DRUG DELIVERY IN BIOLOGICAL TISSUES: AN APPLICATION TO THE ELUTING STENT

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1. ABSTRACT

The drug diffusion process through an arterial eluting stent is studied with a mathematical model. An exact analytical solution is given in the form of an infinite series expansion. The model addresses the role of four controlling parameters and provides qualitative considerations and a quantitative description for drug transport to evaluate feasibility of new drug delivery strategies, and to estimate dose response.

2. INTRODUCTION

The release of a substance in a living tissue for therapeutic purposes is becoming quite common in medicine nowadays, through drug delivery devices [1]. The mechanism of release is quite complex and depends on many concurrent physical and biochemical factors. As a matter of fact, to reach a desired target, the concentration of the drug in the tissue should lie within a given range and it is recognized that the time and quantity of release of the drug is crucial for the therapy [2]. The elution process is influenced by many factors, such as properties of the drug (hydrophily), coating (material structure) as well as the transport characteristics of the arterial wall. Mathematical models predicting the dynamics of solute concentration and mass flux are of interest for biomedical engineers and clinicians, as they offer a simple tool for optimizing the drug delivery design and technology [3]. The present work provides a fundamental study of the mass transfer process of a substance across two homogeneous faced media and directly applies to the drug-eluting stent. The whole drug is initially in a polymeric matrix coating the metallic structure and is subsequently released into the arterial wall. Being interested in the pharmacokinetics only, the mechanical effects of the stent are neglected.

The time-space diffusion-transport equation for the drug dynamics is presented in the general case. Due to the prevalent flux direction, the problem is formulated in one dimensional case in terms of nondimensional variables. This results in a coupled system of partial differential equations in two faced domains with a interface condition. The problem exhibits a strong analogy with the thermal process of heat conduction between two slab-shaped regions with different thermal properties and a similar method for solving the differential problem is used [4]. A Sturm-Liouville system is set, the correspondent eigenvalue equation is solved and the solution is expressed in a long-time form.

A number of numerical experiments is carried out over several configurations of typical stent design parameters. The results can be used to design novel drug delivery systems, as well as to optimize a drug delivery protocol to be used in therapy and diagnostics.

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3. THE MATHEMATICAL MODEL

A drug-eluting stent is a metallic prosthesis implanted into the arterial wall and coated with a layer of biocompatible polymeric gel that encapsulates a therapeutic drug. Such a drug, released in a controlled manner, is aimed at healing the vascular tissues or to prevent a possible restenosis [1,2]. In the present work we are interested in the mechanism of drug elution into the arterial tissue.

Let us consider a stent coated by a thin layer (1) of drug and embedded into the arterial wall (layer 2) and let us indicate by c_1, c_2 the (volume averaged, nondimensional) concentrations in the two layers (fig. 1). Because the dominant flux and most of the diffusive process occur across the direction normal to the two-layer medium, we limit our study to a 1D model and we denote the space coordinate by *x*. To slow down the drug release rate, a permeable membrane (called *topcoat*) is located at the interface ($x = 0$) between the two layers. Using the second Kedem-Katchalsky equation [5] the mass flux is proportional to the concentration difference as:

$$-D_1 \frac{\partial c_1}{\partial x} = -D_2 \frac{\partial c_2}{\partial x} = P\left(\frac{c_1}{k_1 \varepsilon_1} - \frac{c_2}{k_2 \varepsilon_2}\right) \qquad \text{at } x = 0 \tag{1}$$

with D_i diffusion coefficients, ε_i medium porosities, and k_i partition coefficients (*i=1,2*) and *P* the permeability coefficient. Let us define the following nondimensional variables and constants:

$$\frac{x}{L_2} \to x \qquad \frac{D_2}{L_2^2}\, t \to t \qquad \gamma = \frac{D_1}{D_2} \qquad L = \frac{L_1}{L_2} \tag{2}$$

with L_i (*i=1,2*) layer thickness. The diffusion process in the coating is described by the following dimensionless equations:

$$\begin{aligned} &\frac{\partial c_1}{\partial t} - \gamma \frac{\partial^2 c_1}{\partial x^2} = 0 && \text{in } [-L,0] \\ &\frac{\partial c_1}{\partial x} = 0 && \text{at } x = -L \\ &\gamma \frac{\partial c_1}{\partial x} = \frac{\partial c_2}{\partial x} && \text{at } x = 0 \end{aligned} \tag{3}$$

In the wall, the phenomenon is governed by a set of similar equations:

$$\begin{aligned} &\frac{\partial c_2}{\partial t} - \frac{\partial^2 c_2}{\partial x^2} = 0 && \text{in } [0,1] \\ &-\frac{\partial c_2}{\partial x} = \phi\left(\frac{c_1}{\sigma} - c_2\right) && \text{at } x = 0 \\ &c_2 = 0 && \text{at } x = 1 \end{aligned} \tag{4}$$

with:

$$\phi = \frac{P\,L_2}{D_2 k_2 \varepsilon_2} \qquad \sigma = \frac{k_1 \varepsilon_1}{k_2 \varepsilon_2} \tag{5}$$

At the initial time ($t = 0$) the drug is contained only in the coating and it is uniformly distributed at maximum concentration ($c_1 = 1, c_2 = 0$) and, at following times, it is released into the wall [6]. The two-layered diffusion problem (3)-(4) is analogous to the problem of transient heat conduction between two slab-shaped bodies of different thermal properties, when a temperature jump is initially present, except for the inner boundary condition (4.2) [4].

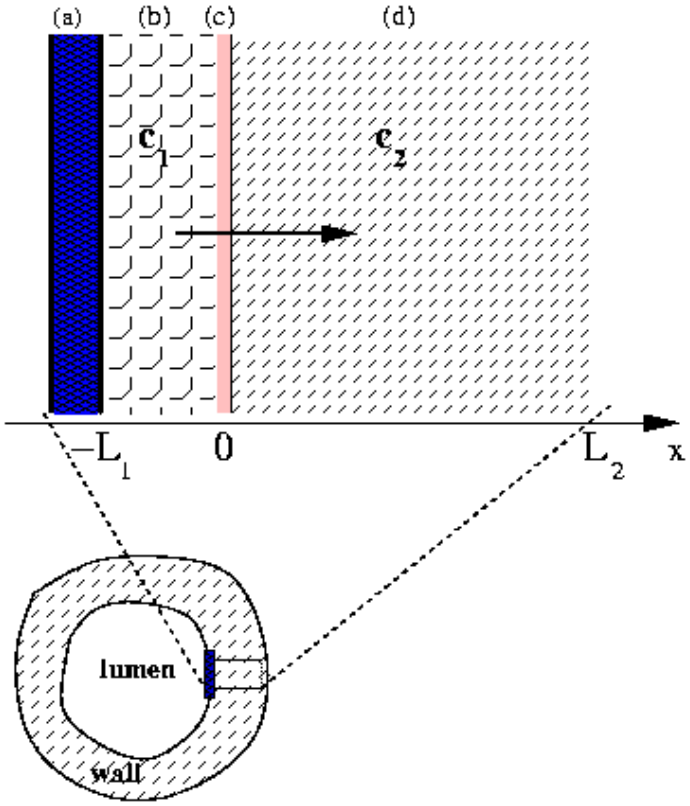

Fig. 1: Cross section of a stented artery with the sequence of layers for drug-dynamics: (a) stent strut, (b) coating, (c) topcoat, (d) arterial wall.

4. ANALYTICAL SOLUTION

The solution of the previous equations is obtained by separation of variables:

$$c_i(x,t) = X_i(x) G_i(t) \qquad i=1,2 \tag{6}$$

Substitution in eqns. (3)-(4) yield the two ODE's:

$$\frac{1}{\gamma}\frac{G_1'}{G_1} = -\lambda_1^2 \qquad \frac{G_2'}{G_2} = -\lambda_2^2 \tag{7}$$

which admit the solutions: $G_1(t) = e^{-\gamma\lambda_1^2}$ and $G_2(t) = e^{-\lambda_2^2 t}$. The condition $G_1 = G_2$ implies $\lambda_1 = \frac{1}{\sqrt{\gamma}}\lambda_2$.

