Numerical modeling of local pharmacokinetics associated with drug-eluting stent

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**NANYANG
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**NUMERICAL MODELING OF LOCAL
PHARMACOKINETICS ASSOCIATED WITH
DRUG-ELUTING STENT**

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ABSTRACT

Atherosclerotic plaque formation in the arterial wall is the major cause of stenotic coronary disease. To restore distal blood supply and overcome restenosis presented by bare-metal stents, drug-eluting stent (DES) implantation is widely used. However, the long-term efficacy of this mode of treatment is not well-established. A detailed study of the drug delivery system is expected to give a better insight about what is required to improve the design of DES to achieve its long-term effect. Physiological transport forces, biological tissue properties, drug physiochemical properties and stent design are believed to play important roles in drug release, its subsequent deposition and distribution in the arterial wall. Therefore, it is important to consider these factors when modeling drug delivery system.

In this study, a 2-dimensional model where drug transfer was coupled with luminal and transmural flow was used to investigate post-stenting local pharmacokinetics in arterial wall. Moreover, drug interaction with binding sites was also considered and treated as a reversible binding process. Paclitaxel and heparin were used to examine the effect of drug nature on local pharmacokinetics. Using this model, the effects of blood velocity, inter-strut distance, strut shape, and strut length-to-height ratio on local pharmacokinetics were also investigated. Further, the single-layered arterial wall model was extended to multi-layered model to examine the impact of drug and tissue properties associated with different layers of the arterial wall. Finally, atherosclerotic plaque was incorporated in the model to study the effect of plaque's geometry and nature on local pharmacokinetics.

The results suggest that coupling luminal and transmural flow in the presence of binding sites extensively alters the local pharmacokinetics. It is therefore suggested that they should be incorporated together in the modeling for a better and more physiologically realistic representation of the system. Moreover, plaque acts as a barrier to drug transfer as well as a potential drug reservoir which in turn leads to different arterial wall local pharmacokinetics results, depending on the nature and geometry of the plaque. It is therefore further suggested that the presence of plaque should be considered in the model. The study on stent-structure associated factors reveals that they markedly alter local pharmacokinetics and need to be optimized for effective therapeutic outcome. In summary, this modeling study has provided further insights on the local pharmacokinetics associated with DES and may be useful to improve the design of stent and thus enhance the long-term therapeutic efficacy of DES.

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NOMENCLATURE

c_c	Drug concentration in the coating	Mol m^{-3}
c_l	Drug concentration in the lumen	Mol m^{-3}
$c_{w,b}$	Arterial wall bound drug concentration	Mol m^{-3}
$c_{w,f}$	Arterial wall free drug concentration	Mol m^{-3}
D_c	Diffusion coefficient of drug in the coating	$\text{m}^2 \text{s}^{-1}$
D_l	Diffusion coefficient of drug in the lumen	$\text{m}^2 \text{s}^{-1}$
D_w	Diffusion coefficient of drug in the arterial wall	$\text{m}^2 \text{s}^{-1}$
J_v	Transmural velocity	m s^{-1}
K	Darcian permeability	m^2
L_p	Hydraulic conductivity of the endothelium	$\text{m s}^{-1} \text{Pa}^{-1}$
n_c	Tangent vector in the coating subdomain	
n_l	Tangent vector in the lumen subdomain	
n_w	Tangent vector in the arterial wall subdomain	
p_l	Blood pressure in the lumen	Pa
p_{per}	Perivascular wall pressure	Pa
p_w	Pressure in the arterial wall	Pa
P_c	Topcoat permeability coefficient	m s^{-1}
P_{end}	Endothelium permeability coefficient	m s^{-1}
P_{eq}	Equivalent permeability coefficient	m s^{-1}
R	Radius of lumen	m

r	Any radial position in the lumen	m
t_l	Tangent vector in the lumen	
U_0	Mean inlet velocity	$m\ s^{-1}$
u_l	Blood velocity in the lumen	$m\ s^{-1}$
$u_{l_z}(r)$	Lumen blood velocity in the axial direction (z) at any radial position (r)	$m\ s^{-1}$
u_w	Velocity of the transmural flow of blood plasma	$m\ s^{-1}$
v_{l_r}	Lumen blood velocity in the radial direction (r)	$m\ s^{-1}$
$\bar{C}$	Average drug concentration	$Mol\ m^{-3}$
α	Rate constant	s^{-1}
γ_w	Hindrance coefficient of the arterial wall	
ε_c	Porosity of coating	
ε_w	Porosity of arterial wall	
κ_w	Binding capacity of the arterial wall	
μ_l	Blood viscosity	$Pa\ s$
μ_p	Plasma viscosity	$Pa\ s$
ρ_l	Blood density	$Kg\ m^{-3}$
ρ_p	Plasma density	$Kg\ m^{-3}$
σ	Standard deviation	
σ_d	Osmotic reflection coefficient	
τ_w	Wall shear stress	Pa
∇p	Pressure drop across the endothelium	Pa
$\nabla \pi$	Oncotic pressure difference across the endothelium	Pa

$\Gamma_{c,l}$	Coating-lumen interface
$\Gamma_{c,w}$	Coating-arterial wall interface
Γ_{end}	Endothelium
Γ_{li}	Luminal inlet boundary
Γ_{lo}	Luminal outlet boundary
Γ_{stent}	Stent metal surface
Γ_{sym}	Axis of symmetry boundary
Γ_{per}	Perivascular wall
Γ_{wi}	Arterial wall inlet boundary
Γ_{wo}	Arterial wall outlet boundary
Ω_c	Coating subdomain
Ω_l	Lumen subdomain
Ω_w	Arterial wall subdomain

Chapter 1

Introduction

1.1 Background

1.1.1 Coronary Artery

Based on the direction of blood flow with respect to the heart, conduit blood vessel is divided into two groups, namely artery and vein. While arteries carry blood away from the heart, veins carry blood towards the heart. Except pulmonary and umbilical arteries, all arteries carry oxygen-rich blood. Among them, those deliver oxygen-rich blood to the myocardium are known as coronary arteries. Most common coronary arteries are left coronary artery and right coronary artery, which generate from left aortic sinus and right aortic sinus, respectively. Left coronary artery bifurcates into the left anterior descending artery and the left circumflex artery and usually supplies blood

Figure 1.1: Overview of coronary arteries [1]

to the left ventricle, left atrium and the interventricular septum. On the other hand, right coronary artery, which bifurcates into the right posterior descending artery and marginal artery, usually supplies blood to the right ventricles, right atrium and sinoatrial nodal artery. All these arteries are shown in Figure 1.1.

Meanwhile, a schematic diagram of the anatomical structure of a typical coronary artery is given in Figure 1.2. Arterial wall mainly consists of three distinct layers, namely intima (innermost layer adjacent to the lumen) followed by media and adventitia. Intima is comprised of proteoglycan collagen fibers and media, which is the muscular part of the arterial wall, consists of smooth muscle cells (SMC) and elastic connective tissue. Meanwhile, adventitia contains loose connective tissue and some small capillaries such as lymphatic and vasa vasorum, which are connected with perivascular wall. In addition, there are some thin layers in the arterial wall. Endothelium, a layer of endothelial cells that are connected through tight junctions, presents next to the lumen, which plays an important role in controlling vascular tone, regulating transport into the wall and modulating inflammatory response [2]. A fenestrated layer of impermeable elastic tissue is present between intima and media, which is called internal elastic lamina. Moreover, an elastic layer of connective

Figure 1.2: Schematic diagram of anatomical structure of a typical coronary arterial wall (not to scale)

tissue, namely external elastic lamina is available between media and adventitia.

1.1.2 Atherosclerosis

Atherosclerosis is one of the most common cardiovascular diseases due to accumulation and deposition of fatty substances, cholesterol, calcific material in the arteries (Figure 1.3). It begins with damage to endothelium due to elevated levels of cholesterol, hypertension, smoking and hemodynamic factors. To overcome these damages, the immune system of the body initiates some chemicals signals that cause white blood cells to absorb these cholesterol and other fatty-materials. Indeed, white blood cells are transferred into foam cells first before absorbing other materials. They also provoke SMC proliferation in the artery.

Meanwhile, fat-laden foam cells accumulate and form a patchy deposit that is covered with a fibrous cap called atherosclerotic plaque. As they progress, they thicken the

Figure 1.3: Mechanism of Atherosclerotic plaque formation [3]

arterial wall and therefore result in a narrow artery that reduces blood flow and increases blood pressure. In the chronic stage, plaque ruptures and leads to thrombosis that rapidly slow or stop the blood flow in the downstream.

1.1.3 Atherosclerosis Treatments

The extent of severity, type and size of the artery determine the method of treatment for atherosclerosis, either by medically or surgically. Surgical technique includes coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI). In CABG, arteries from other parts of the body are grafted to the coronary arteries to bypass the region laden with atherosclerotic plaque in order to resume adequate distal blood supply. CABG is preferred for the cases where multiple blockages are present and patient with diabetes [4]. On the other hand, for the less severe situations with partial blockage and more stable plaques, less invasive PCI such as percutaneous transluminal coronary angioplasty (PTCA) and stent implantation are implemented.

PTCA was first introduced by Andreas Gruentzig in 1977 [5] and quickly adopted by others due to its high success rates [6]. In PTCA, a balloon-tipped catheter is inserted in the artery and inflated at the disease site to open the artery, which resumes adequate distal blood flow as shown in Figure 1.4(a). However, the long-term patency of PTCA is restricted due to recoil of the vessel wall [7]. After few months of PTCA, the vessel wall becomes too weak to withstand with the compressed plaque. To prevent recoil of the artery, a bare- wire stent is permanently implanted to provide structural support to the inflated artery.

A stent is a metal scaffold that can be implanted either by self-expansion or balloon-expansion and is capable of long-term support to the stenotic region (Figure 1.4(b)). Bare-metal stent (BMS) implantation has been used successfully with high success rates in comparison to the angioplasty alone [8,9]. However, there are still some limitations and the major ones are those related to the ‘in-stent restenosis’ process

Figure 1.4: (a) Balloon angioplasty, (b) Stent implantation in the coronary artery [10] leading to stent failure. As a stent is implanted into the artery, it causes some extent of arterial wall injury due to radial stress from balloon inflation [11,12] and expansion of stent, which results in elevating stress level [11,13]. The arterial injury and nature of the stents provoke an inflammatory and healing response, which induce SMC proliferation and hence tissues re-growth in the injured area through the wires of the stent leading to restenosis. To overcome restenosis, drug-eluting stents (DES) are being increasingly proposed and used in treating atherosclerotic and stenotic coronary disease [14].

