma over an arterial cross section are included. Also, an infinite mass transfer coefficient at the adventitial boundary surface is considered and a non-uniform initial concentration in the coating is assumed. Such a model can be used to study the effect of different coating parameters and configurations on the drug release. Transformation and separation-of-variables method lead to a 1D Sturm-Liouville problem with discontinuous coefficients and an exact analytical solution for local concentrations is found. Drug concentration profiles are given and the influence on the physico-chemical parameters is discussed.

INTRODUCTION

Application of endovascular drug-eluting stent (DES) for prevention and cure of restenosis is an emerging technology which combines mechanical support of restricted lumen with local drug delivery [1]. 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.

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 in time [2].

Due to the involvement of so many factors, prediction of drug release appears as a formidable task and mathematical models constitute a predictive tool for designing coating and stent platform for drug delivery. The first step in modelling is to identify all the relevant ingredients entering into the drug dynamics in the arterial wall. For example, 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. Another important effect is due to the convective flow due to a pressure drop across the arterial wall. In some circumstances such effects are deemed important, and a comprehensive model to guarantee generality is worth to be defined [3; 4]

In a recent study a purely diffusive model has been presented [5]. With such an approach the concentration is expressed in an analytical form as finite sum of eigenfunctions. This work extends that model by adding the convection and metabolic terms in the wall layer. Through a change of variable the problem is amened to a pure diffusion problem. Finally, the concentration solution is expressed in the form of a Fourier series.

Compared to a fully numerical method, the analytical approach provides a greater 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 relevant aspects of the drug dynamics. By showing relationships among the variables and material parameters, it can be used to identify simple indexes or clinical indicators of biomechanical significance.

The model enables the effect of important factors such as drug diffusivity, cell metabolism, coating thickness, and membrane permeability to be analyzed. Tuned in optimal way, they can be used to design novel release mechanisms, as well as to improve drug delivery protocols used in therapy and diagnostics.

THE MATHEMATICAL MODEL

A drug-eluting stent (DES) consists of a metallic stent platform (*strut*) coated with a polymeric layer that encapsulates a therapeutic drug (Fig. 1). Such a coating is made of a drug loaded polymeric matrix covered with a rate-limiting barrier (membrane) that provides a more controlled and sustained drug release. Such a drug is aimed at minimizing the occurrence of clinically adverse events such as restenosis after stent implantation. In the present work we are interested only in the mechanism of drug elution into the arterial tissue.

Figure 2 shows a cross-section of a stent strut 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 Refs. [6; 7]. Both the coating and the arterial wall are treated as porous media. Because most of the mass transport process occurs along the direction normal to the two layers (radial direction), we restrict our study to a simplified 1D model. In particular, we consider a radial line crossing the metallic strut, the coating and the arterial

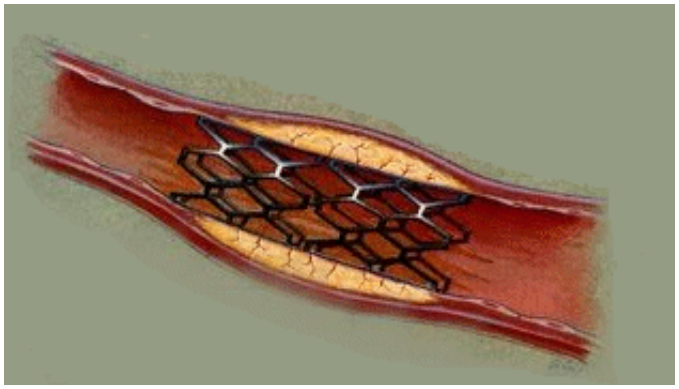

Figure 1. Sketch of a stented artery.

wall and pointing outwards and, being the wall thickness 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 it is distributed with maximum, possibly nonuniform, concentration $C_1 f(x)$ and, subsequently, it is released into the wall. Here, and throughout this paper, a mass volume-averaged concentration $c(x,t)$ (mg/ml) is considered. Since 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 (1^{st} layer) is described by the following 1D averaged diffusion equation, and related boundary initial conditions:

$$\begin{aligned} &\frac{\partial c_1}{\partial t} + \frac{\partial}{\partial x}\left(-D_1 \frac{\partial c_1}{\partial x}\right) = 0 && \text{in } [-L_1, 0] \\ &-D_1 \frac{\partial c_1}{\partial x} = 0 && \text{at } x = -L_1 \\ &c_1 = C_1 f(x) && \text{at } t = 0 \end{aligned} \qquad (1)$$

where D_1 (cm^2/s) is the drug diffusivity in the porous coating and $0 \leq f(x) \leq 1$.

