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A three-dimensional mathematical model for drug delivery from drug-eluting stents

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Abstract

Current drug-eluting stent (DES) technology is not optimized with regard to the pharmacokinetics of drug release, more research on the drug-eluting stent design and flux of drug release to the arterial wall is necessary. Considering a three-dimensional (3D) cylindrical mathematical model, a novel free drug mass transfer release has been formulated and applied for better estimation of the drug concentration in the tissue. The transport equations involved both convection and diffusion equations. Besides, a reversible reaction in the arterial wall was considered. The present model was solved by an appropriate numerical simulation method and the predicted results were compared with in vivo data. To find out the rate-limiting step, the time scale analysis was also applied. The obtained results showed that the binding process is more limited by convection and diffusion, where convection is the rate-controlling step. It is also demonstrated that the presented approach has advantages over the prior free drug mass transfer models, including better data prediction and satisfying mass transfer consistency.

Keywords: *Drug Eluting Stent, Three-Dimensional Model, Free Drug Mass Transfer, Reversible Binding, Limiting Step*

1. Introduction

Heart problems have been successfully treated with drug-eluting stents nowadays, preventing the need for more invasive procedures such as coronary artery bypass surgery. The reduced risk of re-blocked arteries from drug-eluting stents can resolve the need for repeating angioplasty procedures, which carry the risk of complications such as the heart attack and

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stroke. The stents are coated with a drug that is slowly eluted to prevent the growth of scar tissue in the artery wall. This helps the artery to remain smooth and open, ensuring excellent blood flow. Drug-eluting stents are safe and effective in most circumstances, having a lower rate of restenosis than bare-metal stents. Even with utilizing stents, 10-20 percent of arteries become blocked again [1]. Consequently, better improvement of the stents to reduce the problems of re-blocking and restenosis are necessary. Designing a drug delivery system with consistent and reliable elution is a great challenge in biomechanical engineering. As a result, further understanding of the drug release flux and kinetics is necessary for designing a stent-based drug delivery system to enhance the therapeutic efficiency and to minimize the local arterial toxicity. Many questions about these stents are still remain: How much of the drug should be coated on the stent? What is the rate of drug elution? What is the best model for prediction of drug elution?

Several authors have investigated the role of geometry on the design of stent [2-4], polymeric coating [5], release of drug from non-erodible polymer coated stent [6-12] and biodegradable polymer coated stent [13-21]. However, drug transport through the arterial wall and the mechanism of drug binding with constituents of arterial wall need further attention. While the convective and diffusive elements of drug transport are well recognized, the problem of drug binding is more controversial.

One of the methods to evaluate the characteristics of drug elution from the stent into the arterial wall and to optimize the physico-chemical parameters is the mathematical modeling of drug delivery system. Mathematical modeling has appeared in recent years as a powerful tool to simulate the drug delivery processes in DES. Computational modeling of drug transport through the arterial wall will improve the general knowledge about DES mechanisms.

The first mathematical model of arterial drug transport assumed constant partition of binding and free drug concentration [9] which was too simple to well predict the drug concentration profile in the arterial tissue. Some authors assumed equilibrium models involving a linear reaction term [6,22,23], while others considered simple loss terms [7,9,24,25]. However, it is generally accepted that a non-linear reversible reaction is required to describe binding [26]. Therefore, one and two-dimensional saturable binding models have been utilized in most cases [27-30]. But, these models do not satisfy the mass conservation equation and tend to infinity with increasing time [28,29]. In addition, the mechanisms of drug release, transport and binding within the stent and arterial wall have rarely been investigated simultaneously [26-29].

In this study, a three-dimensional mathematical model was used to strictly predict the arterial drug concentration and flux after the drug is released from the stent. The model takes into account the convection and diffusion within the arterial wall, consisting of a non-linear reversible binding kinetics to describe the drug interactions with the elements of arterial wall. Furthermore, a new approach for the mass of drug released from the stent was applied in place of Higuchi diffusion-limited dissolution kinetics [29] which was compared with some

previous studies and in vivo data. Finally, a time scale analysis was presented to reveal the mechanisms governing drug distribution into the arterial wall.