1.1.4 Drug-eluting Stent

Different kind of anti-proliferative (paclitaxel, rapamycin) and/or anti-thrombotic (heparin) drugs are used in DES. Drug is either coated directly to the metal strut surface or loaded with biodegradable/non-biodegradable polymer matrix first and then coated to the strut surface. Paclitaxel and rapamycin act as an active pharmacological agent, which has the potential to enter and break the cell cycle and inhibit SMC proliferation and migration [15,16]. On the other hand, heparin has some active binding sites that bind circulating antithrombin, which catalyzes the inhibition of activated coagulation factor thrombin [17]. Although there are a few recent studies showing that DES is superior over BMS even after 5 years of stenting [18], long-term efficacy of DES is still not well-established. Although the exact mechanism of restenosis is still not clear, it is believed that factors or mechanisms, which can reduce cellular and tissue injury and improve the effective delivery of drugs would be essential in any effective drug-eluting system.

Studies have shown that there are several factors that affect the degree of restenosis like stent design [19], geometry and size of the artery [20], degree of endothelium injury [21,22], type of stent expansion [23] and local fluid dynamics [24]. Stent geometry has a significant effect on local hemodynamics which is commonly implicated in the pathogenesis of vascular diseases since it creates the areas of flow recirculation, flow separation and alters wall shear stress (WSS) [25]. When stent is placed in the artery, the protrusion of stent strut disrupts the blood flow and creates some stagnant zones around the strut. Meanwhile, Wentzel *et al.* [24] investigated the relationship between local variations in shear stress and neointimal hyperplasia and reported that low shear stress regions showed maximal neointimal hyperplasia,

whereas higher shear stress showed minimal neointimal hyperplasia. Surprisingly, all current stent designs are optimized based on WSS only and incorporation of the drug-delivery efficiency in optimizing DES is expected to give an ideal solution for this mode of treatment.

Therefore, a detailed study of the stent based drug delivery system is very important to get a better insight about what is required to improve the design of stent. Efficiency of DES based drug delivery system is directly dependent on local drug pharmacokinetics, which is related to drug deposition and distribution in the arterial wall. Drug concentration should be kept within the therapeutic window for sufficient time in order to get the best therapeutic outcome since too high drug concentration has a toxic effect while too low concentration cannot exert the therapeutic action [26]. Similarly, due to inhomogeneous drug distribution, drug amount may also approach the toxic threshold in certain regions of the arterial wall. Therefore, the measure of drug distribution homogeneity in the arterial wall is very crucial criteria in evaluating local pharmacokinetics associated with DES.

1.1.5 Local Pharmacokinetics of Drug-eluting Stent

Physiological transport forces, biological tissue properties, drug physiochemical properties and design of stent are the main factors that govern the local pharmacokinetics in the arterial wall [27]. Diffusive and convective forces actually determine the extent of physiological forces that govern the transport of drug. Lovich *et al.* [28], using in vitro perfusion apparatus, reported that presence of physiological transmural hydrostatic pressure gradient favored drug deposition in the arterial wall in comparison to the diffusion alone, which suggests that transmural convection plays an important role in drug transport. Further, it has been reported that amount of drug

deposition for both paclitaxel and heparin in the endovascular application are exceeded than that from perivascular delivery [28,29], which also confirms the importance of transmural flow.

On the other hand, Levin *et al.* [30] showed the influence of specific binding to intracellular proteins for arterial transport of rapamycin, paclitaxel and dextran by determining the tissue-loading and elution kinetics, drug diffusion, tissue binding capacity and distribution in the bovine carotid artery. They also reported that binding capacity for hydrophobic drug (paclitaxel and rapamycin) was very high in comparison to that of hydrophilic drug (dextran). Meanwhile, hydrophilic drug shows 35 times higher drug diffusivity than hydrophobic drug in the arterial wall [31,32]. As a result, drug pharmacokinetics is drastically influenced by the nature of the drug.

Further, paclitaxel that binds specifically to microtubules distributes heterogeneously in the arterial wall because of nonuniform distribution of the specific binding sites [30]. Moreover, Lovich *et al.* [28] showed that the presence of binding sites changed along the arterial thickness for hydrophilic drug heparin. While endothelium has maximum number of binding sites, adventitia has minimum. Apart from the inhomogeneous binding site density along the thickness of the arterial wall, it has been also shown that drug diffusion coefficient and arterial wall porosity are different in different layers of the arterial wall for heparin [33].

Local pharmacokinetics is also dependent on arterial wall physiological status. It was reported that uninjured region of endothelium after stent implantation altered drug distribution homogeneity in the arterial wall near the endothelium for some drugs [32,34] but less important for drugs of which transport was dominated by transmural flow [35]. Stent is obviously inserted in the atherosclerotic plaque laden region and

Baldwin *et al.* [36] investigated the effect of atherosclerosis on hydraulic conductance that was related to transmural flow and subsequently to transport of drug in the arterial wall. They reported that presence of atherosclerotic plaque increased hydraulic conductance in comparison to the normal artery. In the chronic stage of atherosclerosis when plaque ruptures and/or stent implantation results injury, thrombus forms in the lumen. Hwang *et al.* [37] examined paclitaxel transport and retention for different blood components in thrombus and reported that paclitaxel diffusivity was maximum in fibrin followed by fibrin-red blood cell and white-blood cell thrombus. They also reported that binding and retention time in the thrombus were increased linearly with red cell fraction.

Due to presence of so many factors, it is very difficult to carry out experiment and investigate the local pharmacokinetics associated with DES. Specially, in order to investigate the effect of stent design, it is very expensive to manufacture variety of stent based on different design and assessment in critical clinical environment is very challenging. Hence, mathematical modeling is an attractive alternative tool to predict the local pharmacokinetics related to DES.

1.1.6 Mathematical Modeling of Drug-eluting Stent

Using computational simulations, Hwang *et al.* [38] showed the effect of physiological transport forces on drug deposition and distribution for both hydrophobic and hydrophilic drugs in the arterial wall. However, this study and some other computational studies only considered diffusion and transmural flow during modeling drug transport in the arterial wall [39,40] assumed that as soon as drug reached either endothelium or coating-lumen interface it was washed away by the luminal blood. On the other hand, in some studies drug transport was coupled with luminal blood flow

assumed negligible transmural flow and therefore drug transport in the arterial wall was governed by diffusion only [41,42]. In the prior study, the efficacy of DES was shown to depend on the applied dose and drug release kinetics while drug accumulation in the arterial wall was influenced by the relative values of the diffusion coefficient in the coating and in the arterial wall was shown in the later work.

Meanwhile, interactions of drug with the arterial tissue in all aforementioned models were neglected. Lovich *et al.* [43] reported the importance of binding of drug by incorporating the reversible bound drug in the model. Interactions of drug with the binding sites were defined by a reversible chemical reaction in 1-dimensional (1D) model by Sakharov *et al.* [44], which was further improved by Migliavacca *et al.* [45] for 2-dimensional (2D) case. None of these studies coupled all the factors, which affect the local pharmacokinetics. Furthermore, Hwang *et al.* [37] predicted how different thrombus geometry and position of strut in the thrombus with respect to the arterial wall affected drug pharmacokinetics and these findings were further validated by a novel rat model. They reported that thrombus between artery and strut could reduce arterial uptake, whereas overlying thrombus that restricted arterial drug washout increased arterial drug deposition. Recently, Balakrisnana *et al.* [46] using a 2D model also predicted that thrombus size altered arterial drug deposition.

Recognizing the role fluid dynamics plays in particle mechanics or mass transport, it is believed that local fluid dynamics around the strut would influence the drug delivery from DES. As mentioned earlier, local fluid dynamics is predominantly influenced by the stent design and therefore it is very important to investigate the effect of stent design on local drug pharmacokinetics. Drug deposition in the arterial wall in steady-state condition has been shown to be influenced by the degree of strut embedment,

inter-strut distance (ISD), location of the drug release and, not surprisingly, flow profiles around the struts [47]. Mograin *et al.* [42] also investigated the effect of ISD and degree of strut embedment in a transient condition and these results were different from those found from steady-state condition previously. Effect of stent design was also studied in some studies where drug distribution in the arterial wall was shown to be influenced by circumferential and longitudinal ISD [38,48]. Therefore, it becomes an important issue to analyze the effect of stent design on local pharmacokinetics to make an efficient stent.

1.2 Motivations and Objectives

As physiological transport properties, arterial ultrastructure, drug-binding properties have shown as influential factors which dictate local drug pharmacokinetics in the arterial wall associated with DES, it is important to consider these factors to develop a physiologically realistic drug delivery model. Further, since binding capacity, transport properties and arterial wall porosity for drug are different in different arterial wall layers, it is believed that a multi-layered model would give different scenario. Moreover, presence of atherosclerotic plaque as well as its geometry and nature may alter the local pharmacokinetics.

Therefore, the specific objectives of this research are:

1. Develop a model to describe the drug delivery system associated with DES coupling transmural and luminal flow in the presence of binding sites.
2. Study the effect of fluid dynamics (blood velocity, stent-structure associated parameters) on local drug pharmacokinetics in the arterial wall.

3. Investigate the effect of multi-layered arterial wall and the presence of atherosclerotic plaque on local drug pharmacokinetics in the arterial wall.

Chapter 2

Two Dimensional Model Development

2.1 Overview

This chapter will outline the development and implementation of a 2D numerical model to elucidate the local pharmacokinetics associated with DES. The geometry of the model, governing equations in different sub-domains, boundary and initial conditions, model parameters will be presented, followed by a brief description of the solver used, including mesh generation in 2D. The method of data analysis specific to drug pharmacokinetics will be described. Finally, the results will be verified to ensure spatial and temporal resolution independent solution.

2.2 Geometric Model

A simple coil stent with circular strut similar to CardioCoil stent (Medtronic InStent Inc., MN, USA) [49] was used in this study which is shown in Figure 2.1. Although in reality there are 11 struts each of 0.15 mm diameter and located 0.7 mm center-to-center distance [50], only 3 struts which were found to be adequate in describing the pharmacokinetics, were used in this study in order to capture the physics better and reduce the computational overload.

Thickness of the drug-loaded polymer coating on the stent was considered 0.005 mm. Physiologic dimensions were modeled after typical coronary artery, with lumen diameter of 3 mm and arterial wall thickness of 0.9 mm. Initially, no distinction was

Figure 2.1: Typical CardioCoil Stent(not to scale)

made between different arterial wall layers and hence considered as a single-layered porous medium. Since different physiologic post-deployment scenarios in terms of degrees of strut embedment in the arterial wall have been reported clinically [51], half-embedded strut configurations were considered. The stent as well as the coronary artery is symmetric about the flow axis and therefore a 2D model was used as shown in Figure 2.2.