Similarly, in the second layer, the drug dynamics is described by the following advection-diffusion equation and related boundary-initial conditions:

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

where D_2 (cm^2/s) is the diffusivity of drug inside the arterial wall. The quantity $2\delta_2$ (cm/s) accounts for a constant convection parameter due to the filtration velocity of the plasma (see [8] for the meaning of the physical quantities). The last term on the l.h.s. of Eq. (2.1) represents the drug reaction rate 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 $\beta_2 > 0$ (s^{-1}) as an effective first-order reaction rate coefficient.

To close the previous system of Eqs. (1)-(2), the conditions at the interface $x = 0$ (the so-called inner boundary conditions)

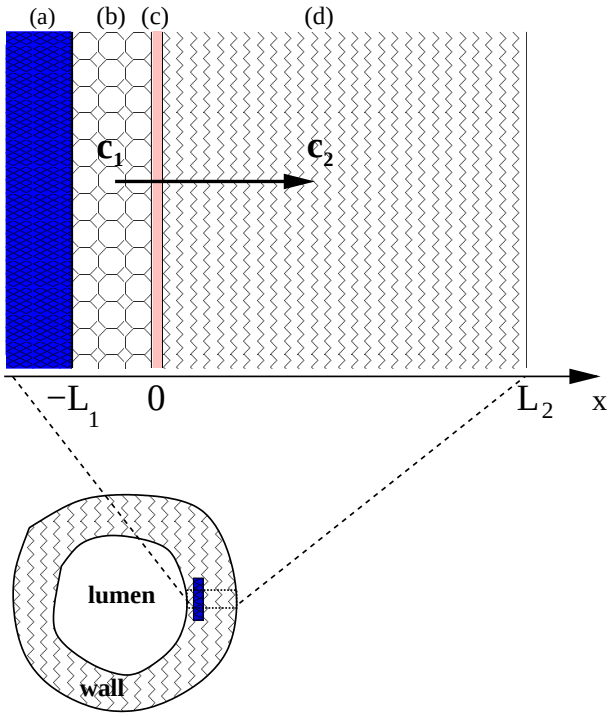

Figure 2. Cross-section of a stented artery with a zoomed area near the wall that shows the metallic mesh and the two-layer medium at the adventitial side described by the model (1)-(2): (a) stent strut, (b) coating, (c) topcoat, (d) arterial wall. Due to an initial difference of concentration, drug is eluting 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 release towards the lumen (lumenal side).

have to be assigned. One of them is obtained by imposing continuity of the mass flux:

$$D_1 \frac{\partial c_1}{\partial x} = D_2 \frac{\partial c_2}{\partial x} \qquad \text{at } x = 0 \qquad (3)$$

The permeable membrane (called *topcoat*) of permeability P (cm/s) 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 possible concentration jump. In the present case, the mass transfer through the topcoat can be described using the second Kedem-Katchalsky equation [9]. Thus, the continuous flux of mass passing across the membrane normally to the coating is expressed by:

$$-D_1 \frac{\partial c_1}{\partial x} = P(c_1' - c_2') \qquad \text{at } x = 0 \qquad (4)$$

In Eq. (4) the fluid-phase concentration c' is used. This is related to the volume-averaged concentration c through the formula $c' = \dfrac{c}{k\varepsilon}$ (with k partition coefficient, ε porosity).

