How the Sirolimous-Releasing Dynamics change when Adventitia Layer and Drug Metabolism are taken into Account?

S. M. Vahedi, M. Valipour

***Abstract*—**Nowadays, the drug-eluting stent application has boomed as an effective treatment for coronary artery blockage. Experimental determination of the spatio-temporal variation of drug concentration in the arterial wall as well as the polymeric coating is very expensive and even impossible for many cases. In this paper, the volume-averaged porous media equations were developed to solve for transport through the porous arterial layers. The established equations are solved numerically by using the finite-volume method. The effects of adding adventitia layer and the drug consumption at the surface of Vasa vasorum cells in the mathematical modeling were considered as two important factors on drug pharmacokinetics. These models have been presented in two types of interface conditions, real porosity, and equal porosity, for the coating-media and media-adventitia interfaces, respectively. It was assumed that the injuries due to the angioplasty procedure penetrate to the depth of the media layer to have a more realistic simulation. The results showed that drug-containing polymer is diffusion-dominated and the porosity difference of the layers is the most effective factor for drug release dynamics in comparison to adding the adventitia layer and considering the sink condition there. Neglecting the adventitia layer causes a faster drug depletion during release action. While considering the drug reaction and washing out via Vasa vasorum cells have an inverse effect. The results show that although these two factors have a significant impact on the arterial drug uptake, the polymer does not change due to its low porosity. Utilizing the real porosities results in a considerable increase in concentration level. Therefore, dome shape of temporal variation of the normalized drug concentration profile in the media layer becomes more tapered when the difference of porosities not taken into account. Altogether, the results imply on the noticeable effect of interface condition on drug dynamics.

***Keywords*—** Atherosclerosis, Convection-diffusion-reaction equation, Drug-Eluting Stents (DES), Pharmacokinetics, Porous media.

I. Introduction

ANGIOPLASTY is one of the most useful, common and a minimally invasive treatment for arteries blockage and atherosclerosis. Preventing the movement of the stent due to heart pulsation and assuring its fixed position the diameter of the expanded stent is considered higher than the artery's [1-4]. A high tension imposed to the arterial wall due to this procedure can cause injury which leads to Smooth Muscle Cells (SMCs) migration from media layer to Intima layer and eventually causes restenosis [5]. The probability of the restenosis after stent implantation is the main concerns of using DES. In order to over-come this problem, polymers have been used widely as a local drug delivery system and became the most effective approach to delivering treating agents [5].

Understanding of spatio-temporal drug distribution in polymer and the tissue is need-ed to produce more efficient devices. Several one-dimensional models have been pro-posed to fundamentally analyze drug release from the coating and drug-vascular tissue interactions [4-8]. In fundamental studies, simpler one-dimensional models give many useful hints on the underlying physics and allow a systematic analysis of a wide range of parameters[4]. This model has been employed by many of the researchers from single homogeneous layer to the most complicated multi-layered structure and solved numerically and analytically [6]. Hwang et al. [5] studied the effect of the convective term in the arterial wall for both hydrophilic and hydrophobic drugs. They considered a basic model in two space dimensions in order to investigate the role of convection with respect to the drug distribution inside the wall. Their models had been obtained from their macroscopical observations. The effect of thrombus on drug uptake was considered by Balakrishnan et al. [9]. They found that local thrombotic response to stent deployment can also affect arterial drug distribution by forming a mural layer that impedes drug penetration into target lesions. Borghi et al. [10] focused on the impact of luminal blood flow on drug wash out. Heparin was their working drug. They showed that after 24h only about 0.002% of heparin is dissolved into the bloodstream. So they concluded that considering the luminal washout does not have a noticeable impact on the arterial drug uptake. The calculations by Vairo et al. [11] indicated the insignificancy of the drug concentration profile in the arterial wall when the lumenal blood flow be taken into account. They showed that increase in velocity of luminal flow has no effect on drug release profiles from the coating when the strut embedment remains fixed. The luminal drug transfer of sirolimus, as a hydrophobic drug, was subjected to the study of Kolachalama et al. [12]. They put a two-phase computational model into use for stent-deployed in ideal arterial bifurcations simulating blood flow and drug transport. Simulations predicted that heterogeneous drug distribution

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patterns are sensitive to relative stent position and luminal flow. They took the interstitial flow through the porous arterial wall into consideration. Their results showed that the inclusion of transmural convection increases the volume weighted average of drug concentrations within the tissue by less than 1% and is therefore negligible. The effect of coating characteristics on an idealized geometry of stent was investigated by Balakrishnan et al. [13]. They utilized a single-species approach, either neglecting the effect of drug binding or using an approximate model to represent binding and partitioning in the vessel wall. They also focused on local hemodynamics ignoring anisotropic diffusion, coating and tissue porosity, plasma filtration in the tissue and protein effects.

To the best of our knowledge, no one studied the effect of adding the adventitia layer yet. Also, many of the researchers did not consider the coating and tissue porosities into account. In the present study, the adventitia layer has been taken into consideration as a pure diffusion and a diffusion-reaction layer, separately. The injured coronary artery has been modeled as a multi-layered structure. Denudation of endothelium, intima and IEL layers is assumed. Moreover, since the strut cut through the media layer, 40% embed-ment is assumed as a depth of injury. So, the polymeric gel has a direct contact with the media layer. The sirolimus concentration distribution as a working agent was also con-sidered in the media and adventitia layers as well as coatings. Almost 16 days of drug release was simulated, and area under concentration of coating, media and adventitia layers has been calculated and compared with previous studies results of a healthy artery.