Figure 2.2: 2D schematic diagram of the stent (not to scale)

2.3 Model Description

2.3.1 Governing Equation

As drug transport is coupled with luminal and transmural flow, the models presented

here include fluid dynamics model to describe luminal and transmural flow, and solute dynamics models for mass transfer. A schematic diagram of the computational domain is given in Figure 2.3.

2.3.1.1 Fluid Dynamics

Blood was considered an incompressible, Newtonian fluid and its flow through the lumen subdomain (Ω_l) was assumed to be steady and laminar and these were described by the Navier-Stokes equation (Eq. 1) and continuity equation (Eq. 2):

$$-\mu_l \nabla^2 \mathbf{u}_l + \rho_l (\mathbf{u}_l \cdot \nabla) \mathbf{u}_l + \nabla p_l = 0 \quad (1)$$

$$\nabla \cdot \mathbf{u}_l = 0 \quad (2)$$

where $\mathbf{u}_l$ and p_l are, respectively, the steady-state blood velocity and blood pressure in the lumen, ρ_l is the blood density and μ_l is the blood dynamic viscosity. It has been shown that blood viscosity becomes shear-independent for the shear rates above 100 s^{-1} [52] and Reynolds number above 100 [53]. Since a 3 mm diameter coronary artery with steady blood flow of 0.1224 m s^{-1} results in shear rate 326.4 s^{-1} and Reynolds

Figure 2.3: Schematic representation of the computational domain

number 110.89, blood was considered as a Newtonian fluid in this study. Blood was also considered as a Newtonian fluid in earlier work based on the physical dimension of the coronary artery, which is similar to that used in this study, where blood flow dynamics in stented coronary artery was investigated [25]. Moreover, in a study of flow in a realistic carotid bifurcation model, Perktold *et al.* [54] reported slightly higher WSS values using a non-Newtonian versus Newtonian viscosity model. However, overall WSS patterns were preserved, which is largely consistent with previous reports in idealized models.

Meanwhile, steady-state inlet velocity based on the average flow condition over one cycle was used to overcome the computational overhead. Coupling transient Navier-Stokes equation with the transient mass transfer equations requires lots of computational memory and time as computer needs to solve the flow equations for every time steps in order to solve the corresponding mass transfer equations. It has been observed that to ensure a numerically stable solution, the required time step for transient flow equations is in the order of 10^{-1} , whereas, the minimum time steps for transient mass transfer equation is in the order of 10^2 . So, as an initial approach steady-state approximation would be sufficient to examine the role of fluid flow in drug delivery. Steady-state approximation was used in earlier computational studies where mass transfer pattern in a human right coronary artery was investigated [55].

Moreover, although steady-state computational fluid dynamics models are not capable of reproducing the complex, transient behavior of physiological flow patterns, some studies [56,57] have shown that they do provide a reasonable approximation to the time-averaged WSS behavior. Furthermore, these studies demonstrated that the shape

of the inlet velocity profile, i.e. uniform versus fully developed versus realistic has little effect on downstream flow patterns beyond a relatively short entrance length.

The endothelium (Γ_{end}) due to tight junctions, only allows the blood plasma to pass through it into the subendothelial and interstitial space. Hence, the transmural flow of the blood plasma inside the arterial wall subdomain (Ω_w) was modeled by the Darcy's equation (Eq. 3) and continuity equation (Eq. 4):

$$\mathbf{u}_w - \nabla \cdot \left(\frac{K}{\mu_p} \nabla p_w \right) = 0 \quad (3)$$

$$\nabla \cdot \mathbf{u}_w = 0 \quad (4)$$

where $\mathbf{u}_w$ and p_w are, respectively, the velocity of the transmural flow of blood plasma and the pressure in the arterial wall, μ_p is the dynamic viscosity of the blood plasma, and K is the Darcian permeability coefficient of the arterial wall.

2.3.1.2 Solute Dynamics

Drug transfer inside the coating subdomain (Ω_c) was modeled by the transient diffusion equation (Eq. 5):

$$\partial_t c_c + \nabla \cdot (-D_c \nabla c_c) = 0 \quad (5)$$

where c_c and D_c are the concentration and the diffusion coefficient of drug in the coating, respectively. The transport of the released drug from the coating in Ω_l was coupled with the luminal blood flow and hence modeled by the transient convection-diffusion equation (Eq. 6):

$$\partial_t c_l + \nabla \cdot (-D_l \nabla c_l + c_l \mathbf{u}_l) = 0 \quad (6)$$

where c_l and D_l are the concentration and the diffusion coefficient of drug in the lumen, respectively. For modeling drug transport through Ω_w , it is important to note that drug in the porous arterial wall is available either as a free drug form in the extracellular element or as a bound drug form in the binding sites. Furthermore, bound drug attached with the binding sites do not transport and hence only free drug is transported through the arterial wall due to diffusion and transmural flow of the blood plasma. Interaction of free and bound drug was characterized by a reversible reaction. Therefore, the free drug transport inside the arterial wall was modeled as transient diffusion-convection-reaction equation (Eq. 7), whereas bound drug concentration was modeled as a simple reaction equation (Eq. 8) [58]:

$$\partial_t c_{w,f} + \nabla \cdot \left(-D_w \nabla c_{w,f} + \frac{\gamma_w c_{w,f} \mathbf{u}_w}{\varepsilon_w} \right) = -\alpha \left(c_{w,f} - \frac{c_{w,b}}{\kappa_w} \right) \quad (7)$$

$$\partial_t c_{w,b} = \alpha \left(c_{w,f} - \frac{c_{w,b}}{\kappa_w} \right) \quad (8)$$

where $c_{w,f}$ and $c_{w,b}$ are the arterial wall free and bound drug concentration, respectively. D_w and κ_w are the drug diffusion coefficient and binding capacity in the arterial wall, respectively. γ_w is the hindrance coefficient and ε_w is the porosity of the arterial wall. α is the rate constant defined as a rate at which the binding sites adsorb the drug.

2.3.2 Boundary and Initial Conditions

To solve all the equations (Eq. 1 to Eq. 8) appropriate boundary conditions (BC) and initial conditions (IC) were carefully considered and assigned which are given in Table 2.1.

2.3.2.1 Velocity Boundary Conditions

A fully-developed, parabolic and unidirectional velocity profile was assumed at the luminal inlet boundary Γ_{li} (Eq. 9, Eq. 10), where $u_{l_z}(r)$ is the lumen blood velocity in the axial direction (z) at any radial position (r) and v_{l_r} is the velocity in the radial direction (r). U_0 is the average inlet velocity and R is the radius of the lumen. At the luminal outlet Γ_{lo} , all the forces were set to zero (Eq. 11, Eq. 12), where $\mathbf{t}_l$ and $\mathbf{n}_l$ are the tangent vector and normal vector in Ω_l , respectively. No-slip BC was considered

Table 2.1: Boundary and initial conditions for various governing equation

Navier-Stokes Equation in Ω_l			Diffusion Convection Equation in Ω_l		
$u_{l_z}(r) = 2U_0 \left(1 - \left(\frac{r}{R}\right)^2\right)$	Γ_{li}	Eq. 9	$c_l = 0$	Γ_{li}	Eq. 24
$v_{l_r} = 0$	Γ_{li}	Eq. 10	$-D_l \nabla c_l \cdot \mathbf{n}_l = 0$	Γ_{lo}	Eq. 25
$\mathbf{n}_l \cdot \{-p\mathbf{I} + \mu_l [\nabla \mathbf{u}_l + (\mathbf{u}_l)^T]\} \mathbf{n}_l = 0$	Γ_{lo}	Eq. 11	$-D_c \nabla c_c \cdot \mathbf{n}_c = P_c \left(\frac{c_c}{\varepsilon_c} - c_l\right)$	$\Gamma_{c,l}$	Eq. 26
$\mathbf{t}_l \cdot \mathbf{n}_l = 0$	Γ_{lo}	Eq. 12	$-D_l \nabla c_l \cdot \mathbf{n}_l = P_{end} \left(\frac{c_{w,f}}{\kappa_w \varepsilon_w} - c_l\right)$	$\Gamma_{w,l}$	Eq. 27
$u_l = 0$	$\Gamma_{c,l}$	Eq. 13	$\frac{\partial c_l}{\partial r} = 0$	Γ_{sym}	Eq. 28
$\frac{\partial u_l}{\partial r} = v_l = 0$	Γ_{sym}	Eq. 14	$c_l = 0$	Ω_l	Eq. 29
$\mathbf{n}_l \cdot \mathbf{u}_l = J_v$	$\Gamma_{w,l}$	Eq. 15	Diffusion Convection Reaction Equation in Ω_w		
Darcy's Equation in Ω_w			$-D_w \nabla c_{w,f} \cdot \mathbf{n}_w = P_{end} \left(c_l - \frac{c_{w,f}}{\kappa_w \varepsilon_w}\right)$	$\Gamma_{w,l}$	Eq. 30
$-\mathbf{n}_w \cdot \mathbf{u}_w = -J_v$	$\Gamma_{w,l}$	Eq. 16	$-D_w \nabla c_{w,f} \cdot \mathbf{n}_w = P_{eq} \left(\frac{c_c}{\varepsilon_c} - \frac{c_{w,f}}{\kappa_w \varepsilon_w}\right)$	$\Gamma_{c,w}$	Eq. 31
$u_w = 0$	$\Gamma_{c,w}$	Eq. 17	$c_{w,f} = 0$	Γ_{per}	Eq. 32
$\mathbf{n}_w \cdot \mathbf{u}_w = 0$	$\Gamma_{wi} \cup \Gamma_{wo}$	Eq. 18	$-D_w \nabla c_{w,f} \cdot \mathbf{n}_w = 0$	$\Gamma_{wi} \cup \Gamma_{wo}$	Eq. 33
$P_w = P_{per}$	Γ_{per}	Eq. 19	$c_{w,f} = 0$	Ω_w	Eq. 34
Diffusion Equation in Ω_c			Reaction Equation in Ω_w		
$-D_c \nabla c_c \cdot \mathbf{n}_c = 0$	Γ_{stent}	Eq. 20	$c_{w,b} = 0$	Ω_w	Eq. 35
$-D_c \nabla c_c \cdot \mathbf{n}_c = P_c \left(c_l - \frac{c_c}{\varepsilon_c}\right)$	$\Gamma_{c,l}$	Eq. 21			
$-D_c \nabla c_c \cdot \mathbf{n}_c = P_{eq} \left(\frac{c_{w,f}}{\kappa_w \varepsilon_w} - \frac{c_c}{\varepsilon_c}\right)$	$\Gamma_{c,w}$	Eq. 22			
$c_c = 0$	Ω_c	Eq. 23			

at the coating-lumen interface $\Gamma_{c,l}$ making all velocity components zero (Eq. 13) and axial-symmetry BC was specified along the axis of symmetry Γ_{sym} (Eq. 14). At the luminal side of Γ_{end} , only the transmural velocity in the normal direction (J_v) was specified (Eq. 15) and this was calculated using the Kedem-Katchalsky equations [59] which is defined as:

$$J_v = L_p (\nabla p - \sigma_d \nabla \pi)$$

where L_p is the hydraulic conductivity of the endothelium, ∇p is the pressure drop across the endothelium, $\nabla \pi$ is the oncotic pressure difference across the endothelium and σ_d is the osmotic reflection coefficient. A constant hydraulic conductivity was considered:

$$L_p (|\tau_w|) = 0.392 \times 10^{-12} \ln(|\tau_w + 0.015|) + 2.7931 \times 10^{-12}$$

where $|\tau_w| = \frac{4\mu_l U_0}{R}$, is the wall shear stress. Oncotic pressure difference was neglected for simplicity and this assumption was validated by Sun *et al.* [60], where numerically calculated transmural velocity was compared with experimental results.