Variable transformation

Let us define the following nondimensional variables and constants:

$$\bar{x}=\frac{x}{L_2} \qquad \bar{t}=\frac{D_2}{L_2^2}t \qquad \bar{c_1}=\frac{c_1}{C_1} \qquad \bar{c_2}=\frac{c_2}{C_1}$$
$$\gamma=\frac{D_1}{D_2} \qquad L=\frac{L_1}{L_2} \qquad \phi=\frac{PL_2}{D_2k_2\varepsilon_2} \qquad \sigma=\frac{k_1\varepsilon_1}{k_2\varepsilon_2}$$
$$\delta=\frac{\delta_2 L_2}{D_2} \qquad \beta=\frac{\beta_2 L_2^2}{D_2} \tag{5}$$

By setting:

$$\bar{x}\to x \qquad \bar{t}\to t \qquad \bar{c_1}\to c_1 \qquad \bar{c_2}\to c_2$$

the two differential problems (1) – (2) with B.C.'s (3) and (4) may be rewritten in a dimensionless form as:

$$\begin{aligned}
&\frac{\partial c_1}{\partial t}=\gamma\frac{\partial^2 c_1}{\partial x^2} && \text{in } [-L,0]\\
&\frac{\partial c_1}{\partial x}=0 && \text{at } x=-L\\
&\gamma\frac{\partial c_1}{\partial x}=\frac{\partial c_2}{\partial x} && \text{at } x=0\\
&c_1=f(x) && \text{at } t=0
\end{aligned} \tag{6}$$

$$\begin{aligned}
&\frac{\partial c_2}{\partial t}=\frac{\partial^2 c_2}{\partial x^2}-2\delta\frac{\partial c_2}{\partial x}-\beta c_2 && \text{in } [0,1]\\
&-\gamma\frac{\partial c_1}{\partial x}=\phi\left(\frac{c_1}{\sigma}-c_2\right) && \text{at } x=0\\
&c_2=0 && \text{at } x=1\\
&c_2=0 && \text{at } t=0
\end{aligned} \tag{7}$$

In the second layer, with the following variable transformation [10]:

$$c_2(x,t)=w_2(x,t)e^{\delta x-(\delta^2+\beta)t} \tag{8}$$

the problem (6)–(7) becomes:

$$\begin{aligned}
&\frac{\partial c_1}{\partial t}=\gamma\frac{\partial^2 c_1}{\partial x^2} && \text{in } [-L,0]\\
&\frac{\partial c_1}{\partial x}=0 && \text{at } x=-L\\
&\gamma\frac{\partial c_1}{\partial x}=\left(\frac{\partial w_2}{\partial x}+\delta w_2\right)e^{-(\delta^2+\beta)t} && \text{at } x=0\\
&c_1=f(x) && \text{at } t=0
\end{aligned} \tag{9}$$

$$\begin{aligned}
&\frac{\partial w_2}{\partial t}=\frac{\partial^2 w_2}{\partial x^2} && \text{in } [0,1]\\
&-\gamma\frac{\partial c_1}{\partial x}=\phi\left(\frac{c_1}{\sigma}-w_2e^{-(\delta^2+\beta)t}\right) && \text{at } x=0\\
&w_2=0 && \text{at } x=1\\
&w_2=0 && \text{at } t=0
\end{aligned} \tag{10}$$

THE EIGENVALUE PROBLEM

By separation of variables:

$$c_1(x,t)=X_1(x)G_1(t) \qquad w_2(x,t)=X_2(x)G_2(t)$$

Eqs. (9)–(10) yield the ODE's:

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

having as solution:

$$G_1(t)=e^{-\gamma\lambda_1^2 t} \qquad G_2(t)=e^{-\lambda_2^2 t} \tag{11}$$

By imposing: $G_1=G_2e^{-(\delta^2+\beta)t}$ [11], we have the following relationship:

$$\lambda_1=\sqrt{\frac{\lambda_2^2+\delta^2+\beta}{\gamma}} \tag{12}$$

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

$$X_1''=-\lambda_1^2X_1 \qquad \text{in } [-L,0] \tag{13}$$
$$X_1'=0 \qquad \text{at } x=-L \tag{14}$$
$$\gamma X_1'=X_2'+\delta X_2 \qquad \text{at } x=0 \tag{15}$$

$$X_2''=-\lambda_2^2X_2 \qquad \text{in } [0,1] \tag{16}$$
$$X_2=0 \qquad \text{at } x=1 \tag{17}$$
$$\gamma X_1'+\frac{\phi}{\sigma}X_1=\phi X_2 \qquad \text{at } x=0 \tag{18}$$