2. Model development

Sirolimus, initially known as rapamycin, is a macrolide immunosuppressant agent with a unique mechanism of action. It is a fermentation product isolated from a strain of *Streptomyces hygroscopicus* found in the soil samples of Rapa Nui in Easter Island. Sirolimus inhibits the T-lymphocyte activation and proliferation, as well as the antibody production. It binds to FK-binding protein-12 (FKBP-12) to form a complex which inhibits the activation of mammalian target of rapamycin (mTOR), a key regulatory kinase. The inhibition of mTOR suppresses cytokine-driven T-cell proliferation resulting in the inhibition of cell cycle progression from G_1 to S phase [31,32].

In order to estimate the drug distribution and investigate its biological effects, a mathematical model has been employed. The drug delivery process is described by the drug transport through the arterial wall and its reversible binding. To accomplish this, a cylindrical three-dimensional axisymmetric geometry was used in all cases (Fig. 1). The stent struts are too thin relative to the arterial wall and their actual geometry can be considered as a surface. In this way, the governing equation for diffusion of drug into the arterial wall is considered as:

$$\frac{\partial C}{\partial t} = \frac{D_r}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C}{\partial r}\right) + \frac{D_\varphi}{r^2}\frac{\partial^2 C}{\partial \varphi^2} + D_z\frac{\partial^2 C}{\partial z^2} - V_{Wall}\frac{\partial C}{\partial r} - \frac{\partial b_{REC}}{\partial t} - \frac{\partial b_{ECM}}{\partial t} \quad (1)$$

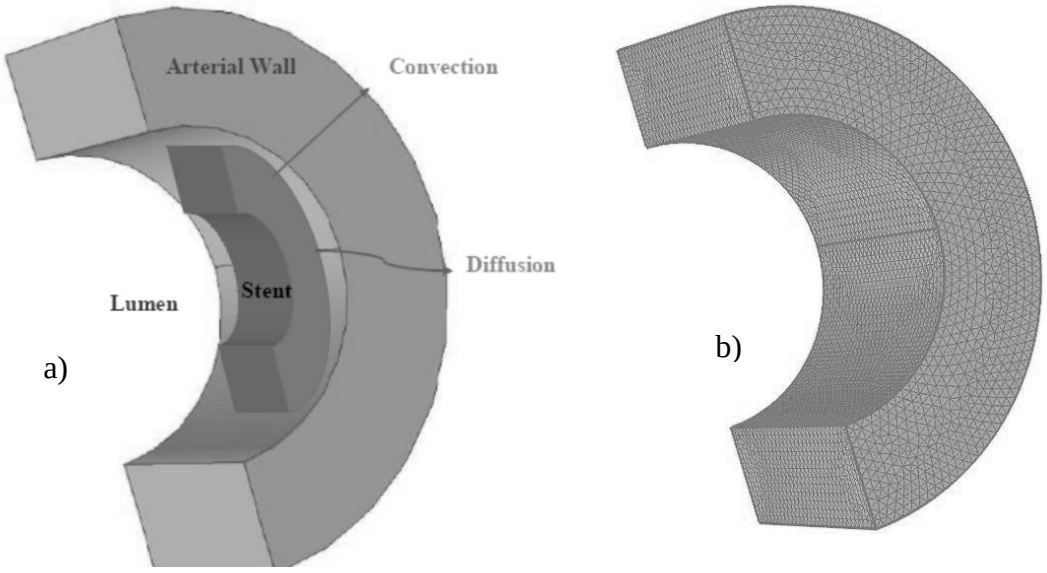

Figure 1. The model geometry (a) Three-dimensional arterial wall with stent (b) Computational mesh.

Where, C is the molar concentration of free drug per unit volume of tissue, b_{REC} is the molar concentration of receptor bound drug and b_{ECM} is the concentration of unbound drug in the extracellular matrix (ECM). $D_n(r, \varphi, z)$ is the transmural drug diffusivity in the cylindrical coordinates, V_{Wall} is the transmural convective velocity through the arterial wall and t is time. The

reversible binding in the wall can be described by the following expressions [29]:

$$\frac{\partial b_{REC}}{\partial t} = k_{on}^{REC} C.(b_{REC0} - b_{REC}) - k_{on}^{REC} k_d^{REC} b_{REC} \quad (2)$$

$$\frac{\partial b_{ECM}}{\partial t} = k_{on}^{ECM} C.(b_{ECM0} - b_{ECM}) - k_{on}^{ECM} k_d^{ECM} b_{ECM} \quad (3)$$

Where, b_{REC0} and b_{ECM0} denote the local molar concentrations of receptor and ECM sites, k_{on}^{ECM} and k_{on}^{REC} are the respective binding on-rate constants and k_d^{ECM} and k_d^{REC} are the respective equilibrium dissociation constants.