For Darcy's equation (Eq. 3) and continuity equation (Eq. 4) at the wall side of Γ_{end} , a transmural velocity (J_v) opposite to the normal direction was assumed, where $\mathbf{n}_w$ is a normal vector in Ω_w (Eq. 16). No-slip BC was assumed at the wall side of $\Gamma_{c,w}$ (Eq. 17). Furthermore, symmetry BC was assumed for wall boundaries at both the arterial wall inlet (Γ_{wi}) and outlet (Γ_{wo}) (Eq. 18) because the minimum distance from the nearest strut is 2.5 times larger than the radius of lumen (around 26 times larger than the strut diameter) and hence pressure change along the flow axis is negligible.

Finally, a constant pressure condition (p_{per}) was considered at the perivascular wall (Γ_{per}) (Eq. 19).

2.3.2.2 Concentration Boundary and Initial Conditions

Drug was assumed impermeable to the stent metal surface Γ_{stent} (Eq. 20), where $\mathbf{n}_c$ is a normal vector in Ω_c . Both at the coating and luminal side of $\Gamma_{c,l}$, a diffusive flux in the normal direction was assumed (Eq. 21, Eq. 26), where P_c is the permeability coefficient of the topcoat of the coating and ε_c is the porosity of the coating. Similarly, at both side of $\Gamma_{c,w}$ another diffusive flux was considered (Eq. 22, Eq. 31), where P_{eq} is the equivalent permeability coefficient where topcoat of the coating is in contact with the endothelium. Initially, the entire loaded drug was inside Ω_c with unity concentration (Eq. 23) while there was no drug in Ω_l (Eq. 29) and Ω_w (Eq. 34, Eq. 35). Drug concentration was considered zero at Γ_{li} (Eq. 24) and convective flux was assumed at Γ_{lo} (Eq. 25). At both sides of Γ_{end} a wall-to-lumen flux was assumed (Eq. 27, Eq. 30), where P_{end} is the permeability coefficient of Γ_{end} . Axial symmetry BC was assumed at Γ_{sym} (Eq. 28).

It was further considered that, there was no free drug at Γ_{per} due to adventitial clearance through vasa vasorum, lymphatic drainage and loss into connective tissues (Eq. 32) [27] as vasa vasorum are continuously filled with fresh blood in physiologic condition. Moreover, using zero concentration, zero flux and a specified concentration at Γ_{per} , it has been shown that low density lipoprotein deposition in the arterial wall is not affected [61]. Symmetry BC was considered at both Γ_{wi} and Γ_{wo} (Eq. 33) assumed that concentration gradient along the flow axis was insignificant in these boundaries.

2.3.3 Model Parameters

All model parameters for this study were carefully extracted from the literature which are given in Table 2.2. Moreover, it is important to mention that anisotropic nature of drug diffusivities was considered as motion of drug molecules in the arterial wall is direction-dependent. In realistic physiological system, most drugs interact with layered arterial ultrastructure and therefore they travel faster axially than transmurally [62].

Table 2.2: Blood material property and drug property

Blood Material Property					
Property			Value		Reference
Blood density	ρ_l	Kg m ⁻³	1057		[64]
Blood viscosity	μ_l	Pa s	0.0035		[64]
Plasma density	ρ_p	Kg m ⁻³	1025		[40]
Plasma viscosity	μ_p	Pa s	0.00042		[40]
Darcian permeability	K	m ²	2×10 ⁻¹⁸		[65]
Pressure drop across endothelium	∇p	Pa	5933.333		[60]
Perivascular wall pressure	p_{per}	Pa	3999.672		[60]
Drug Property					
Property			Value		Reference
			Paclitaxel	Heparin	
Diffusion coefficient in lumen	D_l	m ² s ⁻¹	7.66×10 ⁻¹¹	1.45×10 ⁻¹⁰	[31,32]
Diffusion coefficient in coating	D_c	m ² s ⁻¹	1×10 ⁻¹⁵	1×10 ⁻¹⁵	[40]
Diffusion coefficient in arterial Wall	D_w	m ² s ⁻¹	2.2×10 ⁻¹³	7.73×10 ⁻¹²	[31,32]
Binding capacity in arterial wall	κ_w		20	1	[30]
Rate constant	α	s ⁻¹	2×10 ⁻⁵	8.19×10 ⁻⁴	[33,55]
Endothelium permeability coefficient	P_{end}	m s ⁻¹	4×10 ⁻⁷	4×10 ⁻⁷	[32]
Topcoat permeability coefficient	P_c	m s ⁻¹	1×10 ⁻¹⁰	1×10 ⁻¹⁰	[45]
Porosity of arterial wall	ε_w		0.61	0.61	[33]
Porosity of coating	ε_c		0.1	0.1	[40]
Hindrance coefficient of arterial wall	γ_w		1	1	[40]

The mean inlet velocity was $U_0 = 0.1224 \text{ m s}^{-1}$ based on the mean value of coronary flow waveform over one cycle of 0.8 s as shown in Figure 2.4 from in-vitro calibration by Cho *et al.* [63].

Figure 2.4: Coronary blood velocity profile

2.4 Solution

2.4.1 Mesh Generation

A finite element mesh was generated for the model with triangular mesh elements

Figure 2.5: Typical mesh presentation (mesh around a single strut is zoomed in at top)

based on the Delaunay algorithm [66]. Finer mesh elements were used adjacent to the struts, endothelium and perivascular wall to capture better the physics in these regions, which is shown in Figure 2.5. Total number of elements used for the model was 14089, more specifically 4772 for the lumen, 8666 for the arterial wall and 651 for the struts. Meanwhile, total number of mesh points was 7394.

2.4.2 Solution Algorithm

All equations were solved using a commercially available finite element method (FEM) based software COMSOL Multiphysics^{TM}, version 3.4. Non-linear Steady-state flow equations were solved using an affine invariant form of the damped Newtonian type iterative method [67]. Based on the initial guess the software forms a linearized model of the equations first and subsequently forms a discretized linearized model after FEM discretization, which is finally solved by the Newtonian method. On the other hand, FEM discretization of the time dependent mass transfer equations produces a system of ordinary differential equations (ODE) and differential algebraic equations (DAE).

The software uses a special version of DAE solver DASPK that is an implicit time-stepping scheme based on variable-order variable-stepsize backward differentiation formulas (BDF) to solve the above mentioned ODE or DAE system of equations [68]. It is important to mention that all linear system of equations were solved using an unsymmetric-pattern multifrontal package (UMFPACK), a linear system solver [66].

2.4.3 Mesh and Time-step Independent Solution

To ensure the numerical solution of all governing equations, it is important to verify that the solution must be independent of the number of mesh elements and time-step

used by the solver to solve the transient equations. Therefore, a sensitivity test was carried out on amount of drug present in the coating and arterial wall. Table 2.3 shows results for three different number of mesh elements. For both paclitaxel and heparin

Table 2.3: Effect of number of mesh element on arterial drug amount

Amount of paclitaxel (mol)			
Number of mesh elements	Coating	Arterial wall free	Arterial wall bound
7606	1.761630e-17	2.993008e-13	1.506758e-11
14089	1.767666e-17	3.002702e-13	1.511473e-11
27359	1.772802e-17	3.003389e-13	1.511877e-11
Amount of heparin (mol)			
Number of mesh elements	Coating	Arterial wall free	Arterial wall bound
7606	1.232076e-13	3.580546e-13	3.790656e-13
14089	1.237314e-13	3.583858e-13	3.794226e-13
27359	1.238146e-13	3.583977e-13	3.794481e-13

the maximum relative change of the solution after 5 days and 24 hours, respectively, were less than 0.5% for two successive mesh numbers. Meanwhile, when the number of mesh elements reduced to almost half and subsequently doubled from 14089, the relative change in the solution was still less than 0.5%, which confirmed the stability of the solution.

On the other hand, Table 2.4 shows the amount of drug available in the coating and arterial wall after 1 hour of stent implantation for different time-step. Since for small time-step high computational memory is required, simulation carried out upto one hour only for comparison. It was also verified that for higher time-step (3600 s, 1800 s for paclitaxel and 360 s, 60 s for heparin) the results did not differ after 5 days and 24 hours of stenting for paclitaxel and heparin, respectively. Meanwhile, maximum 10^{-3}

% relative change was found in the solution for both paclitaxel and heparin amount within the time-step shown below. Therefore, 3600 s and 360 s were used as a time-step for this study for paclitaxel and heparin, respectively.

Table 2.4: Effect of time-step on arterial drug amount

Amount of paclitaxel (mol)			
Time-step (s)	Coating	Arterial wall free	Arterial wall bound
5	4.575355e-11	8.712829e-12	3.777438e-13
10	4.575355e-11	8.712829e-12	3.777438e-13
60	4.575392e-11	8.712644e-12	3.777491e-13
3600	4.575392e-11	8.712644e-12	3.777491e-13
Amount of heparin (mol)			
Time-step (s)	Coating	Arterial wall free	Arterial wall bound
5	4.573348e-11	2.761300e-12	2.306236e-12
10	4.573348e-11	2.761300e-12	2.306236e-12
60	4.573337e-11	2.761311e-12	2.306272e-12
360	4.573337e-11	2.761311e-12	2.306272e-12

2.5 Data Analysis

Amount of drug available both inside the coating and arterial wall (free and bound form) as a fraction of initial loaded drug inside the coating with respect to the days of stent implantation was used to investigate the drug release and deposition scenario. On the other hand, concentration variation (CV) was used to evaluate the homogeneity of drug distribution in the arterial wall, which is defined as follows:

$$\text{Concentration Variation} = \frac{\text{Standard Deviation}}{\text{Average Concentration}} = \frac{\sigma}{\bar{C}}$$

Average concentration was defined as a ratio of the amount of drug available in the whole arterial wall to the arterial wall volume. Therefore, the lower the CV the more

homogeneous the drug distribution is and minimum possible CV is zero corresponding to a zero standard deviation, which indicates an equal drug concentration at every point.