The general solution of the ordinary differential Eqs. (13) and (16) is:

$$\begin{aligned}
X_1(x)&=a_1\cos(\lambda_1 x)+b_1\sin(\lambda_1 x)\\
X_2(x)&=a_2\cos(\lambda_2 x)+b_2\sin(\lambda_2 x)
\end{aligned} \tag{19}$$

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. (14) and (17), we have:

$$\sin(\lambda_1 L)a_1+\cos(\lambda_1 L)b_1=0 \tag{20}$$
$$a_2\cos(\lambda_2)+b_2\sin(\lambda_2)=0 \tag{21}$$

From the interface conditions (15) and (18), it follows:

$$\gamma\lambda_1 b_1-\delta a_2-\lambda_2 b_2=0 \tag{22}$$
$$\frac{\phi}{\sigma}a_1+\gamma\lambda_1 b_1-\phi a_2=0 \tag{23}$$

Eqs. (20)–(23) 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:

$$\sigma\gamma\lambda_1 \tan(\lambda_1 L)\,[\lambda_2 + (\phi-\delta)\tan\lambda_2] - \phi(\lambda_2 - \delta\tan\lambda_2) = 0 \quad (24)$$

where λ_1 is related to λ_2 by virtue of Eq. (12).

Solving Eq. (24), the coefficients are evaluated in cascade as:

$$a_2 = (-\tan\lambda_2)\, b_2 = \tilde{a}_2\, b_2 \quad (25)$$

$$b_1 = \left(\frac{\lambda_2 + \delta\tilde{a}_2}{\gamma\lambda_1}\right) b_2 = \tilde{b}_1\, b_2 \quad (26)$$

$$a_1 = \left(-\frac{\tilde{b}_1}{\tan(\lambda_1 L)}\right) b_2 = \tilde{a}_1\, b_2 \quad (27)$$

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

In general, the nonlinear system of Eqs. (12) and (24) admits as solution an infinite number of couples $\lambda_{1m}, \lambda_{2m}$, $m = 1,2,....$ Subsequently, the constants $\tilde{a}_{2m}$, $\tilde{b}_{1m}$ and $\tilde{a}_{1m}$ are obtained from Eqs. (25), (26) and (27) respectively, and thus the corresponding eigenfunctions X_{1m} and X_{2m} defined in Eq. (19) may be written as [11]:

$$\begin{aligned} X_{1m} &= b_{2m}\left[\tilde{a}_{1m}\cos(\lambda_{1m}x) + \tilde{b}_{1m}\sin(\lambda_{1m}x)\right] = b_{2m}\tilde{X}_{1m} \\ X_{2m} &= b_{2m}\left[\tilde{a}_{2m}\cos(\lambda_{2m}x) + \sin(\lambda_{2m}x)\right] = b_{2m}\tilde{X}_{2m} \end{aligned} \quad (28)$$

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. (11) are obtained as:

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

Thus, the general solution of the problem (9)–(10) is given by a linear superposition of the fundamental solutions (28) in the form:

$$\begin{aligned} c_1(x,t) &= \sum_{m=1}^{\infty} A_m \tilde{X}_{1m}(x)\, e^{-\gamma\lambda_{1m}^2 t} \\ w_2(x,t) &= \sum_{m=1}^{\infty} A_m \tilde{X}_{2m}(x)\, e^{-\lambda_{2m}^2 t} \end{aligned} \quad (29)$$

where $A_m := b_{2m}$ are computed by applying the initial condition. By evaluating Eq. (29.1) at $t = 0$ and multiplying it by $\tilde{X}_{1n}$, after integration we get:

$$\int_{-L}^{0} \sum A_m \tilde{X}_{1m}\tilde{X}_{1n}\, dx = \int_{-L}^{0} f(x)\tilde{X}_{1n}\, dx \qquad n = 1,2,.... \quad (30)$$

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

$$\int_{0}^{1} \sum A_m \tilde{X}_{2m}\tilde{X}_{2n}\, dx = 0 \qquad n = 1,2,.... \quad (31)$$

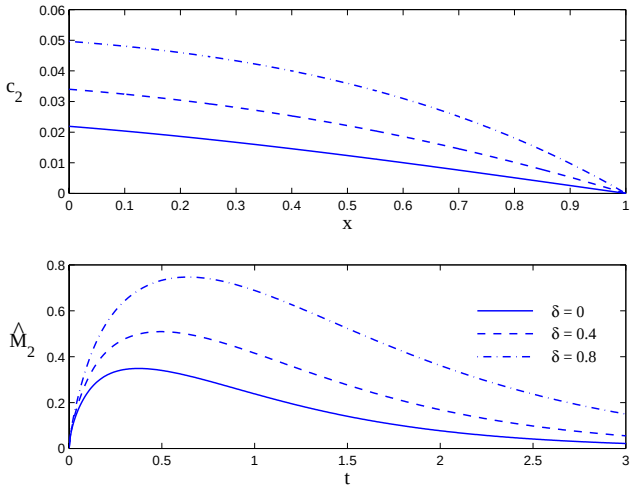

Figure 3. Wall concentration profiles for three values of δ at $t = 1$ (above) and normalized mass (below).

By combining Eqs. (30) and (31) and by using the orthogonality property of $\tilde{X}_{1m}, \tilde{X}_{2m}$ [8], we have, for $f(x) = 1$:

$$A_m = \frac{\tilde{a}_{1m}\sin(\lambda_{1m}L) + \tilde{b}_{1m}\,(\cos(\lambda_{1m}L) - 1)}{\tilde{N}_m\lambda_{1m}} = -\frac{\tilde{b}_{1m}}{\tilde{N}_m\lambda_{1m}} \qquad m = 1,2,....$$

Finally, using the inverse of the transformation (8), the complete solution for concentration reads:

$$\begin{aligned} c_1(x,t) &= \sum_{m=1}^{\infty} A_m \tilde{X}_{1m}(x)\, e^{-\gamma\lambda_{1m}^2 t} \\ c_2(x,t) &= \sum_{m=1}^{\infty} A_m \left[\tilde{X}_{2m}(x)\, e^{\delta x}\right] e^{-\left(\lambda_{2m}^2 + \delta^2 + \beta\right)t} \end{aligned}$$

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

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

A relevant quantity is the normalized mass:

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

that indicates the drug fraction left in the wall at time t compared with the initial total mass.

NUMERICAL RESULTS AND DISCUSSION

The physical problem depends on a large number of parameters, 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 a well-posed

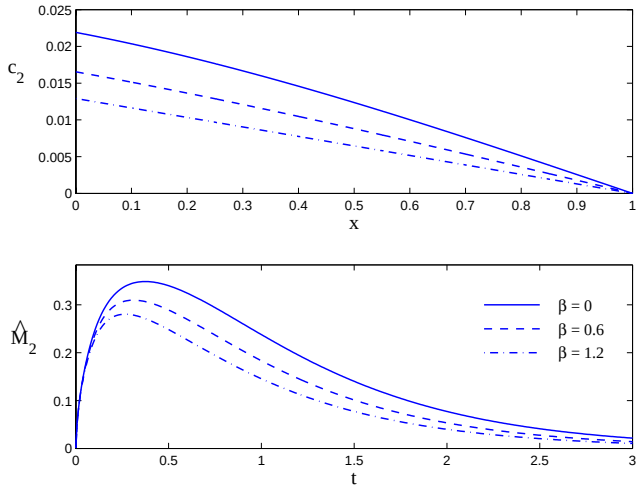

Figure 4. Wall concentration profiles for three values of β at $t = 1$ (above) and normalized mass (below).

model. The physical parameters considered for the simulations are the following:

$$L_1 = 5 \cdot 10^{-4} cm \qquad L_2 = 10^{-2} cm \qquad P = 10^{-6} cm/s$$
$$D_1 = 10^{-10} cm^2/s \qquad D_2 = 7 \cdot 10^{-8} cm^2/s$$
$$k_1 = 1 \qquad k_2 = 1 \qquad \varepsilon_1 = 0.1 \qquad \varepsilon_2 = 0.61 \quad (32)$$

These have been chosen according to a physical basis and in agreement with the typical scales in DES and data in literature for the arterial wall and heparin drug in the coating layer [1]. Actually, it has been shown that the problem depends only on the six nondimensional operational parameters defined by Eq. (5). The four ratios ϕ, σ, L, γ are derived from Eq. (32) as:

$$\phi = 0.234 \qquad \sigma = 0.164 \qquad L = 0.05 \qquad \gamma = 0.0014$$

and their effect and sensitivity on the solution have been analyzed in a recent work [5]. Here, these values are left unchanged as reference parameters. We are interested to investigate the effect of δ, β only, aimed to understand the relative importance on the convection and on the drug reaction rate inside the wall. Starting from the reference values:

$$\delta = 0 \qquad \beta = 0$$

we let them vary in a convenient range consistent with physical quantities.