II. Conceptual Model

A detail of the computational domain, including the coronary arterial tissue, polymer, stent strut and drug loading on its surfaces have been shown, schematically, in Fig 1. Despite the fact that the depth and amount of the damage is not clear, studies predict a high probability of endothelium, IEL and intima layers denudation during angioplasty [14,15]. In the present study, it was assumed that the polymer has a direct contact with the media layer. At first, the drug with its maximum concentration in loaded to the polymer. During the release procedure drug mass into the polymer decreases, monotonically. But, into the tissue, firstly drug increases, then reaches to the maximum and finally decreases. The coronary artery has a circular cross section of 3mm diameter, and the axial changes in properties are negligible. Therefore the geometry can be reduced to 2D.

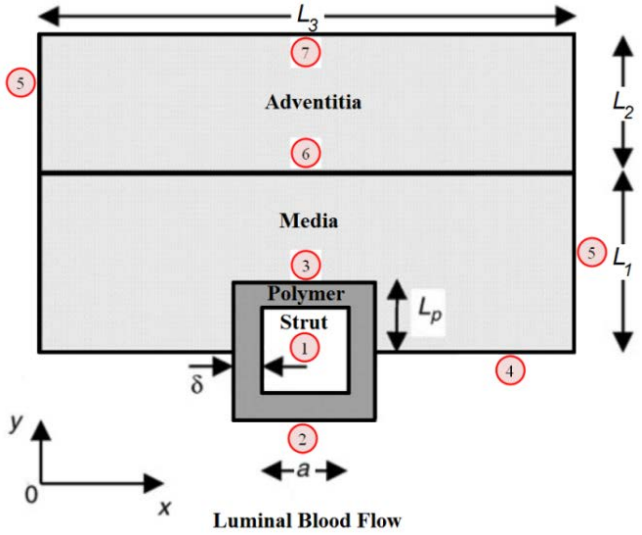

Fig. 1 Schematic representation of the computational domain.

The artery is considered as two humongous porous layers with different characteristics listed in table 1, and the porous media theory can be employed to write the governing equations.

Table 1. The values of dimensions and model parameters.

Dimensions	Values	Reference.
L_1	200μm	[16]
L_2	800μm	
L_3	1000μm	[16]
L_p	8880μm	[16]
a	140μm	[17]
δ	50μm	[18]
Model parameters	**Values**	**Reference(s)**
C_0	10^{-5}M	[19]
D_1	$0.1\mu m^2 s^{-1}$	[18]
D_2	$0.1\mu m^2 s^{-1}$	[20]
D_3	$12\mu m^2 s^{-1}$	[21]
k_a	$10^4 M^{-1} s^{-1}$	[22]
k_d	$0.01 s^{-1}$	[5]
S_0	10^{-5}M	[20]
ε_1	0.1	[23]
ε_2	0.61	[23]
ε_3	0.85	[23]

III. Mathematical Model

Considering above assumptions and the conceptual model, the computational domain can be divided into three parts as it was shown in figure 1. The continuity equation for the polymer can be written as follows [24]:

$$\frac{\partial C_1}{\partial t} = D_1 \frac{\partial^2 C_1}{\partial x^2} + D_1 \frac{\partial^2 C_1}{\partial y^2} \quad (1)$$

The plasma flow can not change its way through the polymer layer. Therefore, convective term in the polymer layer is omitted.

Continuity equations for the free and bounded drug into the tissue can be expressed as below:

$$\frac{\partial C_2^f}{\partial t} = D_{2x} \frac{\partial^2 C_2^f}{\partial x^2} + D_{2y} \frac{\partial^2 C_2^f}{\partial x^2} - k_a (S_0 - B) C_2^f + k_d B \quad (2)$$

$$\frac{\partial B}{\partial t} = +k_a(S_0 - B)C_2^f - k_d B \quad (3)$$

Adventitia layer is generally modeled as a diffusion-reaction layer [8].

$$\frac{\partial C_3}{\partial t} = D_{3x}\frac{\partial^2 C_3}{\partial x^2} + D_{3y}\frac{\partial^2 C_3}{\partial x^2} + \beta C_3 \quad (4)$$

A. Boundary conditions

Three types of conditions are used at the boundaries. As the stent strut is impermeable, no mass flux could penetrate through its surfaces specified by number 1. Due to the stent strut protrusion into the lumen and considering 40% embedment, polymer surfaces are in contact with luminal blood flow and media tissue, simultaneously. The surfaces are specified with numbers 2 and 3, respectively. Washing out of the drug into the bloodstream along the surfaces determined by number 2 is negligible because of the hydrophobicity nature of the sirolimus whereas drug uptakes through the polymer-media interface indicated by number 3. The drug is diffused into the tissue and then bounded into both the protein and the smooth muscle cells, immediately. Loosing drug at media-lumen interface is neglected.