2.6 Conclusion

A 2D model has been developed to investigate the local pharmacokinetics related to DES in coronary artery. This model was used to study how different physiological factors and fluid dynamic affect the pharmacokinetics. Finally, this model was improved further by considering a multi-layered arterial wall and the presence of atherosclerotic plaque.

Chapter 3

Effect of Coupling Binding, Luminal and Transmural Flow on Local Pharmacokinetics

3.1 Overview

This chapter contains the results using the 2D model described in earlier chapter where drug transfer in the presence of binding sites was coupled with both luminal and transmural flow to investigate the drug release, deposition and distribution in the arterial wall. Two model drugs, paclitaxel (hydrophobic) and heparin (hydrophilic), were used to examine how the nature of the drug affected the pharmacokinetics. This study provides further insights which have not been offered in reported models based on either luminal or transmural flow, with or without drug binding.

3.2 Results

Figure 3.1: Luminal and transmural velocity profile

Figure 3.2: Paclitaxel concentration distribution (a) free, (b) bound and (c) total

Figure 3.3: Heparin concentration distribution (a) free, (b) bound and (c) total

An overview of typical velocity profile of luminal and transmural flows in the lumen and arterial wall, respectively, is shown in Figure 3.1. Furthermore, concentration distribution profiles in terms of free, bound and total (free+bound) form for paclitaxel after 5 days of stenting and heparin after 24 hours of stenting in different subdomains are shown in Figure 3.2 and Figure 3.3, respectively.

Meanwhile, quantitatively the amount of free, bound and total paclitaxel and heparin available in the arterial wall and coating with respect to the days and hours of stent implantation, respectively, are shown in Figure 3.4. Maximum 96 % of total paclitaxel is found as a free drug in the arterial wall just after 1 hour of implantation, whereas maximum total amount of paclitaxel (45 %) is found after 11 hours of stenting among which 57 % is free drug. Meanwhile, highest bound drug is found after 1 day, which is almost 96 % of the total drug. After 5 days of implantation, less than 24 % of total drug is available and 98 % of them are in bound form. On the other hand, both free and bound forms of heparin are increased in the initial stage and maximum 12.4 % of total drug is found within 4.5 hours of stenting. It is important to mention that the total heparin amount is started to decrease drastically right after the peak value and less than 1.1 % total drug is found in the arterial wall after 24 hours of stenting.

Based on different mechanisms involved in drug delivery as discussed earlier, four different drug delivery models were studied which are given in Table 3.1. Figure 3.5 and Figure 3.6 illustrate the importance of different transport processes and binding on free and bound drug pharmacokinetics in the arterial wall. Although model C shows maximum 45 % free paclitaxel in the initial stage of stenting followed by model A, B and D, there is no more free drug after 2 days of stenting for Model C. Meanwhile, 0.45 %, 5.5 % and 0.7 % of initial drug loading are available as a free drug in the

Figure 3.4: Drug delivery model for (a) paclitaxel and (b) heparin

arterial wall even after 5 days of stent implantation for model A, B and D, respectively. It is important to mention that the rate of change of free drug amount for model D and A become negligible after 3 days and 2 days of stenting, respectively. On the other hand, for heparin, maximum 9.2 % of initial loading drug is found for model C as a free drug while for model D results 4.9 %. Although model B and C result more drug during the initial stage of implantation, after 24 hours more than 70 % free heparin is found for model A and D compare to model B and C. As shown in Figure 3(c) and Figure 3(d), maximum 28.42 % of total drug is found as a bound form for paclitaxel for model A, whereas model D results maximum 20.4 %. Most importantly, amount of bound paclitaxel from day 2 to day 5 reduced by 14 % and 5.7 % for model

Table 3.1: Different models based on transport forces and binding

Model	Transport and Reaction Processes
A	Diffusion + Transmural Flow + Binding
B	Diffusion
C	Diffusion + Transmural Flow
D	Diffusion + Binding

A and D, respectively. Meanwhile, maximum 6.2 % of initial loading heparin is found for model A while for model D results 4.9 % and 15 % more bound drug is found for model A in comparison to model D after 24 hours of stenting.

CV for both free and bound drug was calculated to examine the effect of different models on drug distribution in the arterial wall. Although the CV of the free paclitaxel is higher for model B compare to model A and C initially, after 2 days of stenting CV

Figure 3.5: Effect of transport forces and binding on free (a,b) and bound (c,d) arterial wall drug deposition

for model B becomes lower than that for model A (Figure 3.6(a)). Although in the initial stage high CV is found for all the models, after 1 day of stenting they become steady. Meanwhile, CV for bound paclitaxel becomes steady for both model A and D after 2 days of stenting and model D always results higher CV than that of model A. On the other hand, Figure 3.6(b) illustrates that after 6 hours of stenting maximum CV for free heparin is found for model D followed by model B, A and C. But after 24 hours, model D results minimum CV, whereas model B results maximum. Results of

Figure 3.6: Effect of transport forces and binding on free (a,b) and bound(c,d) arterial wall drug concentration variation

bound CV reveal that at the initial stage transmural flow decreases the CV but after 24 hours the CV for both model A and D are indistinguishable (Figure 3.6 (d)).

3.3 Discussion

Efficiency of DES based drug delivery system is directly related to the local pharmacokinetics. Drug deposition, retention time and distribution are very crucial for good therapeutic outcome. As mentioned earlier, drug concentration should be kept within the therapeutic window for sufficient time since too high concentration has a toxic effect while too low concentration cannot exert the therapeutic action [26]. Therefore, it is very important to study the drug distribution in the arterial wall as well. Physiochemical properties related to the nature of the drug play a major role in local drug pharmacokinetics in the arterial wall. Hydrophobic paclitaxel has higher binding capacity in the arterial wall compared to hydrophilic heparin while the latter one has high diffusion coefficient both in the lumen and arterial wall. Low binding capacity results in higher rate constant for binding which facilitates to move towards the equilibrium. Whereas, high binding capacity enhances the drug retention time in the arterial wall for paclitaxel. Moreover, due to high diffusion coefficient most of the heparin is washed away with the blood stream in the lumen from the coating and arterial wall-lumen interface and results in low drug content in the arterial wall compared to hydrophobic drug paclitaxel. Actually, balance between drug interaction with the binding sites and physiological transport forces determine the local drug pharmacokinetics in the arterial wall [9].

The released drug from the coating into the arterial wall is either attached with the binding sites or transport through the arterial wall due to concentration and pressure gradient [58]. It could be seen very clearly from Figure 3.5(a) that transmural flow

easily takes away the arterial wall free paclitaxel toward to perivascular wall in the absence of binding sites, whereas in the presence of binding sites, diffusion as well as convection mediated drug transfer in the arterial wall is restricted. Therefore, more heterogeneous drug distribution is found in the presence of binding and homogeneous distribution is found in the presence of transmural flow. As mentioned earlier, once drug is attached with the binding sites, it neither diffuses nor transport by the blood plasma flow and therefore reduces the amount of drug loss from perivascular wall and arterial wall-lumen interface. The effect of binding is more profound in the absence of transmural flow and therefore substantial drug amounts are available to bind with the cells in the arterial wall. When both transmural flow and binding were not considered, amount of drug in the arterial wall was eventually depended on the drug loss from the perivascular wall and endothelium.

Effect of transmural flow on bound drug study reveals that transmural flow becomes an influential factor as time progresses. In the initial stage after stent implantation, transmural flow helps free drug to reach near new binding sites and thus increases the bound drug amount. However, along the course of the treatment when the free drug around the binding sites is started to decrease, it enhances the release of bound drug from the binding sites. This is why the rate at which bound drug decreases after 2 days is higher for model A compare to model D. Therefore, transmural flow is favorable for paclitaxel deposition in first few days after stenting and it also results uniform drug distribution. These findings coherent with previous experimental results where Creel *et al.* [29] showed that more drug deposition was found for endovascular application compare to the perivascular application.

For hydrophilic drug heparin, transmural flow as well as binding has also altered the drug deposition in the arterial wall. Both in the presence and absence of physiologically transmural hydrostatic pressure gradients using calf carotid artery *in vitro* and rabbit illiac artery *in vivo*, it has been reported that convection is an important mechanism for heparin transport in the arterial wall along with diffusion [28]. These findings were further confirmed when higher drug deposition was found in endovascular application in comparison to the perivascular application in the presence of transmural hydrostatic pressure gradients. Convective force actually reduces the drug loss from the endothelium and thus increases the extent of drug deposition. Although heparin binding capacity is very low compare to paclitaxel, binding plays an important role in arterial wall drug deposition which was also reported in earlier works [44,66]. Subsequently, both free and bound heparin distribution in the arterial wall are influenced by the transmural flow and drug interaction with the binding sites. Like paclitaxel, binding also results heterogeneous heparin distribution, whereas more uniform drug distribution is found when transmural flow was considered.

Although this model was improved from earlier works, still few aspects due to computational complexity and lacking of adequate parameters related to more realistic physiologic condition were not considered. First of all, a simple 2D stent geometry was used. This project's initial objective was understanding DES based drug delivery system. Once a realistic model is available, it can be easily implemented to complex geometry. Secondly, a healthy coronary artery was considered which neglects the presence of atherosclerotic plaque and thrombus. Presence of thrombosis has been shown that it alters the drug pharmacokinetics in the arterial wall [37,46]. Moreover, instead of multi-layer arterial wall, a single layer homogeneous arterial wall was assumed. Binding capacity that varies along the distance from the lumen to the

adventitia in the arterial wall [30] and therefore may affect the drug pharmacokinetics. All these drawbacks were improved and will be discussed in chapter 5. However, drug interaction with the cells is a reversible reaction that depends on association and dissociation rate constants was described as a simple reaction equation due to insufficient data for paclitaxel and heparin.

3.4 Conclusion

Numerical models of mass transfer coupled with fluid dynamics have been developed to elucidate the release of drug from DES and its deposition and distribution in the arterial wall. The importance of considering luminal flow, transmural flow and drug binding in the model to better explain the pharmacokinetics is also demonstrated. This model may be useful to improve the design of DES, which may enhance the therapeutic capabilities of DES in the long-term.

Chapter 4

The Role of Fluid Dynamics on Drug Pharmacokinetics Associated with Drug-eluting Stent

4.1 Overview

This chapter deals with the results associated with the effects of blood flow and stent design parameters (ISD, shape of the strut) on local pharmacokinetics. Blood velocity was altered within a physiologically realistic range, whereas ISD was varied according to physically realistic stent design. Circular and square shaped struts were used to study the effect of strut shape and further different rectangular shaped struts were used to analyze the effect of strut-arterial wall contact area.