Results prove that drug is eluting from coating to the wall, with wall concentration decaying in time. Normalized drug mass $\hat{M}_2$ is first raising up to a peak value and then extinguishes in a finite time.

To show the influence of filtration velocity on the drug release, a value of $\delta_2 \simeq 10^{-4} cm/s$ [6] is considered. Simulations for three values of δ in a range compatible with those are carried out to show the trend of the solution with the filtration velocity. Results show that a non zero advection coefficient keeps the concentration higher and prolongs the residence time (Fig. 3). The importance of the reaction term depends on the drug used, on the specific tissue and on individual factors. Typical values of β_2 are of order of magnitude $10^{-4} s^{-1}$ [3]. Consequently $\beta \simeq 0.5$ and the trend of the concentration and wall mass at three increasing values of β is shown in Fig. 4. Raise of β accelerates the drug consumption, diminishes the concentration and reduce the residence time. A negligible variation with δ and β is reported at small times. The sensitivity with δ is larger than with β. The reader is referred to [8] for further details.

CONCLUSIONS

A mathematical model able to predict the evolution of drug concentration in a cross-section of the wall after stenting implantation has been presented. The model considers the basic mechanisms responsible for the drug release due to a combined effect of diffusion and convection. Though limited to an idealized 1D configuration, the present methodology includes the relevant aspects and points out the role of the many concurrent factors in mass transport. It can be used to analyze the effect of stent-based therapeutic agent release and opens new perspectives in drug delivery stent design aimed at a better treatment of atherosclerosis and restenosis.

REFERENCES

[1] D.V. Sakharov, L. V. Kalachev, D. C. Rijken, Numerical simulation of local pharmacokinetics of a drug after intravascular delivery with an eluting stent, *Jour. Drug. Target.*, Vol. 10, n. 6, pp. 507-513, 2002.

[2] C.D.K. Rogers, Drug-eluting stents: role of stent design delivery vehicle and drug selection, *Rev. Cardiov. Med.*, Vol. 3, (supp. 5), S10-S15, 2002.

[3] L. Ai, K. Vafai, A coupling model for macromolecules transport in a stenosed arterial wall, *Int. J. Heat Mass Transf.*, pp. 1568-1591, 2006.

[4] C. Hwang, D. Wu, E.R. Edelman, Physiological transport forces govern drug distribution for stent-based delivery, *Circulation*, vol. 104, n. 5, pp. 600-605, 2001.

[5] G. Pontrelli, F. de Monte, Mass diffusion through two-layer porous media: an application to the drug-eluting stent, *Int. J. Heat Mass Transf.*, available on line, 2 january, 2007.

[6] P. Zunino, Multidimensional pharmacokinetic models applied to the design of drug-eluting stents, *Cardiov. Engineering.: An Intern. J.*, vol. 4, n. 2, 2004.

[7] M. Prosi, P. Zunino, K. Perktold, A. Quarteroni, Mathematical and numerical models for transfer of low-density lipoproteins through the arterial walls: a new methodology for the model set up with applications o the study of disturbed lumenal flow, *J. Biomech.*, Vol. 38, pp. 903-917, 2005.

[8] G. Pontrelli, F. de Monte, Modelling and simulation of drug release in a cardiovascular drug-eluting stent, in preparation, 2007.

[9] A. Kargol, M. Kargol, S. Przestalski, The Kedem-Katchalsky equations as applied for describing substance transport across biological membranes, *Cell. & Molec. Biol. Letters*, Vol. 2, pp. 117-124, 1996.

[10] M.N. Özişik, *Heat conduction*, J. Wiley & Sons, 1993.

[11] C.W. Tittle, Boundary value problems in composite media: quasi orthogonal functions, *J. Appl. Phys.*, vol. 36, 4, pp. 1486-1488, 1965.