The initial and boundary conditions of equations (1) to (3) are:

$$b_{ECM} = b_{ECM0} \quad , t = 0 \quad (5)$$

$$b_{REC} = b_{REC0} \quad , t = 0 \quad (6)$$

$$D_{(r,\varphi,z)} \partial C / \partial(r,\varphi,z) + V_{wall} C = Flux_{in} \quad , r = r_{min} \quad (7)$$

$$C = 0 \quad , r = r_{min} + W \quad (8)$$

Where, r_{min} is the radius of expanded stent and W is the thickness of arterial wall. To obtain the input mass flux ($Flux_{in}$), the mass of drug released from the stent can be expressed by a new correlation:

$$M_{stent}(t) = A - B\,(1 - \exp(-Ct)) - D\sqrt{t}/\sqrt{1+t} \quad (9)$$

Table1

The arterial-wall transport and equilibrium binding parameters of sirolimus.

Parameter	Value	Reference
W	450 µm	[18]
r_{min}	1.75 mm	[18]
Length of stent (L)	3.5 mm	[29]
S	2 cm^2	[28]
f (NEVO)	0.16	[29]
f (CYPHER)	0.06	[29]
V_{Wall}	$5.8Y10^{-6}$	[8]
M_{Drug}	914.2 g/mol	[20]
D_n	2210^{-6} $cm^2.1/s$	[29]
b_{ECM0}	362.7 µM	[28]
b_{REC0}	3.3 µM	[28]
k_d^{ECM}	2.6 µM	[28]
k_d^{REC}	2210^{-4} µM	[28]
k_{on}^{ECM}	2210^{-3} $38^{-1}1/s$	[28]
k_{on}^{REC}	$0.8\ .8^{-1}1/s$	[18]

Where A denotes the initial load of drug per stent (μg), B is the initial pool of first order eluting drug (μg), C is the rate constant (d^{-1}) and D is a constant.

Unlike other modeling approaches such as Tzafriri *et al*. [29] in which the mass of drug released eventually tends to infinity, the following conditions were applied in the present work to suitably satisfy the mass conservation equation:

$$t \to 0 \quad \text{then} \quad M_{stent}(t) = A \qquad (9.A)$$

$$t \to \infty \quad \text{then} \quad M_{stent}(t) = A - B - D \qquad (9.B)$$

Denoting the surface area of the blood-wall interface as S and the efficiency factor for delivery into the wall as f (0<f<1), the input mass flux is expressed as:

$$Flux_{in} = -f \frac{\frac{dM_{stent}}{dt}}{S\, M_{Drug}} \qquad (10)$$

$$\frac{dM_{stent}}{dt} = -B.C.\exp(-Ct) - \frac{D}{2\sqrt{(1+t)^3}\sqrt{t}} \qquad (11)$$

The required parameters for arterial-wall transport and equilibrium binding of sirolimus are given in Table 1. Equations (1) to (11) were solved numerically using the commercial finite element package COMSOL 3.4a. The "Chemical Species Transport" and the "Transport of Diluted Species User Interface" modules were selected to model the chemical species eluted by diffusion and convection. The three-dimensional domain was meshed using 1920 cubic Lagrange elements. The resulting systems of algebraic equations were solved with a variable order backward differentiation formula (BDF) [33], using the time step size and tight tolerances (relative tolerance of 10^{-9} and absolute tolerance of 10^{-10}).

3. Result and discussion

3-1. Determination of model parameters

NEVO™ prototype and CYPHER® [29] stents have been considered in the present approach. According to Eq. (9), the mass of drug released from the stent has four parameters A, B, C and D which were determined by non-linear regression (least-squares method) of experimental data. The non-linear least squares method was applied by utilizing Levenberg-Marquardt algorithm. Finally, a computer program written in MATLAB [34] was used to determine the parameters by minimizing the following objective function:

$$\Theta = \frac{1}{2}\sum_{i}^{NPTS} (M_{Stent}^{cal} - M_{Stent}^{expt})^2 \qquad (12)$$

Where, M_{Stent}^{cal} and M_{Stent}^{expt} are the calculated and experimental amount of drug released from the stent and $NPTS$ is the number of data. Absolute average deviations (*AAD*) was used to compare the correlation with in vivo data:

$$AAD = \frac{100}{NPTS}\sum_{i}^{NPTS} \frac{|M_{Stent}^{cal} - M_{Stent}^{expt}|}{M_{Stent}^{expt}} \qquad (13)$$

The correlated parameters and absolute average deviations are given in Table 2. Comparing the results obtained from Higuchi correlation [29] with the present approach, it is observed that the model parameters completely satisfy mass consistency requirements.