4.2 Results

4.2.1 Effect of Fluid Velocity

The effect of blood velocity on drug deposition and distribution in the arterial wall was analyzed by varying the average inlet blood velocity, from 0.2278 m s^{-1} to 0.01 m s^{-1} , within the range of physiological coronary artery blood flow [57]. In this velocity range, the average luminal velocity varies from 0.2291 m s^{-1} to 0.01 m s^{-1} , whereas average transmural velocity varies from $1.31 \times 10^{-8} \text{ m s}^{-1}$ to $8.16 \times 10^{-9} \text{ m s}^{-1}$, which are shown in Figure 4.1. Meanwhile, it could be seen from Figure 4.2 (a) and Figure 4.2 (b) that at the initial stage of stenting the trends for both free and bound amount of paclitaxel are indistinguishable. However, the differences become lucid for different

Figure 4.1: Effect of inlet velocity on luminal and transmural velocity

velocities after 1 day. When the velocity was increased from 0.01 m s^{-1} to 0.2278 m s^{-1} , there were 45.53% and 23.2% decrease in free and bound arterial paclitaxel amount after 5 days of stent implantation, respectively.

A change in blood velocity also alters the CV of both free and bound drug inside the arterial wall as illustrated in Figure 4.2 (c) and Figure 4.2 (d), respectively. It is quite interesting to observe that after 1 day of stent implantation, maximum CV for free paclitaxel is found for 0.06 m s^{-1} , whereas for bound paclitaxel 0.01 m s^{-1} velocity result highest CV. However, the CV after 3 days and 5 days for both free and bound paclitaxel rise as velocity is increased. After 5 days of stent implantation, for the blood velocity of 0.2248 m s^{-1} and 0.01 m s^{-1} , the free paclitaxel CV are 1.2547 and 1.0631, respectively, and the bound paclitaxel CV are 3.9168 and 3.6347, respectively.

4.2.1 Effect of Inter-Strut Distance (ISD)

The effect of ISD on drug deposition and distribution in the arterial wall was investigated by changing the center-to-center distance between two adjacent struts

Figure 4.2: Effect of velocity on (a) free, (b) bound amount of arterial paclitaxel and (c) free, (d) bound arterial paclitaxel concentration variation

(Figure 4.3). ISD was varied between 0.3 mm to 1 mm and results show that as ISD increases amount of free and bound drug content decreases which is shown in Figure

Figure 4.3: Inter-strut distance (ISD)

4.4 (a) and Figure 4.4 (b). Therefore, maximum free and bound paclitaxel content in the arterial wall are found when the ISD is 0.3 mm. After 5 days of stenting, 19.26 % less free and 9.43 % less bound paclitaxel are found when ISD increases from 0.3 mm to 1 mm. The effect of ISD variation on free and bound paclitaxel distribution are illustrated in Figure 4.4 (c) and Figure 4.4 (d), respectively. Minimum CV is found when the ISD is 1 mm. CV for free and bound paclitaxel are 1.52 and 4.36, respectively, for 0.3 mm ISD after 5 days while CV are reduced to 1.05 and 3.84, respectively, when the ISD is changed to 1 mm.

Figure 4.4: Effect of inter-strut distance on (a) free, (b) bound amount of arterial paclitaxel and (c) free, (d) bound arterial paclitaxel concentration variation

4.2.3 Effect of Strut Shape

The effect of strut shape on drug deposition and distribution, on the basis of constant initial drug loading which refers to both the concentration and mass in the coating, was examined for circular and rectangular struts (Figure 4.5), two commonly used shapes in commercially available stents. As shown in Figure 4.6 (a) and Figure 4.6 (b), negligible change in the amount of free and bound paclitaxel in the arterial wall,

Figure 4.5: Different strut shapes

respectively, for different strut shapes are noted along the course of the treatment. However, circular strut results 4.3 % and 2.52 % more free and bound arterial wall paclitaxel after 5 days of stenting, respectively. On the other hand, Figure 4.6 (c) and Figure 4.6 (d) are showing the influence of ISD change on free and bound arterial wall CV, respectively. Whereas CV of free arterial wall paclitaxel shows negligible effect on strut shape, bound paclitaxel CV is markedly influenced by the strut shape. Quantitatively, rectangular shaped strut results 0.80 % and 18 % more free and bound arterial wall paclitaxel CV, respectively, in comparison to the circular shaped strut.

The effect of strut shape was further tested by changing the length-to-height ratio (LHR) from 0.5 to 2 for a rectangular strut (Figure 4.7) by keeping constant initial drug load in the coating. As shown in Figure 4.8 (a) and Figure 4.8 (b), When LHR

Figure 4.6: Effect of strut shape on (a) free, (b) bound amount of arterial paclitaxel and (c) free, (d) bound arterial paclitaxel concentration variation

is altered from 0.5 to 2, the amount of free and bound arterial paclitaxel increase by 28.35 % and 11.1 %, respectively, after 5 days of stent implantation. On the other

Figure 4.7: Length-to-height ratio (LHR)

hand, Effect of LHR on free and bound paclitaxel CV are illustrated in Figure 4.8 (c) and Figure 4.8 (d), respectively. Although at the initial stage CV for LHR 2 is maximum, after 5 days of stenting it becomes 1.23, whereas CV for LHR 0.5 and 1 are 1.25 and 1.22, respectively. Meanwhile, all along the course of the treatment maximum CV for bound paclitaxel is found when LHR is 2 and only 2 % more CV is found while LHR is altered from 0.5 to 1.

Figure 4.8: Effect of LHR on (a) free, (b) bound amount of arterial paclitaxel and (c) free, (d) bound arterial paclitaxel concentration variation

4.3 Discussion

Variation in blood velocity has negligible effect on drug deposition in the arterial wall only during the initial stage after stent implantation. On the other hand, blood velocity has considerable effect on drug distribution in the arterial wall as soon as the stent is implanted. As velocity increases, more drugs are convectively delivered downstream from the endothelium and also toward the perivascular wall due to increase in transmural flow (Figure 4.1). Although, these processes reduce the local average drug concentration but result in more heterogeneous drug distribution in the arterial wall. When transmural flow was not considered, it was reported that blood velocity had negligible effect on drug release from the coating and its deposition in the arterial wall [42]. This is also obtained by our proposed model without transmural flow which is shown in Figure 4.9 and hence these findings suggest that it is very important to model the drug delivery system properly otherwise it could give wrong direction. Moreover, it has been shown earlier that the presence and direction of transmural hydrostatic pressure gradient alter local pharmacokinetics in the arterial wall [28,29] and therefore

Figure 4.9: Effect of velocity on (a) free and (b) bound amount of arterial paclitaxel (without considering the transmural flow)

it is expected that variation in transmural flow as a result of change in blood velocity may also affects the drug pharmacokinetics. This also suggests that possibly a different pattern of drug delivery under the more physiological pulsatile flow condition could be found, but this is yet to be demonstrated.

Both the amount of paclitaxel and CV in the arterial wall show some extent of dependency on ISD variation. Increasing ISD decreases the arterial wall drug content but increases the drug distribution homogeneity. As shown in an earlier study [25], ISD has significant effect on the flow profiles around the strut. These flow profiles determine whether the released drug from the coating and arterial wall is washed away by the blood flow or trapped in the stagnant zones [25,47]. The drugs in the stagnant zones may be transported into the arterial wall through the endothelium and/or decrease the concentration gradient across the endothelium, which reduces the amount of drug that is convectively delivered distal to the stent. Therefore, as the stagnant zones are more profound for small ISD, increasing ISD results in less amount of arterial wall drug content but increases the drug homogeneity. These results are contradictory to earlier findings. Balakrishnan *et al.* [47] reported that increasing ISD increased both the average arterial drug concentration and drug distribution homogeneity, whereas Mongrain *et al.* [42] reported that increasing ISD decreased both the average arterial drug concentration and drug distribution homogeneity. However, it should be noted that the former study used a simplified numerical model assuming infinite drug source in the coating, which may not be realistic. Moreover, in both studies, transmural flow was neglected. Given that low ISD results in low WSS between the struts [25], which is the main reason for neointimal hyperplasia [24], we believe that there must be a balance between the amount of drug, CV and WSS to achieve the best therapeutic effect of DES.

Except bound drug distribution, strut shape does not appear to have any influence on local arterial wall pharmacokinetics. LHR, however, affects both drug deposition and distribution. As LHR increases, both the arterial wall drug amount and heterogeneity in drug distribution increase. High LHR means that most of the strut is in direct contact with the arterial wall axially, reducing blood-arterial wall contact. For low LHR, however, blood plasma is presented with larger surface area to enter the arterial wall and transfer more released drug from the coating towards the perivascular wall. This explains the lower drug content in the arterial wall in the low than the high LHR case. A similar trend of arterial wall drug amount could be found in Balakrishnan *et al.* [47] but clearly the amount of drug deposited is higher in their case where the effect of transmural flow has been neglected. It is also clear from Figure 4.8 that as the degree of strut embedment increases, more arterial wall drug deposition increases. Since strut shape and strut embedment is directly related to the arterial injury that enhances restenosis, it will be interesting to understand their correlation in order to minimize arterial injury and maximize drug delivery.

4.4 Conclusion

Study on effect of fluid dynamics on local pharmacokinetics related to the drug-eluting stent reveals that design of stent plays an important role on drug deposition and distribution. While all current design of stent is only based on minimum arterial injury and maximum WSS, it is expected that incorporation of local drug pharmacokinetics study in designing DES may give a better solution of stent based treatment.

Chapter 5

A Multi-layered Model: Effect of Atherosclerotic Plaque on Local Pharmacokinetics

5.1 Overview

It has been already shown that binding of drug with the cell in the arterial wall has dramatically altered the local pharmacokinetics. It markedly increases both arterial wall drug deposition and retention time. To reduce model complexity, previous single-layered model was based on the assumption that the arterial wall behaved as one layer of porous medium with homogeneous transport and binding properties. So, it was expected that in a multi-layered model where the arterial wall was treated as a number of layers of porous medium with different properties those dictate local pharmacokinetics would give a better insight. Moreover, atherosclerotic plaque that presents adjacent to the endothelium in the luminal side is believed to influence the local pharmacokinetics.

In this chapter, previously developed 2D model was extended to a multi-layered model to investigate the local pharmacokinetics in the arterial wall. Thereafter, atherosclerotic plaque was incorporated and how the presence of plaque as well as its geometry and nature affected arterial wall drug deposition was analyzed.

5.2 Numerical Method

5.2.1 Geometric Model

As mentioned earlier, in the previous model arterial wall was considered as a single-layered porous medium. In this model, arterial wall was treated as two-layered model,

namely media and adventitia. The thickness of media and adventitia were considered 0.4 mm and 0.5 mm, respectively. Due to thin thickness, intima was not considered and hence treated as an interface along with the endothelium. Furthermore, presence of plaque was introduced between endothelium and media, which represented the initial stage of atherosclerosis as shown in Figure 5.1. Thickness of the plaque was varied between 0.1 mm and 0.4 mm to investigate the effect of plaque geometry on local pharmacokinetics.

Figure 5.1: 2D schematic diagram of the model with plaque (not to scale)

5.2.2 Governing Equations

All governing equations were same as described earlier except those for the arterial wall. Blood plasma transport through the plaque and different layers of arterial wall was modeled by the Darcy's equation (Eq. 35) and continuity equation (Eq. 36):

$$\mathbf{u}_i - \nabla \cdot \left(\frac{K_i}{\mu_p} \mathbf{p}_i \right) = 0 \quad (35)$$

$$\nabla \cdot \mathbf{u}_i = 0 \quad (36)$$

where $\mathbf{u}_i$ and p_i are, respectively, the velocity of the transmural flow of blood plasma and the pressure in the i sub-domain, μ_p is the dynamic viscosity of the blood plasma, and K_i is the Darcian permeability coefficient of the i sub-domain while i stands for plaque, media and adventitia. On the other hand, free and bound drug transport through the i sub-domain were governed by transient diffusion-convection-reaction equation (Eq. 37) and reaction equation (Eq. 38), respectively:

$$\partial_t c_{i,f} + \nabla \cdot \left(-D_i \nabla c_{i,f} + \frac{\gamma_i c_{i,f} \mathbf{u}_i}{\varepsilon_i} \right) = -\alpha \left(c_{i,f} - \frac{c_{i,b}}{\kappa_i} \right) \quad (37)$$

$$\partial_t c_{i,b} = \alpha \left(c_{i,f} - \frac{c_{i,b}}{\kappa_i} \right) \quad (38)$$

5.2.3 Model Parameters

Blood plasma properties were considered constant in all layers. Meanwhile, drug properties in different layers are given below in Table 5.1.

Table 5.1: Drug properties in different arterial wall layers

Property	Value			Reference
	Plaque	Media	Adventitia	
Diffusion coefficient	2.2×10^{-13}	2.2×10^{-13}	2.2×10^{-13}	[31]
Binding capacity	25	17	30	[30]
Rate constant	2×10^{-5}	2×10^{-5}	2×10^{-5}	[33]
Porosity	0.61	0.61	0.61	[33]
Hindrance coefficient	1	1	1	[40]

5.3 Results

5.3.1 Effect of Multi-layered Model

Figure 5.2 is illustrating the comparison between single-layered model and multi-layered model on the basis of free and bound drug deposition and CV. It could be seen that single-layered model results more drug deposition over the multi-layered model

arterial wall. While single-layered model gives maximum 30 % of initial coating drug as a free form, multi-layered model gives 28 %. On the other hand, maximum 28 % and 25 % of initial coating drug are found as bound form for single-layered and multi-layered, respectively. It is also clear that initially most of the drug is available in the media and as time progresses drug is transferred to adventitia. It is interesting to see that free drug CV for single-layered model lies between CV for media and adventitia of multi-layered model, whereas for bound drug single-layered model results maximum CV followed by the media and adventitia.

Figure 5.2: Single-layered and multi-layered (a) free, (b) bound amount and (c) free, (d) bound concentration variation comparison

5.3.2 Effect of Plaque Presence and Geometry

As expected, the presence of plaque markedly affects the arterial wall drug pharmacokinetics. Both free and bound drug amount are dramatically reduced in the presence of plaque and as the thickness of the plaque increases, the total amount of paclitaxel in the arterial wall decreases, as shown in Figure 5.3(a) and Figure 5.3(b). In comparison to the no plaque condition, when there is 0.4 mm plaque in the arterial wall which is less than 50 % of the arterial wall thickness, maximum total free and

Figure 5.3: Effect of plaque thickness on amount of (a) free, (b) bound arterial paclitaxel and CV of (c) free, (d) bound arterial paclitaxel

bound arterial wall drug contents are 53.57 % and 44.06 % less. Moreover, after 5 days of stenting 37 % and 11 % less bound drug are found with respect to the no plaque and 0.2 mm thick plaque condition, respectively.

On the other hand, CV for both free and bound drug in media and adventitia are given in Figure 5.4. Except CV for free drug in the adventitia, presence of plaque lowers the CV in media and adventitia. Surprisingly, after 5 days of stent implantation free drug CV in the adventitia is less than those from the situations where 0.1 mm and 0.2 mm

thick plaques are present. Therefore, minimum CV is found for 0.4 mm thick plaque that is 44.57 % and 70.50 % less than the CV of no plaque condition for free and bound drug in the media, respectively, and 7.12 % and 20.33 % less than the CV of no plaque condition for free and bound drug in the adventitia, respectively.

Figure 5.4: Effect of plaque thickness on CV of (a) free, (b) bound paclitaxel in media and (c) free, (d) bound paclitaxel in adventitia

5.3.3 Effect of Nature of Plaque

Sensitivity analysis study based on D_p reveals that both the amount of free and bound

drug increase with increasing D_P at the initial stage but decrease thereafter as shown in Figure 5.5, where D_P is shown as a ratio to the drug diffusion coefficient in the media. Meanwhile, it is important to mention that maximum free and bound drug contents are

Figure 5.5: Effect of paclitaxel diffusion coefficient in plaque on total amount of (a) free and (b) bound arterial paclitaxel

available for high D_P . After 5 days of stenting, 15 % and 36 % more free and bound drugs, respectively, were found when the ratio was changed from 0.5 to 5. On the other hand, while K_P was altered, negligible variation was found both for free and bound drug contents in the initial stage. But, free and bound drug contents are started to decrease as K_P increases afterwards (Figure 5.6). After 5 days of stenting 38.30 % and 9.31 % less free and bound drug, respectively, are found when K_P was changed from 20 to 40.

5.4 Discussion

Our results are clearly showing the difference in pharmacokinetics results between single-layered and multi-layered models. In the single-layered model, it was assumed

that the drug binding capacity was constant, whereas in the multi-layered model different drug binding capacities were used for different layers. As a result of

Figure 5.6: Effect of paclitaxel binding capacity in plaque on total amount of (a) free and (b) bound arterial paclitaxel

overestimated high binding capacity which in turn absorbs more drug and restricts free drug movement, single-layered model results more drug deposition along the course of the treatment than multi-layered model. However, due to lack of sufficient experimental data of drug diffusion coefficient in different layers of the arterial wall, same diffusion coefficient values were used for all the layers. As heparin results different diffusion coefficient in media and adventitia [33], it is expected that paclitaxel will give different values as well and therefore extensive experiments are required to carry out in order to find these values.

Meanwhile, the presence of plaque dramatically affects the local pharmacokinetics of both free and bound paclitaxel in the arterial wall. First of all, presence of plaque acts as a physical barrier to both drug transfer into the arterial wall and transmural hydraulic flux. Figure 5.7 is illustrating the effect of plaque thickness on average

transmural blood plasma velocity. It is very clear that presence of plaque reduces average transmural velocity and as the plaque thickness increases, average transmural velocity decreases. In the presence of 0.4 mm thick plaque, the average transmural velocity is 10.45 % and 7.63 % less than those from without plaque and 0.20 mm thick plaque conditions, respectively. The low transmural velocity for thick plaque lowers the drug transport by convection in the arterial wall and therefore amount of drug loss through the endothelium increases. Secondly, the plaque acts as a drug reservoir.

Figure 5.7: Effect of plaque thickness on average arterial transmural velocity

Substantial amount of drug is attached to the binding sites that could be seen very clearly from Figure 5.8. After 5 days of stent implantation, amount of free and bound drug in the plaque which is 0.2 mm thick are 3.79 % and 33.52 % of total arterial free and bound drug, respectively. These amounts are even higher for thick plaque. In addition, as shown in previous studies that endothelial layer also limits the heparin transfer into the arterial wall [28] and this should be more prominent for paclitaxel as convection plays an important role to paclitaxel drug transfer in the arterial wall [29]. Fortunately, presence of plaque increases drug distribution homogeneity. In the

presence of plaque, drug first distributes in the plaque and a distributed drug enters into the media and subsequently into the adventitia and results homogeneous drug distribution. Study on the effect of D_P and K_P suggested that it is important to

Figure 5.8: (a) Free and (b) bound paclitaxel deposition in different layers

determine the physical properties properly inside the plaque. Higher D_P forces the drug to diffuse fast into the arterial wall and thus it enhances the drug loss from the perivascular wall as well. It also increases the luminal washout of drug through the endothelium. Furthermore, the decrease trend in total arterial wall drug deposition due to increase in K_P indicates that more drug is available in bound form in the plaque which restricts the transport of free drug. These results are consistent with the findings reported earlier where increased drug diffusivity in the clot decreased arterial wall drug uptake and high drug binding capacity with clot delayed arterial uptake [37].

5.5 Conclusion

Drug pharmacokinetics in the arterial wall is shown to be affected by the presence of plaque and its thickness. As such, it is important to consider a model involving plaque

in investigating drug delivery from DES to improve the design to achieve best therapeutic outcome. Based on the results using the simple geometry, it is expected that a more realistic 3-dimensional plaque geometry will elucidate the physiological condition better.

Chapter 6

Conclusion

6.1 Summary

Homogeneous distribution of sufficient amount of drug for sufficient time in the arterial wall ensures better therapeutic outcome of DES based treatment that could be controlled through effective stent design. In order to design stent effectively, it is very important to understand the factors, which dictate drug release kinetics from the stent, its deposition and distribution, profile in the arterial wall. In this study, a model was developed considering all the factors, which dictate local pharmacokinetics in the arterial wall. Then how the local fluid dynamics affected arterial wall local pharmacokinetics was analyzed. This model was then extended assumed arterial wall as a multi-layered model. Finally, the effect of atherosclerotic plaque on drug delivery was examined. Achievements based on the above investigations are:

1. Drug transfer in the lumen and arterial wall should be coupled with luminal flow and transmural flow, respectively. As drug binding with the cell in the arterial wall markedly increases the drug retention time, it is also need to be considered in the modeling.
2. Change in luminal blood velocity alters drug pharmacokinetics in the arterial wall. As luminal velocity increases, it subsequently increases transmural blood plasma velocity. As a result, not only luminal wash out from the endothelium increases but also drug loss through the perivascular wall increases which in turn reduce both arterial drug amount and distribution homogeneity.

3. The results obtained from the effect of stent design reveal that drug pharmacokinetics, WSS distribution and arterial injury should be considered together during the stent design stage and optimized for better outcome.

4. Influence of atherosclerotic plaque study shows that plaque acts as a barrier to drug transfer as well as a potential drug reservoir. As the thickness of plaque increases, less amount of drug can reach in the arterial wall. Moreover, atherosclerotic plaque material properties are also important for local pharmacokinetics. Therefore, it would be worthy to load drug in the coating based on the geometry and nature of atherosclerotic plaque for better therapeutic outcome.

6.2 Limitations

The obvious limitation of this study was there were neither *in vitro* nor *in vivo* experiments to validate the numerical results. Such studies would be very expensive and time consuming and beyond the scope of this work. In this study, results from the numerical simulations were compared with earlier experimental findings qualitatively. Moreover, all the material properties used in the simulation did not correspond to the realistic physiologic condition. Most importantly, due to the lack of sufficient experimental data, constant diffusion coefficient value was used for media, adventitia and plaque and it has been shown that variation in diffusion coefficient alters local pharmacokinetics [42] that confirms the importance of accurate diffusion coefficient determination. In physiologically realistic condition, stent may be implanted in curved coronary artery and fluid dynamics in curved arteries is quite complex [70]. Moreover, macromolecular transport has been shown to be affected by the presence of curve artery [71]. However, to overcome computation overhead, straight artery was used in this study. As fluid dynamics alter the local pharmacokinetics, it would be interesting

to investigate in curved coronary artery. Fluid flow equations in lumen and arterial wall along with the mass transfer and reaction equations require large computational memory and time in 3D geometry. Both the stent and artery used in this study were asymmetric about the flow axis, making it a 2D modeling studies, the work should be extended into the more complex 3D stent structure and vascular geometry.

6.3 Future Directions

On the basis of backgrounds, results and limitations of these study, major suggestions for future research are summed up as follows:

1. Couple mass transfer equations with transient Navier-Stokes equation considering a realistic pulsatile flow at the luminal inlet. In order to reduce the computational cost, it would be better to simulate the transient flow equation first for few cycles and using these results, generate flow fields for expected number of cycles. Finally, solve the all mass transfer equations separately.
2. Investigate velocity and concentration distribution profile in dimensionless form in order to get a better insight of the local pharmacokinetics.
3. Investigate the effect of curved arterial wall on local pharmacokinetics.
4. In the presence of atherosclerotic plaque, it is unlikely to have a symmetric artery and therefore it is very important to study the local pharmacokinetics considering 3D geometry with realistic plaque geometry.
5. Despite the high initial success rate, long-term complications such as restenosis and thrombosis have been reported with all current metallic DES. To overcome the shortcomings of metallic DES, biodegradable polymeric DES has attracted much attention. Meanwhile, one of the most important factors that affect the rate of polymer degradation which in turn affect the local pharmacokinetics is the surrounding

medium. The realistic physiological condition inside the human body is dynamic and investigation of polymer degradation and drug delivery under dynamic condition is still an unsolved issue. Moreover, it has been already shown that fluid dynamics alters the local pharmacokinetics of metallic DES and therefore it would be interesting to investigate how fluid dynamics affects promising future biodegradable stent. This study may include effect of fluid velocity and design of stent (in dynamic condition) on polymer degradation and drug delivery *in vitro* followed by developing a mathematical model. It could be also extended imposing realistic pulsatile flow *in vitro* and even further through carry out some *in vivo* experiments for validation.

REFERENCES

- [1] <http://www.ohsu.edu>.
- [2] Corti, R., and Badimon, J. J., 2002, "Biologic aspects of vulnerable plaque," *Current Opinion in Cardiology*, 17(6), pp. 616-625.
- [3] <http://www.britannica.com/EBchecked/topic/40935/atherosclerotic-plaque>.
- [4] Smith, S. C., Jr., Feldman, T. E., Hirshfeld, J. W., Jr., Jacobs, A. K., Kern, M. J., King, S. B., III, Morrison, D. A., O'Neill, W. W., Schaff, H. V., Whitlow, P. L., Williams, D. O., Antman, E. M., Adams, C. D., Anderson, J. L., Faxon, D. P., Fuster, V., Halperin, J. L., Hiratzka, L. F., Hunt, S. A., Nishimura, R., Ornato, J. P., Page, R. L., and Riegel, B., 2006, "ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention--Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention)," *Circulation*, 113(1), pp. 156-175.
- [5] Gruntzig, A., and Schneider, H. J., 1977, "Percutaneous dilatation of chronic coronary stenosis: Experiment and morphology," *DIE PERKUTANE DILATATION CHRONISCHER KORONARSTENOSEN - EXPERIMENT UND MORPHOLOGIE*, 107(44), pp. 1588.
- [6] Detre, K., Holubkov, R., Kelsey, S., Cowley, M., Kent, K., Williams, D., Myler, R., Faxon, D., Holmes Jr, D., Bourassa, M., Block, P., Gosselin, A., Bentivoglio, L., Leatherman, L., Dorros, G., King Iii, S., Galichia, J., Al-Bassam, M., Leon, M., and Robertson, T., 1988, "Percutaneous transluminal coronary angioplasty in 1985-1986 and 1977-1981," *New England Journal of Medicine*, 318(5), pp. 265-270.
- [7] Waller, B. F., Orr, C. M., Vantassel, J., Peters, T., Fry, E., Hermiller, J., and Grider, L. D., 1996, "Coronary artery and saphenous vein graft remodeling: A review of histologic findings after various interventional procedures - Part II," *Clinical Cardiology*, 19(10), pp. 817-823.
- [8] Serruys, P. W., de Jaegere, P., Kiemeneij, F., Macaya, C., Rutsch, W., Heyndrickx, G., Emanuelsson, H., Marco, J., Legrand, V., Materne, P., Belardi, J., Sigwart, U., Colombo, A., Goy, J. J., van den Heuvel, P., Delcan, J., Morel, M.-a., and The Benestent Study, G., 1994, "A Comparison of Balloon-Expandable-Stent Implantation with Balloon Angioplasty in Patients with Coronary Artery Disease," *New England Journal of Medicine*, 331(8), pp. 489-495.

- [9] Fischman, D. L., Leon, M. B., Baim, D. S., Schatz, R. A., Savage, M. P., Penn, I., Detre, K., Veltri, L., Ricci, D., Nobuyoshi, M., Cleman, M., Heuser, R., Almond, D., Teirstein, P. S., Fish, R. D., Colombo, A., Brinker, J., Moses, J., Shalmonovich, A., Hirshfeld, J., Bailey, S., Ellis, S., Rake, R., Goldberg, S., and The Stent Restenosis Study, I., 1994, "A Randomized Comparison of Coronary-Stent Placement and Balloon Angioplasty in the Treatment of Coronary Artery Disease," *New England Journal of Medicine*, 331(8), pp. 496-501
- [10] [http:// www.nhlbi.nih.gov](http://www.nhlbi.nih.gov)
- [11] Rogers, C., Tseng, D. Y., Squire, J. C., and Edelman, E. R., 1999, "Balloon-Artery Interactions During Stent Placement : A Finite Element Analysis Approach to Pressure, Compliance, and Stent Design as Contributors to Vascular Injury," *Circulation Research*, 84(4), pp. 378-383.
- [12] Van Erven, L., Post, M. J., and Borst, C., 1991, "Arterial wall injury, arterial wall healing and restenosis," *Lasers in Medical Science*, 6(3), pp. 271-279.
- [13] Holzapfel, A. G., Stadler, M., and Gasser, T. C., 2005, "Changes in the Mechanical Environment of Stenotic Arteries During Interaction With Stents: Computational Assessment of Parametric Stent Designs," *Journal of Biomechanical Engineering*, 127(1), pp. 166-180.
- [14] Swanson, N., and Gershlick, A. H., 2005, "Drug Eluting Stents in Interventional Cardiology - Current Evidence and Emerging Uses," *Current Drug Targets - Cardiovascular & Hematological Disorders*, 5, pp. 313-321.
- [15] Fattori, R., and Piva, T., 2003, "Drug-eluting stents in vascular intervention," *The Lancet*, 361(9353), pp. 247-249.
- [16] Van Der Hoeven, B. L., Pires, N. M. M., Warda, H. M., Oemrawsingh, P. V., Van Vlijmen, B. J. M., Quax, P. H. A., Schalij, M. J., Van Der Wall, E. E., and Jukema, J. W., 2005, "Drug-eluting stents: Results, promises and problems," *International Journal of Cardiology*, 99(1), pp. 9-17.
- [17] Hirsh, J., Warkentin, T. E., Shaughnessy, S. G., Anand, S. S., Halperin, J. L., Raschke, R., Granger, C., Ohman, E. M., and Dalen, J. E., 2001, "Heparin and low-molecular-weight heparin: Mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety," *Chest*, 119(1 SUPPL.), pp. 64S-94S.
- [18] Morice, M.-C., Serruys, P. W., Barragan, P., Bode, C., Van Es, G.-A., Stoll, H.-P., Snead, D., Mauri, L., Cutlip, D. E., and Sousa, E., 2007, "Long-Term Clinical Outcomes With Sirolimus-Eluting Coronary Stents: Five-Year Results of the RAVEL Trial," *Journal of the American College of Cardiology*, 50(14), pp. 1299-1304.

- [19] Rogers, C., and Edelman, E. R., 1995, "Endovascular Stent Design Dictates Experimental Restenosis and Thrombosis," *Circulation*, 91(12), pp. 2995-3001.
- [20] Kastrati, A., Mehilli, J., Dirschinger, J., Pache, J., Ulm, K., Schuhlen, H., Seyfarth, M., Schmitt, C., Blasini, R., Neumann, F.-J., and Schomig, A., 2001, "Restenosis after coronary placement of various stent types," *The American Journal of Cardiology*, 87(1), pp. 34-39.
- [21] Schwartz, R. S., Huber, K. C., Murphy, J. G., Edwards, W. D., Camrud, A. R., Vlietstra, R. E., and Holmes, D. R., 1992, "Restenosis and the proportional neointimal response to coronary artery injury: results in a porcine model," *Journal of the American College of Cardiology*, 19(2), pp. 267-274.
- [22] Kornowski, R., Hong, M. K., Tio, F. O., Bramwell, O., Wu, H., and Leon, M. B., 1998, "In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia," *Journal of the American College of Cardiology*, 31(1), pp. 224-230.
- [23] Grenacher, L., Rohde, S., Gänger, E., Deutsch, J., Kauffmann, G., and Richter, G., 2006, "In Vitro Comparison of Self-Expanding Versus Balloon-Expandable Stents in a Human Ex Vivo Model," *CardioVascular and Interventional Radiology*, 29(2), pp. 249-254.
- [24] Wentzel, J. J., Krams, R., Schuurbiers, J. C. H., Oomen, J. A., