MATHEMATICAL MODELING OF CONVECTIVE DIFFUSIVE MASS TRANSFER WITH APPLICATIONS TO STENT BASED DRUG DELIVERY

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Abstract : Application of endovascular drug eluting stent for prevention and cure of restenosis is an emerging technology. Drug release depends on many factors such as the coating geometry and physic-chemical properties and drug characteristic such as diffusivity and solubility.
A comparison of analytical and numerical methods is made in this study. Artery is assumed to be symmetric with the strut residing inside the wall. Coating and arterial wall are treated as porous media. Mass transfer occurs in radial direction. At initial time drug is contained only in the coating, non-uniformly distributed and subsequently released into the wall.
Diffusion equation and advection-diffusion equation and related boundary initial conditions. A method of transformation and separation of variables give exact analytical solution for local concentration is obtained. Numerical methods based on Crank-Nicholson finite difference scheme is adapted to get solution of the governing equations. The effect of important factors such as drug diffusivity, cell metabolism, coating thickness and membrane permeability is analyzed

Keywords: Drug eluting stent, convective diffusive mass transfer, mathematical modeling, reaction rate, concentration.

Introduction : In the study of controlled drug delivery, mathematical modeling of the release process plays a significant role as it establishes a mechanism of drug (solute) release and provides more general guidelines for the development of other systems. Numerous successful controlled drug delivery systems have been developed as a result of an almost arbitrary selection of components, configurations and geometrics.
A drug eluting stent is a peripheral coronary stent placed into narrowed diseased peripheral or coronary arteries that slowly release a drug to block cell proliferation which prevents fibrosis together clots (thrombus) could otherwise block the stented artery, a process called restenosis. Drug eluting stents have reduced restenosis [1] and target lesion revascularization compared with bare metal stents [2].
Initial studies in drug eluting stents explained how the physicochemical properties of the drugs employed and the binding sites of target tissues contributed to drug transport and retention in the arterial wall [3]. As clinical concern for DES thrombosis continues to emerge in association with issues of stent design [4].
Drug release depends on many factors such as coating, geometry and physio-chemical properties and drug characteristics such as diffusivity and solubility. As the impact of flow and interaction of rheology with stent design evolves, the pattern of blood flow must be considered [5].
A purely diffusive model has been presented by Pontrelli & Monte [6]. Compared to a fully numerical method, the analytical approach provides a greater insight into physical sense of the drug delivery process. A one dimensional model of mass convection-diffusion in stent based drug delivery is considered by Pontrelli & Monte [7]. This model considers diffusion from a stent placed at the wall after implantation.
In the present study a stent placed at the wall of a cylindrical tube is considered. The wall of the cylinder is considered as porous media, through which mass transfer occurs. The governing equations are analytically solved and depicted graphically.

Mathematical Model: The drug- eluting stent consist of a metallic stent platform called strut coated with polymeric layer made of drug loaded matrix. The figure shows cross section of artery where drug eluting stent is placed.

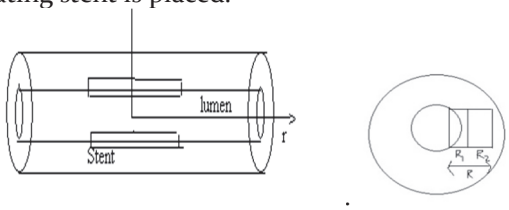

Fig.1. Schematic of Physical Configuration.

The wall is considered homogeneous fluid filled porous media .Mass transfer in radial direction is considered to dominate over mass transfer in axial direction. At $t = 0$ the drug is contained only in the coating .Metallic strut is impermeable to solute and diffusion towards lumen is assumed to be zero. It is also assumed that there is no slip of velocity at the wall of the artery. The governing equations for such a flow is given by

Region 1 $[r = R_1 \; to \; r = R_2]$

$$\frac{\partial c_1}{\partial t} = \frac{1}{r}\frac{\partial}{\partial r}\left(rD_1\frac{\partial c_1}{\partial r}\right) \quad (2.1)$$

Region 2 $[r = R_2 \; to \; r = R]$

$$\frac{\partial c_2}{\partial t} + v\frac{\partial c_2}{\partial r} = \frac{1}{r}\frac{\partial}{\partial r}\left(D_2\frac{\partial c_2}{\partial r}\right) - \beta_2 c_2 \quad (2.2)$$