Table 2

Elution kinetic parameters of Sirolimus. AAD for both stents is also compared with Higuchi model [29].

Stent Type	A (μg)	B (μg)	C (d^{-1})	D (μg)	AAD
NEVO (Present work)	160.16	137.04	0.0564	23.12	4.76
CYPHER (Present work)	174.89	104.95	0.0531	69.94	5.62
NEVO [29]	-	-	-	-	7.21
CYPHER [29]	-	-	-	-	5.32

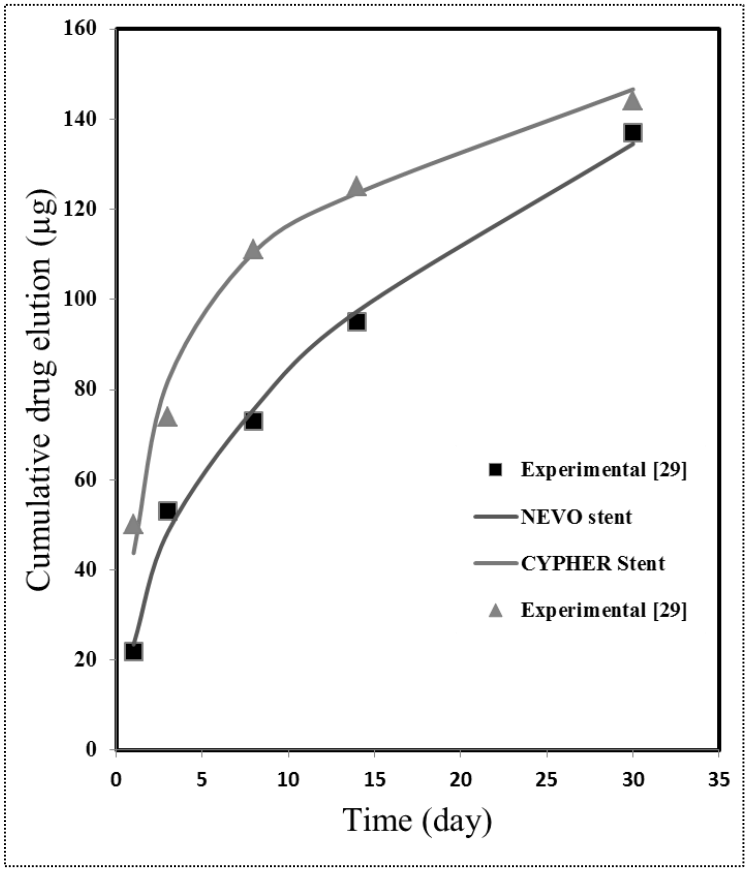

Figure 2. The cumulative mass of drug eluted from NEVO and CYPHER stents (With permission of [29]).

Fig. 2 shows the predicted cumulative mass delivery data. In the first five days, CYPHER stent releases drug about twofold greater than NEVO. However, over time, the amount of drug delivery from both stents will be the same. Based on the parameters specified in Table 1, the numerical solution of Eqs. (1) to (11) is provided in Figs. 3-5. The Sirolimus tissue content for both stents with in vivo data is shown in Fig. 3. It demonstrates linear behavior for both NEVO and CYPHER stents. The slope of lines reveals the difference between the efficiency of drug transfer to the artery.

Table 3
AAD of drug tissue content for NEVO and CYPHER stents and their comparison with Tzafriri *et al*. model [29].

Stent Type	AAD (Tzafriri *et al*. model [29])	AAD (Present work)
NEVO	3.89	1.63
CYPHER	9.62	4.92

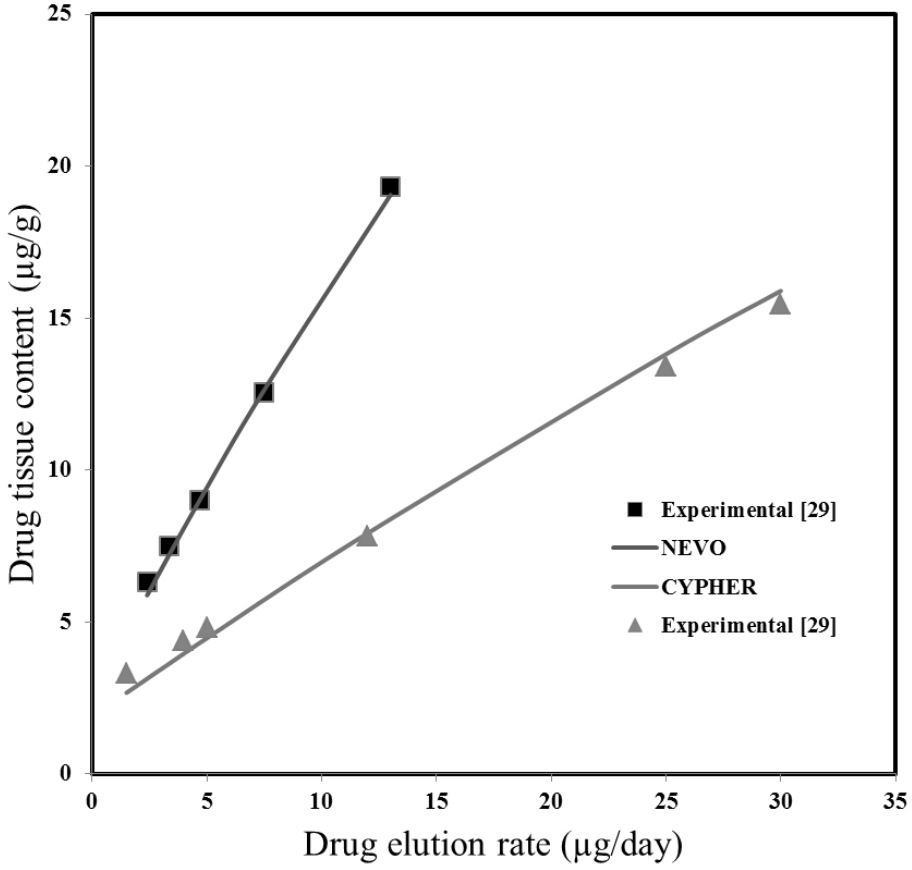

Figure 3. Variation of Sirolimus tissue content versus drug elution rate for NEVO and CYPHER stents (With permission of [29]).

The obtained simulated results are completely comparable to the previous model of Tzafriri *et al*. [29], especially in the case of NEVO stent (Table 3). In addition, both curves intersect the vertical axis, nearly at the same point equal to the initial concentration of receptor ($b_{REC0} = 3 \pm 0.3\ \mu g.g^{-1}$).

Fig. 4 shows the variation of free drug concentration of stents with time. In both cases, the free drug concentration tends a constant value after five days. Furthermore, NEVO stent releases more drug than CYPHER which has been confirmed by Tzafriri *et al.* [29].

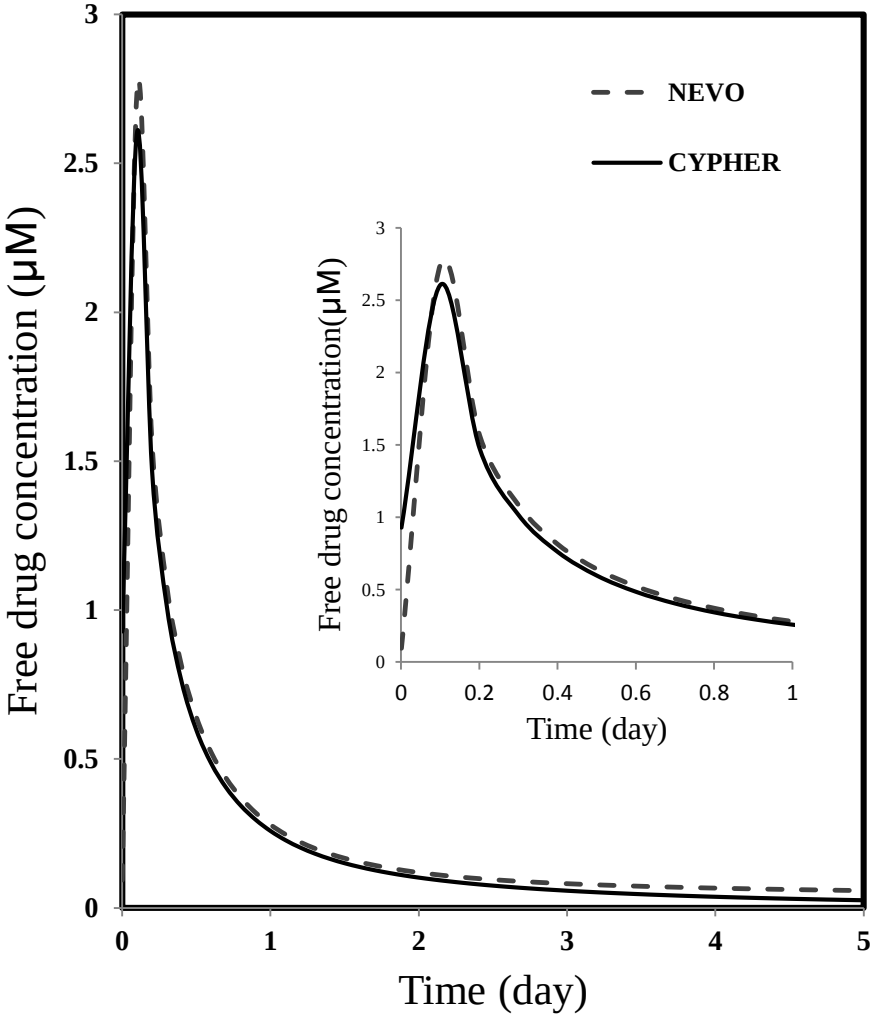

Figure 4. Variation of free drug concentration versus time for NEVO and CYPHER stents.

The variation of receptor concentration versus time for both stents is shown in Fig. 5. The receptor concentration of CYPHER stent reduces faster than NEVO. However, the rate of reduction is slow for both.

3-2. Timescale analysis and rate limiting step

To further analyze the obtained results, it is useful to determine the timescales introduced by Eq. (2). The time scale of drug receptor binding is:

$$t_B = \frac{1}{k_{on}^{REC} b_{REC0}} \tag{14}$$

In the same manner, the timescale characterizing unbinding is:

$$t_{UB} = \frac{1}{k_{on}^{REC} k_d^{REC}} \tag{15}$$

It will also be interesting to compare the timescales of drug binding and unbinding to those of drug convection and diffusion. The time scale for convection in the arterial wall is:

$$t_C = \frac{W}{V_{Wall}} \tag{16}$$

In the case of diffusion it can be expressed as:

$$t_D = \frac{W^2}{D_n} \tag{17}$$

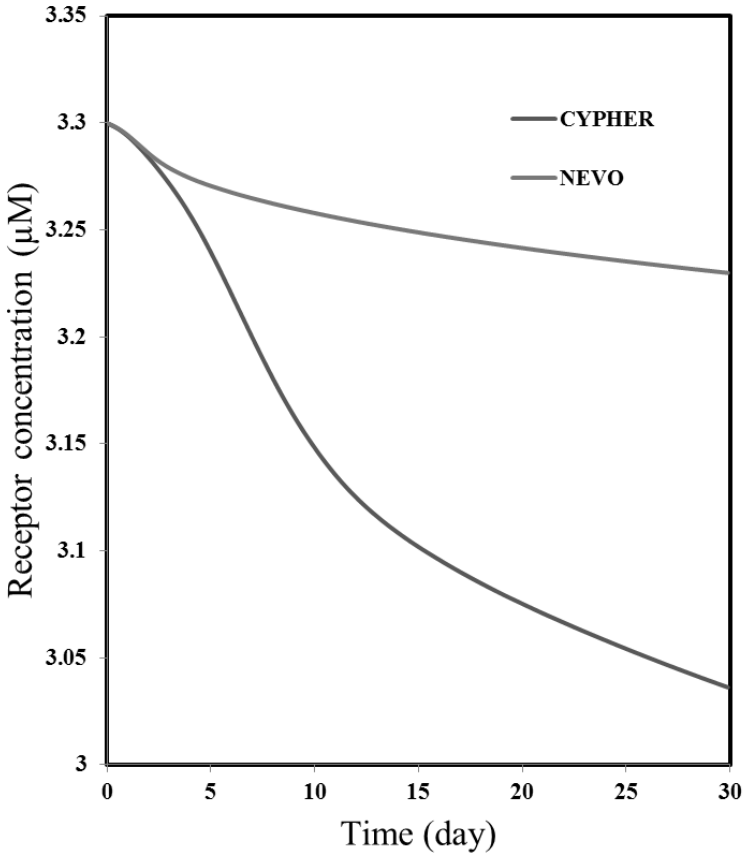

Figure 5. Variation of receptor concentration versus time for NEVO and CYPHER stents.