The spatial problem is amenable to the Sturm-Liouville eigenvalue system:

$$\begin{array}{llll} X_1'' = -\lambda_1^2 X_1 & \text{in } [-L,0] & X_2'' = -\lambda_2^2 X_2 & \text{in } [-L,0] \\ X_1' = 0 & \text{at } x = -L & X_2 = 0 & \text{at } x = -L \\ \gamma\, X_1' = X_2' & \text{at } x = 0 & -X_2' + \phi\, X_2 = \dfrac{\phi}{\sigma} X_1 & \text{at } x = 0 \end{array} \qquad (8)$$

The general solution of the ordinary differential eqns. (8) is:

$$X_1(x) = a_1 \cos(\lambda_1 x) + b_1 \sin(\lambda_1 x) \qquad X_2(x) = a_2 \cos(\lambda_2 x) + b_2 \sin(\lambda_2 x) \qquad (9)$$

where the eigenvalues λ_i and the coefficients a_i and b_i are computed by imposing the outer and inner boundary conditions and solving a trascendental equation (*eigencondition*). After straightforward computations, the eigenfunctions X_{1m} and X_{2m} have the following expression:

$$\begin{aligned} X_{1m}(x) &= A_m\left[-\sigma\left(\tan\lambda_{2m} + \frac{\lambda_{2m}}{\phi}\right)\cos(\lambda_{1m}x) + \frac{1}{\sqrt{\gamma}}\sin(\lambda_{1m}x)\right] \\ X_{2m}(x) &= A_m\left[-\tan\lambda_{2m}\cos(\lambda_{2m}x) + \sin(\lambda_{2m}x)\right] \end{aligned} \qquad (10)$$

Finally, the complete solution of the problem is given by a linear superposition of the fundamental solutions (10) in the form:

$$c_1(x,t) = \sum_{m=1}^{\infty} A_m\, X_{1m}(x)\, e^{-\gamma\lambda_{1m}^2 t} \qquad c_2(x,t) = \sum_{m=1}^{\infty} A_m\, X_{2m}(x)\, e^{-\lambda_{2m}^2 t} \qquad (11)$$

where A_m (*m=1,2,….*) are determined through the initial conditions. From eqns. (11) it is possible to compute the drug mass (per unit area) as function of time in both coating and wall layers as:

$$M_1(t) = \int_{-L}^{0} c_1(x,t)dx = \sum_{m=1}^{\infty} A_m\left(\frac{a_{1m}\sin(\lambda_{1m}L) + b_{1m}\cos(\lambda_{1m}L) - b_{1m}}{\lambda_{1m}}\right)e^{-\gamma\lambda_{1m}^2 t}$$

$$M_2(t) = \int_{0}^{1} c_2(x,t)dx = \sum_{m=1}^{\infty} A_m\left(\frac{a_{2m}\sin(\lambda_{2m}) - \cos(\lambda_{2m}) + 1}{\lambda_{2m}}\right)e^{-\lambda_{2m}^2 t} \qquad (12)$$

5. NUMERICAL RESULTS

The following physical parameters are considered for computational experiments:

$$L_1 = 5\cdot 10^{-4}\,cm \qquad L_2 = 10^{-2}\,cm \qquad D_1 = 10^{-10}\,cm^2/s \qquad D_2 = 7\cdot 10^{-8}\,cm^2/s$$
$$P = 10^{-6}\,cm/s \qquad k = 1 \qquad k_2 = 1 \qquad \varepsilon_1 = 0.1 \qquad \varepsilon_2 = 0.61 \qquad (13)$$

They are chosen on a physical basis and in agreement with the typical scales in drug-eluting stents and with data in literature for the arterial wall and for the heparin drug in the coating layer [1,2]. The physical problem apparently depends on a large number of parameters, each of them ranges in a finite interval, and there is a variety of different limiting cases. Actually the problem is shown to rely only on the four nondimensional controlling parameters:

$$\varphi = 0.234 \qquad \sigma = 0.164 \qquad L = 0.05 \qquad \gamma = 0.0014 \qquad (14)$$

and they are used as mean values for a set of numerical simulations.
The concentration profiles for three value of time are displayed in fig. 2: drug is eluting from coating to the wall, with concentration decaying in time, and going to zero at $x = 1$ (absorption at the wall). A concentration jump occurs at the interface $x = 0$. Both c_1 and c_2 are decreasing: at initial times they have a boundary layer near $x = 0$, at later times they vary almost linearly.

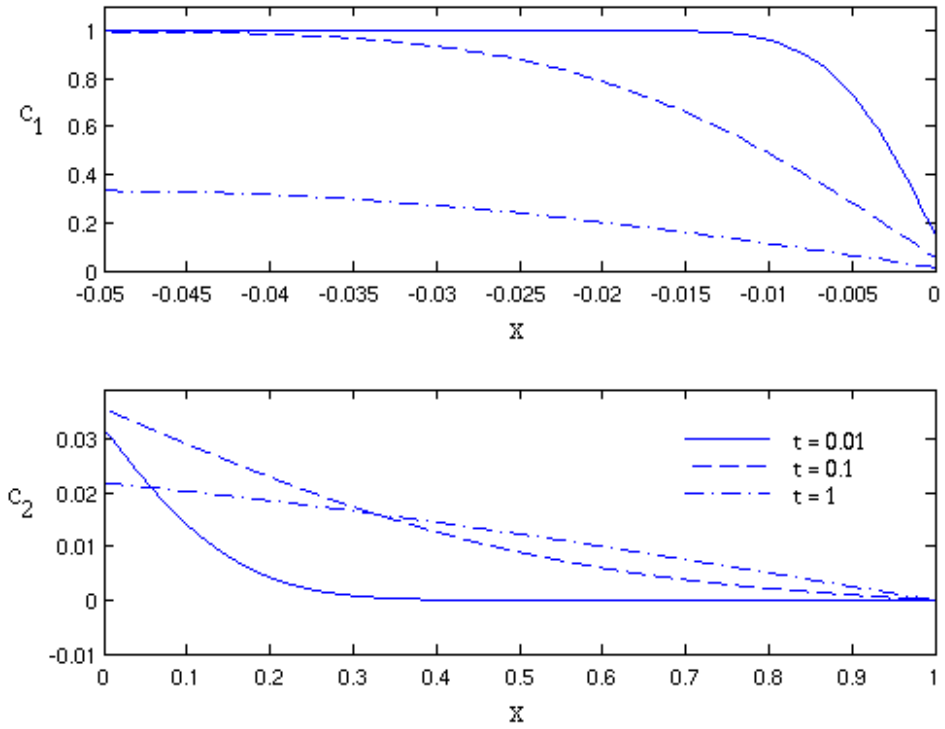

Fig. 2: Drug concentration profiles in the coating (above) and in the wall (below).

Drug mass in the coating layer M_1 is monotonically decreasing, while mass in the wall M_2, first increasing to a maximum M_2^* at time t^*, decreases to zero with the same rate of M_1 (fig. 3). Design parameters governing the rate of drug release can be screened by analyzing the solution dependence and the sensitivity on L, γ, ϕ, σ when they are varied in a limited realistic range one at a time around the mean values in eqn. (14), with the others fixed.

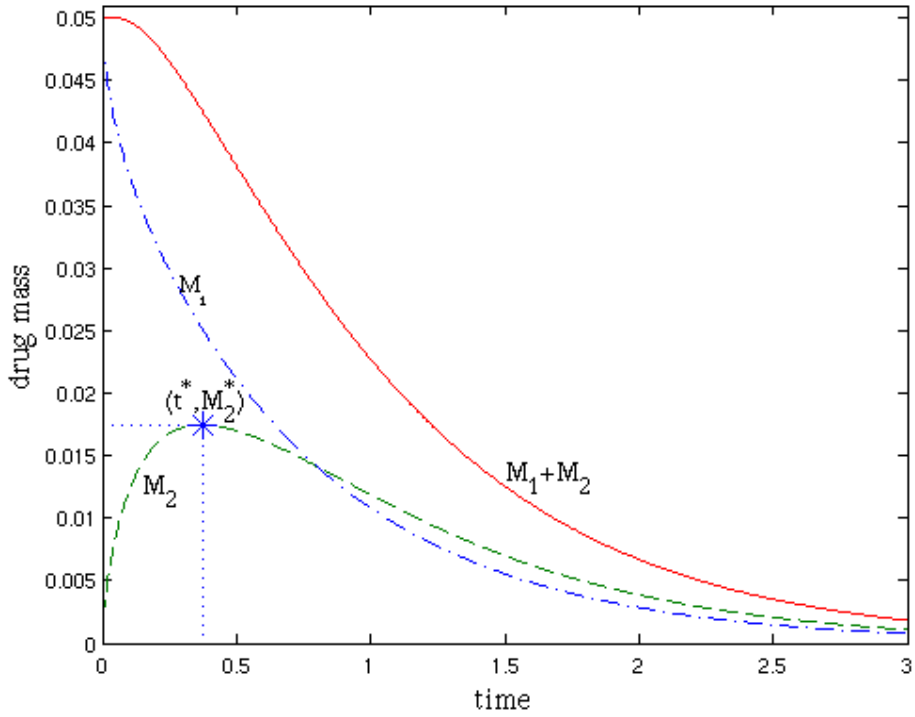

Fig. 3: Drug mass in the coating, in the wall and total mass as function of time.

6. REFERENCES

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