The initial and boundary conditions are given by

$$-D_1\frac{\partial c_1}{\partial r} = 0 \quad \text{at} \quad r = R_1 \quad (2.3)$$

$$c_2 = 0 \quad \text{at} \quad r = R \quad (2.4)$$

$$D_1\frac{\partial c_1}{\partial r} = D_2\frac{\partial c_2}{\partial r} \quad \text{at} \quad r = R_2 \quad (2.5a) \quad -D_1\frac{\partial c_1}{\partial r} = p\left(\frac{c_1}{k_1\epsilon_1} - \frac{c_2}{k_2\epsilon_2}\right) \quad \text{at} \quad t=0 \quad (2.5b)$$

$$c_2 = 0 \quad \text{at} \quad t = 0 \quad (2.6)$$

$$c_1 = c_0 f(r) \quad \text{at} \quad t = 0 \quad (2.7),$$

where k = partition coefficient, ϕ = porosity, β =first order reaction rate coefficient , D_1, D_2 = diffusion coefficients in region 1 and region 2.

Non dimensionalising the above equations using ,

$$\left(r^*, R_1^*, R_2^*\right) = \frac{(r, R_1, R_2)}{R}, \quad t^* = \frac{D_2}{R_2}t, \quad \gamma = \frac{D_1}{D_2},$$

$$\varphi = \frac{PR}{D_2 K_2 \varepsilon_2}, \left(c_1^*, c_2^*\right) = \frac{(c_1, c_2)}{c_0}, \quad \sigma = \frac{K_1\varepsilon_1}{K_2\varepsilon_2},$$

$$\delta = \frac{V_2 R}{D_2}, \; \beta = \frac{\beta_1 R_2}{D_2} \quad (2.8)$$

we get $\frac{\partial c_1}{\partial t} = \gamma\left(\frac{\partial^2 c_1}{\partial r^2} + \frac{1}{r}\frac{\partial c_1}{\partial r}\right)$ (2.9)

in $[R_1, R_2]$

$$\frac{\partial c_1}{\partial r} = 0 \quad \text{at} \quad r = R_1 \quad (2.10)$$

$$\gamma\frac{\partial c_1}{\partial r} = \frac{\partial c_2}{\partial r} \quad \text{at} \quad r = R_2 \quad (2.11)$$

$$c_1 = f(r) \quad \text{at} \quad t = 0 \quad (2.12)$$

$$\frac{\partial c_2}{\partial t} = \frac{1}{r}\frac{\partial c_2}{\partial r} + \frac{\partial^2 c_2}{\partial r^2} - 2\delta\frac{\partial c_2}{\partial r} - \beta c_2 \quad (2.13)$$

in $[R_2, 1]$

$$-\gamma\frac{\partial c_2}{\partial r} = \varphi\left(\frac{c_1}{\sigma} - c_2\right) \quad \text{at } r = R_2 \quad (2.14)$$

$$c_2 = 0 \quad \text{at} \quad r = 1 \quad (2.15)$$

To solve the above equation and to eliminate the convective term the transformation, $c_2(r,t) = w_2(r,t)e^{\delta r - (\delta^2+\beta)t}$ is used, following [8].

The equation (2.13) becomes

$$\frac{\partial w_2}{\partial t} = \frac{1}{r}\frac{\partial w_2}{\partial r} + \frac{\partial^2 w_2}{\partial r^2} + \frac{\delta}{r}w_2 \quad (2.16)$$

$$-\gamma\frac{\partial c_1}{\partial r} = \varphi\left(\frac{c_1}{\sigma} - w_2 e^{-(\delta^2+\beta)t}\right) \quad (2.17)$$

at $r = R_2$,

$$w_2 = 0 \quad \text{at} \quad r = 1 \quad (2.18)$$

Using separation of variables, we get

$$c_2(r,t) = X_1(r)T_1(t) \quad \text{and} \quad w_2(r,t) = X_2(r)T_2(t)$$

Solving (2.9) and (2.16) we get $T_1(t) = e^{-\gamma\lambda_1^2 t}$ and

$T_2(t) = e^{-\gamma\lambda_2^2 t}$ (2.19) $rX_1'' + X_1' + \lambda_1^2 rX = 0$ (2.20)

and $rX_2'' + X_2' + (\delta\lambda_2 r)X = 0$ (2.21)

subject to the boundary conditions,

$X_1' = 0$ at r= R_1, $X_2' = 0$ at r = 1 (2.22a)

$$\gamma X_1' + \frac{\varphi}{\sigma}X_1 = \varphi X_2 \quad \text{at} \quad r = R_2 \quad (2.22b)$$

$$\gamma X_1' = X_2' + \delta X_2 \quad \text{at} \quad r = R_2 \quad (2.22c)$$

Solving the equations (2.20-2.22), we get

$$X_1 = A_1 J_0\left(2\lambda_1\sqrt{r}\right) + A_2 Y_0\left(2\lambda_1\sqrt{r}\right) \quad (2.23)$$

$$X_2 = A_3 U\left(a, 1, 2i\sqrt{\lambda_2}\, r\right) + A_4 L^{-a}\left(2i\sqrt{\lambda_2}r\right)$$

where $a = \frac{i(\delta - 2i\sqrt{\lambda_2})}{\sqrt{\lambda_2}}$ (2.24)

The constants $A_1, A_2, A_3 \; and \; A_4$ are evaluated using boundary conditions. We get the final solution as

$$C_1(r,t) = [A_1 J_0\left(2\lambda_1\sqrt{r}\right) + A_2 Y_0\left(2\lambda_1\sqrt{r}\right)]e^{-\lambda_1^2 t} \quad (2.25)$$

$$W_2(r,t) = [A_3 U\left(a, 1, 2i\sqrt{\lambda_2}\, r\right) + A_4 L^{-a}\left(2i\sqrt{\lambda_2}r\right)]\, e^{-\lambda_2^2 t} \quad (2.26)$$

$$C_2(r,t) = W_2 e^{-(\delta^2+s)t + \delta r} \quad (2.27)$$

The Eigen values λ_i are computed using inner and outer boundary conditions.

The mass/unit area of the drug in the coating and wall layers is given by

$$M_1(t) = \int_{R_1}^{R_2} C_1(r,t)dr,$$

$$M_2(t) = \int_{R_2}^{R} C_2(r,t)dr \quad (2.28)$$

The drug fraction left in the wall at any time t is given by

$$\overline{M_2}(t) = \frac{M_2(t)}{M_1(0) + M_2(0)} \quad (2.29)$$

Results And Discussions: The mathematical model presented, predicts the evolution of drug concentration in a cross section of the wall after the stent is implanted. The combined effect of diffusion and convection is considered .The physical parameters affecting the concentration at any time are effective permeability ε, effective porosity σ, diffusivity ratio γ, convective coefficient δ and reaction coefficient β. The graphs are plotted for different values of these parameters and their effect on concentration and drug fraction left at the wall are analysed.

Fig 2-4 shows variation of drug fraction left in the wall against time. Initially when the large mass is convected to the wall, the convected solute diffuses slowly and reaches zero at large time. The diffusion parameter β, convection parameter δ affects the diffusion most. β=0 shows maximum retention of solute at the wall and diffusion is very slow due to absence of chemical reaction. For β=0.6, due to chemical reaction, the fraction left at the wall is less and gets diffused in a shorter time. Due to increased reaction rate at β=1.2 the solute fraction at wall increases very fast initially but gets diffused very fast. Due to chemical reaction present at the wall the concentration increases initially and gets degraded or convected or diffused in a short time.

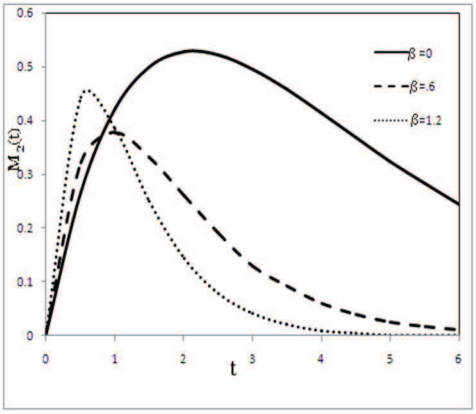

Figure 2. Plot of drug fraction left in the wall vs time for different values of reaction rate.

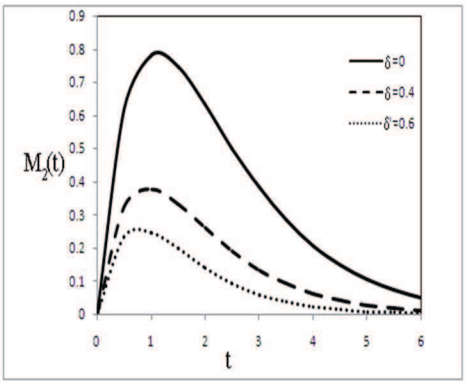

Figure 3. Plot of drug fraction left at the wall for different values of convection parameter

Figure 3 shows variation of solute fraction left at the wall for different values of velocity of fluid. The effect of convection is seen in these graphs. When δ=0, convective term is zero and diffusion alone controls mass transfer. Hence rate of mass transfer is low. The drug fraction left at the wall is high. As convection increases some part of solute gets convected and mass transfer is faster, hence drug fraction left at the wall is low.