No flux condition is assigned to the boundaries specified with numbers 1,2,4 and 5.

$$\frac{\partial C_1}{\partial n} = 0, \qquad \frac{\partial C_2^f}{\partial n} = 0, \qquad \frac{\partial C_3}{\partial n} = 0 \quad (5)$$

The presence of microcapillaries like Vasa vasorum provides a situation in which drug becomes vanished as it reaches that region. So, a perfect sink term is assigned to the adventitia-peripheral interface.

$$C_3(x, L_1 + L_2, t) = 0 \quad (6)$$

Concentration continuity and mass flux continuity conditions have to be satisfied along the interface of polymer-media as well as media-adventitia.

$$C_1 = C_2^f \quad (7)$$

$$C_2^f = C_3 \quad (8)$$

$$-D_1\frac{\partial C_1}{\partial x} = -D_{2x}\frac{\partial C_2^f}{\partial x} \quad (9)$$

$$-D_1\frac{\partial C_1}{\partial y} = -D_{2y}\frac{\partial C_2^f}{\partial y} \quad (10)$$

$$-D_{2y}\frac{\partial C_2^f}{\partial y} = -D_{3y}\frac{\partial C_3}{\partial y} \quad (11)$$

B. Initial Conditions

At first, the whole amount drug is loaded into the polymer, and at this time there is no drug, free or bounded, in the tissue.

$$C_1(x, y, 0) = C_0 \quad (12)$$

$$C_2^f(x, y, 0) = 0 \quad (13)$$

$$B(x, y, 0) = 0 \quad (14)$$

$$C_3(x, y, 0) = 0 \quad (15)$$

C. Numerical Simulation

The governing equations are solved numerically due to their complexities originated from the intrinsic coupling and geometrical variations. The governing equations together with the initial and boundary conditions are solved numerically by using FORTRAN programming. The equations were discretized over a structured and fine square mesh. The problem is unsteady, so the time derivative terms are discretized explicitly and the solution became time-marching. There are three Courant numbers which act as the convergence controllers [25]. They were signed with 1, 2 and 3 for coating, media and adventitia layers, respectively. In order to prevent divergence of the solution, it is just enough to choose suitable cell length and time step to produce three Courant numbers less than 0.5 [25].

$$\text{Courant}_i = \frac{D_i \Delta t}{\Delta x^2}, \quad \text{for i} = 1,2 \text{ and } 3 \quad (16)$$

Where D_i, Δt and Δx are Diffusion coefficient, time step and the cell width, respectively.

D. Grid Study

Figure 2 shows a generated grid on the computational domain. A grid independence study was carried out on the computational mesh before modeling adventitia layer. In order to be sure that the results do not affect by grid size, the program was run in different grid numbers. The maximum amount of free drug experienced by the media layer was chosen for the evaluation. A sample of the results is gathered and tabulated in table 2. A mesh with 300 × 300 cells along x and y directions is selected.

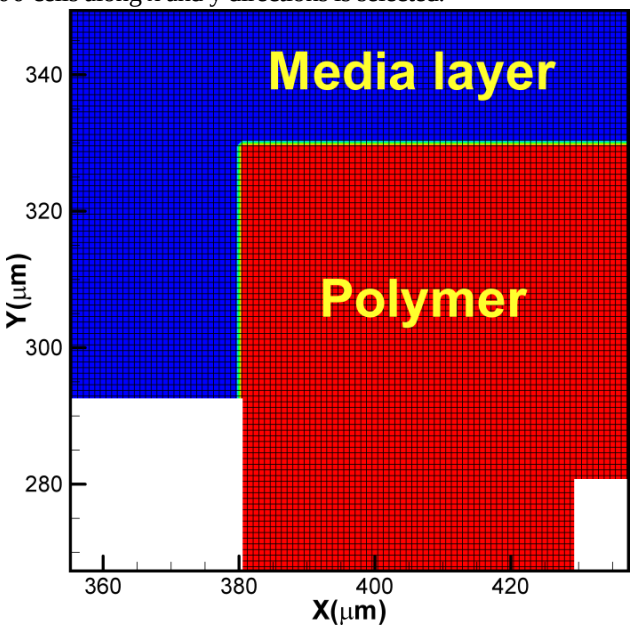

Fig. 2 A view of generated grids.

Table 2. The results of grid study.

Number of cells	100 × 100	130 × 130	200 × 200	300 × 300
m^*	1.002	1.144	1.1678	1.1765
deviation	-	14.17%	2.08%	0.7%

E. Validation

Validation is the next step after the mesh independency study. The present study is validated with the numerical work done by Zhu et al. [26]. Fig. 3 shows that the results of the current numerical simulation are in good agreement with Zhu et al. [26]. Therefore the results are reliable and can be proceed further.

IV. Results and Discussion

The effect of the considering the adventitia layer and the drug consumption occurred at the surface of Vasa vasorum cells have been studied in real porosity, a model proposed by Pontrelli and de Monte [23], and equal porosities, another model utilized by Zhu et al. [26]. To this end, a finite-volume based FORTRAN code has been developed and implemented. So that, the spatial concentration distribution and temporal variation of normalized concentration for both the coating and wall layers are presented in the following, separately.

A. Coating Layer

Showing the spatio-temporal variation of drug concentration, Figs. 4-6 are presented. The drug depletion from the polymer over a period of 400 hours is demonstrated in Fig. 4. It displays the percentage of drug depletion of the model of Zhu et al. [26] and a comparison with the model in which the adventitia layer is added with and without consumption rate. Moreover, from the perspective of hydraulic properties, the results presented for real and equal porosities for all the layers.

Figure 4 shows that considering the adventitia layer causes the polymer to be discharged at a faster rate in comparison with assigning a perfect sink condition at its interface with media layer, proposed by Zhu et al. [26]. Comparing the profiles plotted in Fig. 4 shows that the polymer is not significantly affected by changing the geometry by adding the adventitia layer and considering the drug reaction at the surface of Vasa vasorum cells. Also, it can be seen that assuming the actual porosity for the layers hastens the drug depletion, especially at the middle stage of the procedure. So, it can be concluded that the polymer is more affected by changes in porosities rather than adding adventitia layer. This result is supported by the spatial drug distribution contours which are illustrated in Figs. 5, 6. The time 72 hours is selected to depict its contour plots. These figures clearly proposed that there is a negligible difference in polymer behavior with and without adventitia layer.

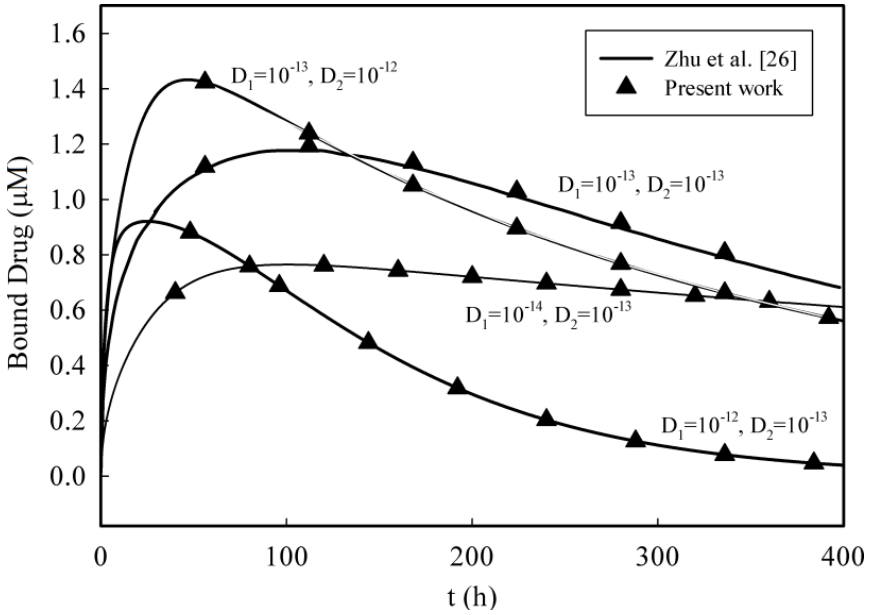

Fig. 3 The comparison of bounded drug between the current numerical study and the work done by Zhu et al. [26].

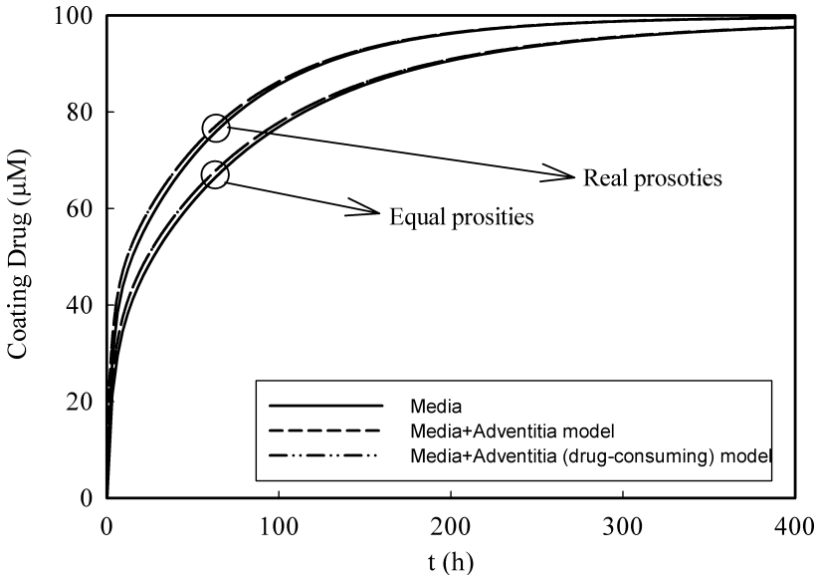

Fig. 4 The temporal variation of normalized drug concentration into the polymeric coating for the three models with real and equal porosities for 400 hours.