For comparison with the binding reaction time, the sum of two time scales can be considered as drug dispersion time ($t_C + t_D = t_{Ds}$). Now, the DamkÖhler numbers of diffusion and convection are defined as:

$$Da_D \equiv \frac{t_D}{t_B} \approx \frac{k_{on}^{REC} b_{REC0} W^2}{D_n} \qquad (18)$$

$$Da_C \equiv \frac{t_C}{t_B} \approx \frac{k_{on}^{REC} b_{REC0} W}{V_{Wall}} = \frac{Da_D}{Pe} \qquad (19)$$

Where, $Pe = V_{Wall} W / D_n$. The resulting calculated timescales and dimensionless numbers are summarized in Table 4.

Table 4
Timescales and dimensionless numbers for Sirolimus.

t_B (h)	t_{UB} (h)	t_D (h)	t_C (h)	t_{Ds} (h)	Da_D	Pe	Da_C
1.05×10^{-4}	1.73	0.28	2.15	2.43	2666.7	0.13	20476.2

As can be seen, the time of reaction binding is small compared to other timescales. This shows a very fast reaction, in which dispersion is the limiting step. Furthermore, dispersion involves both the convection and diffusion that have different orders of magnitude. Diffusion is about eightfold faster than convection. As a result, convection is the rate-controlling step in the diffusion-reaction process. A similar deduction can be found with the Damköhler number.

Small Damköhler numbers may occur in highly porous gels or when the transport path in the tissue is very small. In contrast, drug binding to most tissues, including arterial and various tumors, is generally characterized by large diffusion Damköhler numbers, implying that binding is diffusion-limited [35]. As can be noted in Table 4, DamkÖhler number of convection is quite large compared to diffusion.

4. Conclusions

In this paper, a simultaneous 3D transport-reaction model for mass dynamics from a drug-eluting stent has been developed that takes into account the arterial drug concentration and flux into the arterial wall. The mathematical model was validated using in vivo data to quantitatively characterize the drug release profiles. The approach includes non-equilibrium mass transfer terms combined with the chemo-physical properties of the drug which lead to more accurate results compared to some previous studies that have a significant impact in stent design. The mass consistency of present approach in the boundaries and its great AAD in comparison to previous studies of drug elution flux to arterial wall has been revealed. The time-dependent local drug delivery plays a critical role in understanding the influence of dose escalation and optimal duration of elution on local drug deposition and anticipated biological effects. In addition, referring to timescale analysis of binding, unbinding, convection and diffusion steps, it was demonstrated that convection is the rate-controlling step of the process. When the rate of drug absorption by the stented artery exceeds the rate of drug elution, the drug is diluted systemically prior to arterial uptake.

In general, this modeling methodology offers a useful tool for predicting the local drug delivery at future time points, improving the drug release efficiency, optimal stent design for drug release and to provide valuable insights into local vascular drug-delivery systems.

Nomenclature

b_{REC}	Molar concentrations of receptor bounded drug	***Greek Symbols***	
b_{ECM}	Molar concentrations of unbounded drug	Θ	Objective function
b_{REC0}	Initial local molar concentration of receptor	μ	Micro
b_{ECM0}	Initial local molar concentration of ECM sites	*Subscripts and Superscripts*	
C	Molar concentration of free drug per unit tissue volume	Cal	Calculated
$D_n(r,\varphi,z)$	Transmural drug diffusivity	ECM	Unbounded site
f	Efficiency factor	Expt	Experimental
k_d^{REC}	Equilibrium dissociation constant of receptor	REC	Receptor cites
k_{on}^{REC}	Binding on-rate constant of receptor	***Abbreviations***	
k_d^{ECM}	Equilibrium dissociation constant of ECM sites	*AAD*	Absolute Average Deviation
k_{on}^{ECM}	Binding on-rate constant of ECM	*NPTS*	Number of experimental points
M_{Drug}	Molecular weight of drug	*DES*	Drug eluting stent
M_{stent}	Mass of drug released from the stent		
r_{min}	Radius of expanded stent		
S	Surface area of the blood-wall interface		
t	Time		
V_{Wall}	Transmural convective velocity		
W	Thickness of the arterial wall		

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