Figure 4. compares effect of diffusivity ratio λ and permeability ratio ε. As diffusivity ratio γ increases the diffusivity of solute in region 2 decreases. Hence more solute gets deposited at the wall. As permeability increases, due to increased flow of liquid, more solute gets convected.

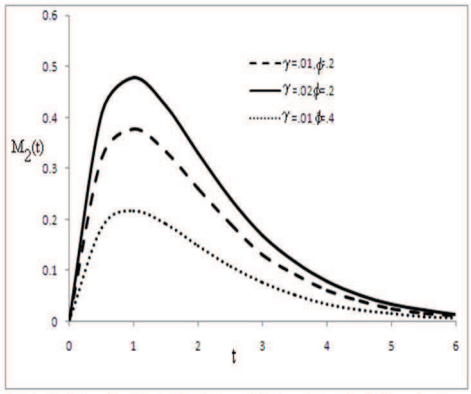

Figure 4. Plot of drug fraction left at the wall at any time for different values of diffusivity and permeability

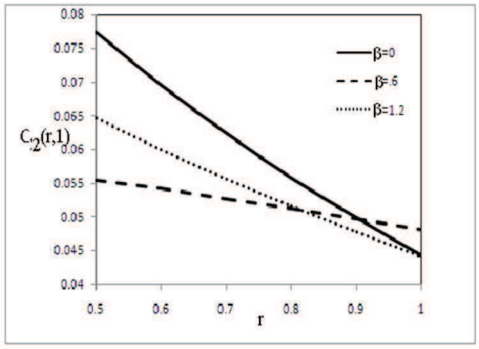

Figure 5. Plot of radial concentration profile for different values of reaction parameter

Figure 5-7 shows plot of concentration in region 2 in radial direction. Concentration generally decreases in radial direction. As β increases from 0 to 0.6 initial concentration decreases. The β=0.6 curve starts at a lower concentration, but more solute is convected to the wall, indicating moderate reaction rate is more ideal for drug transfer.

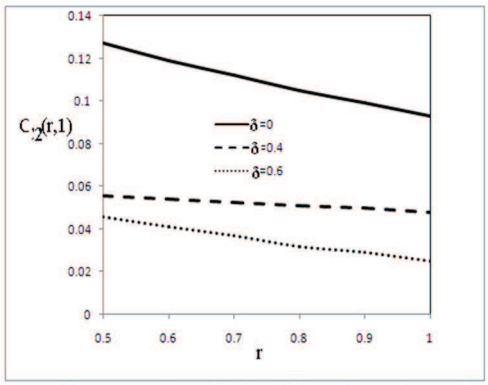

Figure 6. Radial concentration profile for different values of convection parameter

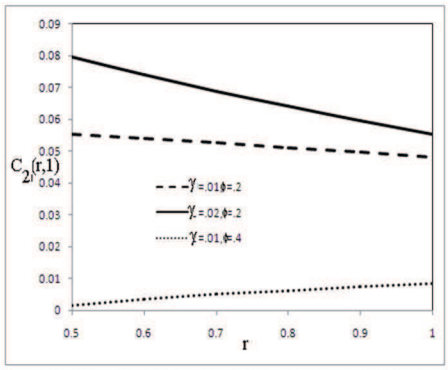

Figure 7. Radial concentration profile for different values of diffusivity and permeability

Convection is another factor which influences concentration. In the absence of convection more solute diffuses to the wall. Convection term results in loss of solute with reference to a particular site. Figure 7 shows effect of diffusivity and permeability on mass transfer. As permeability increases more solute gets convected to the wall and results in loss of solute.

Conclusion: In the present analysis mass transfer due to convective diffusion in a stented arterial wall is analysed. The conditions assumed here are ideal, as the convective effects due to flow of blood in the lumen and permeability of arterial wall etc. are not considered. The results show relevant aspects of convective and diffusive mass transfer with first order chemical reaction. The effect of reaction coefficient β is to enhance mass transfer thereby decreasing mass fraction left in the wall.

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