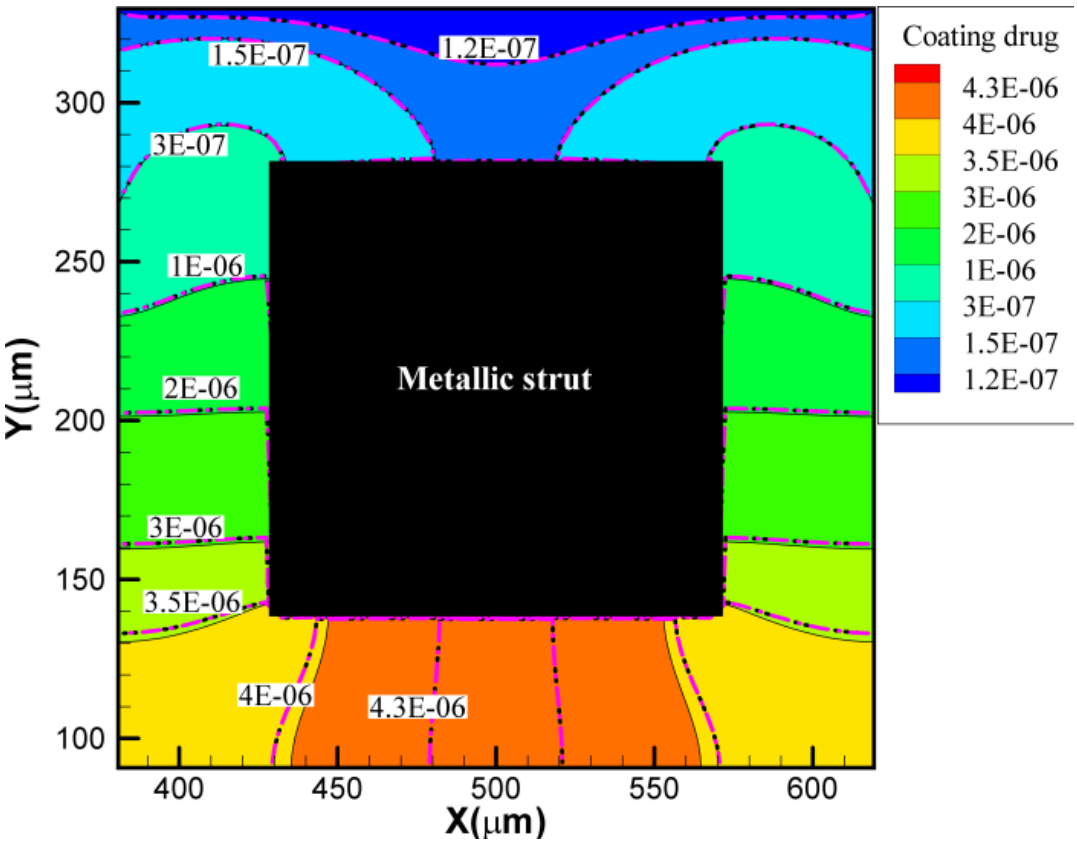

Fig. 5 The drug concentration distribution at the time 72h into the polymeric coating for the three models with real porosities.

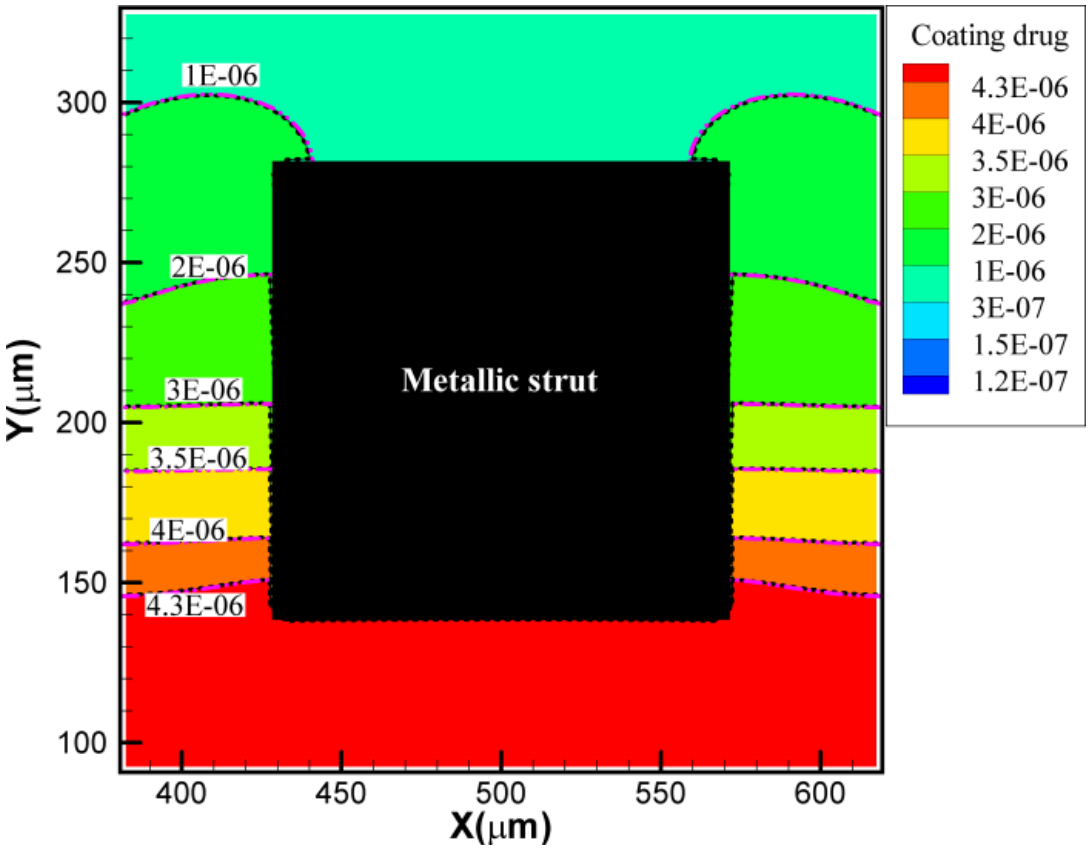

Fig. 6 The drug concentration distribution at the time 72h into the polymeric coating for the three models with similar porosities.

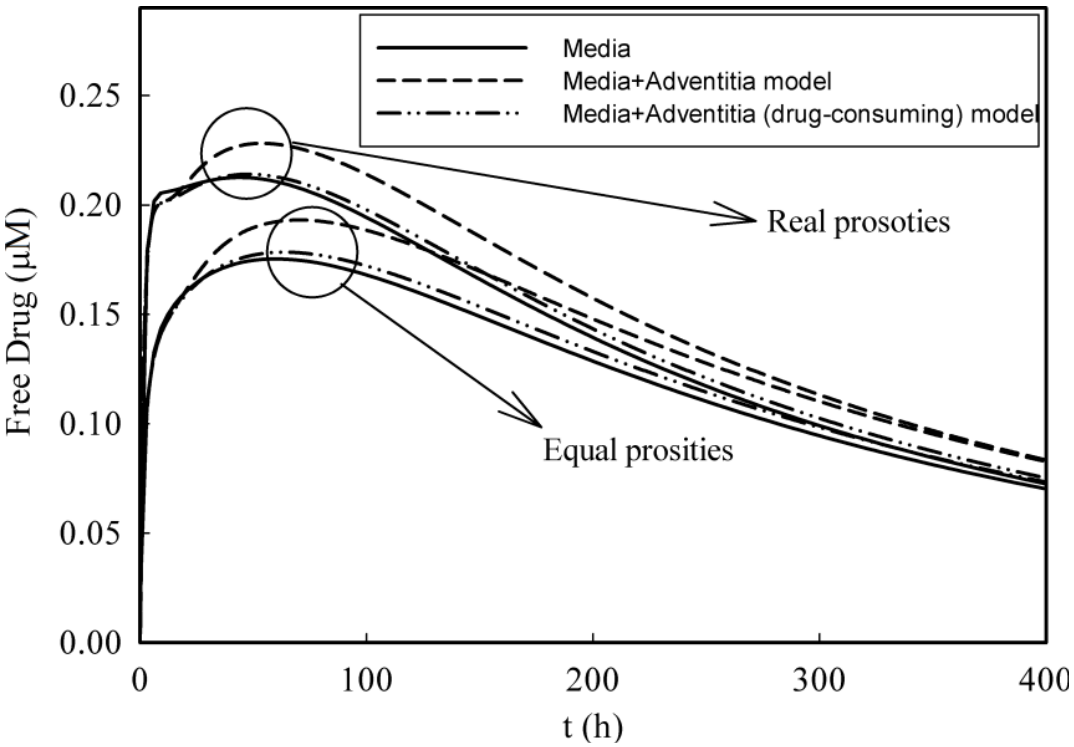

Fig. 7 The temporal variation of normalized free drug concentration into the media layer for the three models with real and equal porosities for 400 hours.

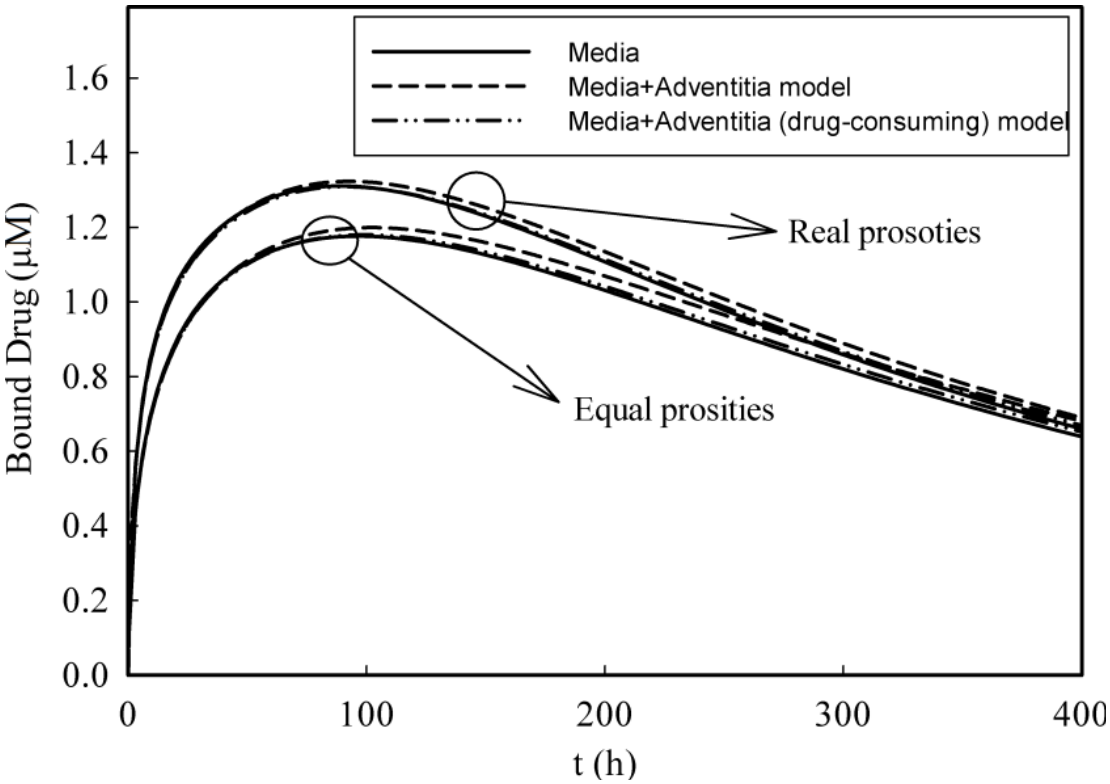

Fig. 8 The temporal variation of normalized bounded drug concentration into the media layer for the three models with real and equal porosities for 400 hours.

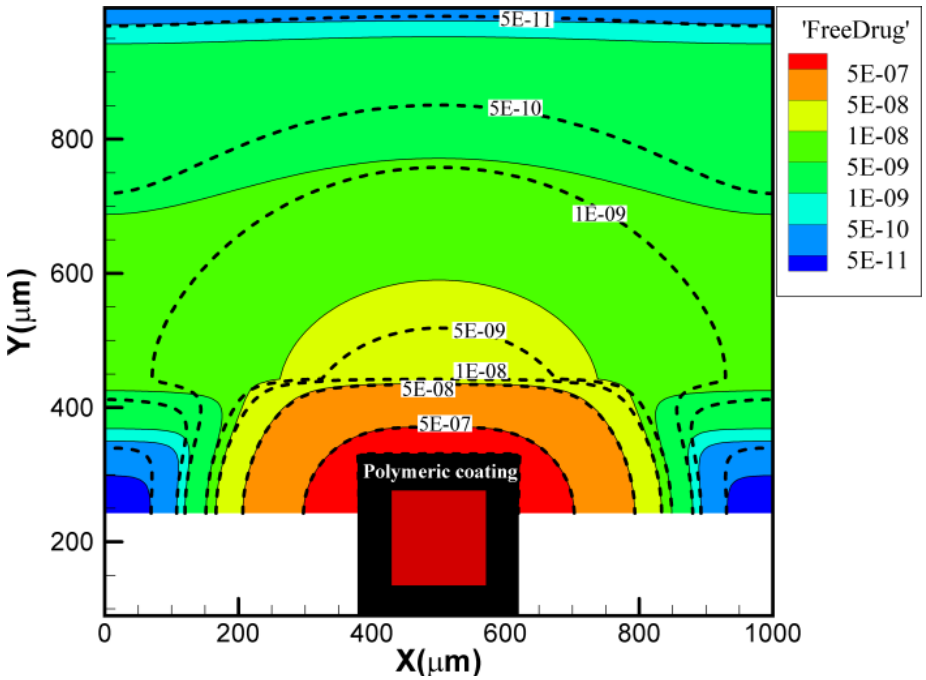

Fig. 9 The comparison between the drug concentration distribution at the time 72h into the arterial tissue with and without drug consumption via Vasa vasarum for the real porosity model.

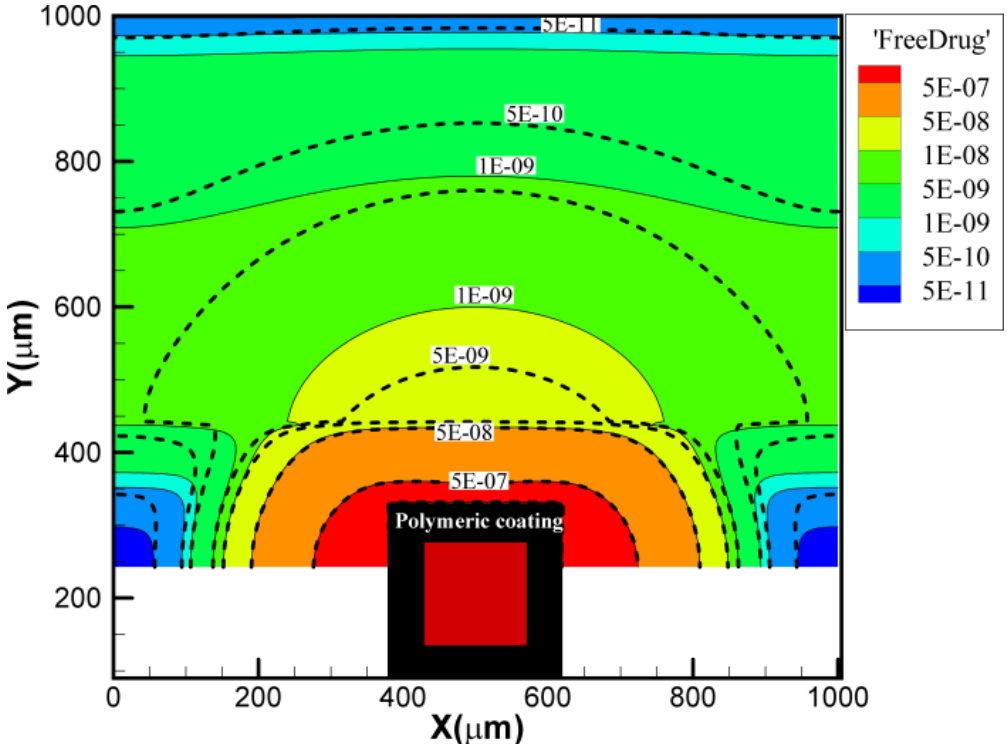

Fig. 10 The comparison between the free drug concentration distribution at the time 72h into the arterial tissue with and without drug consumption via Vasa vasarum for the equal porosity model.

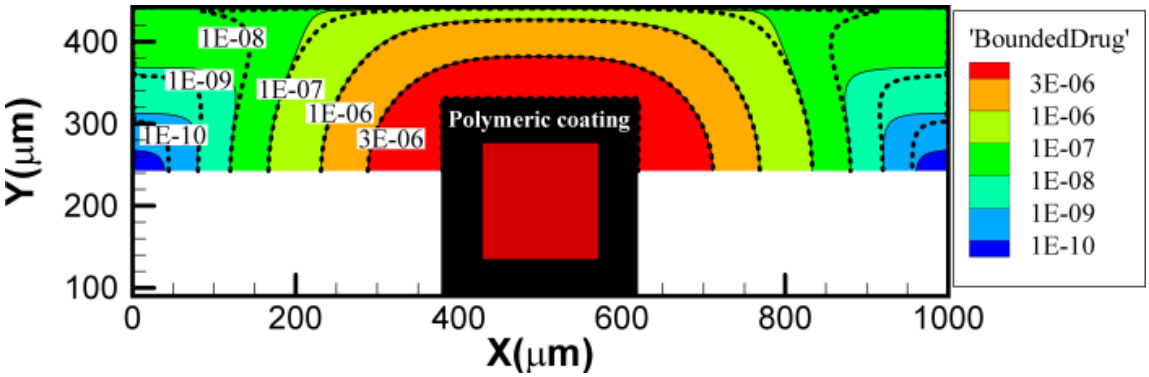

Fig. 11 The comparison between the bounded drug concentration distribution at the time 72h into the arterial tissue with and without drug consumption via Vasa vasarum for the real porosity models.

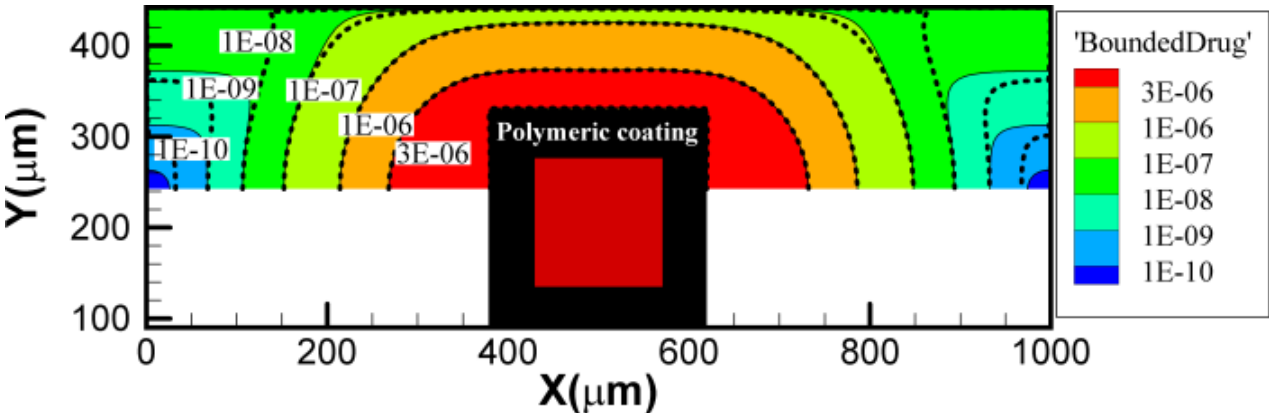

Fig. 12 The comparison between the bounded drug concentration distribution at the time 72h into the arterial tissue with and without drug consumption via Vasa vasarum for the same porosity model.

B. Wall Layer

As the sirolimus enters into the media layer, it immediately bound into the protein cells. therefore, the drug will be existed in two phases, free and bound, simultaneously into the media layer. Figures 7 and 8 show the temporal variation of sirolimus normalized concentration into the media layer. The figures show that adding adventitia layer causes the drug to be at a slightly higher concentration, especially at the duration of effect, namely during the middle stage of releasing procedure. On the other hand, it is clear that taking drug consumption into account causes a drug reduction at any time. The porosity ratio of the polymer and media layers, as well as the media and adventitia layers, are about 6 and 1.4, respectively. Taking these ratios into account lead the concentration to rise at any time. The same results could be concluded by rigorous analyzing of the profiles plotted in figure 7.

The free drug concentration distribution of sirolimus into the arterial wall, the media and adventitia layers, is illustrated in Figs. 9, 10. Fig. 9 shows a significant difference between considering and neglecting the consumption rate at the time 72h. In other words, this figure suggests researchers not to ignore the effect of drug consumption by the Vasa vasarum cells and other microcapillaries. Comparing Figs. 9, 10, applying the real porosities causes an increase in concentration level of the tissue.

Figures 11 and 12 show the bound drug concentration distribution of sirolimus into the media layer. A negligible difference between considering and neglecting the sink term, the drug consumption, can be inferred by comparing the contour plots. Also, taking real porosities into account leads to a slight increase in the drug concentration.

V. Conclusions

In the present study, a polymeric-based drug-eluting stent was simulated, and the importance of drug reaction as a sink term into the adventitia layer was studied. To this end, the adventitia layer has been mathematically modeled in two forms, with and without reaction. Each layer was considered macroscopically homogenous with its distinct properties. A sink term added to the adventitia layer to consider the drug metabolism and drug washout via vasa vasorum. The importance of real porosities was also investigated, simultaneously. The porous media theory was utilized to model the injured coronary artery and drug release dynamics from the non-homogeneous arterial tissue and the polymeric coating. Volume-averaged porous media equations were employed to solve for transport through the porous arterial layers.

- The results revealed that considering the vasa vasorum drug consumption and drug metabolism in cells of the arterial wall, simulated as sink terms, are inevitable. Although they had a negligible effect on drug release process from the polymer, the drug concentration in artery tissue, especially in the adventitia layer was influenced by them, significantly.
- It was concluded that drug reaction decreases the drug concentration level from the tissue. The effect of reaction term depends on time, and its impact was great when the concentration was in its highest amount.
- The dome shape of the profile of mass changes over the time becomes heighten when the real porosities be taken into account.

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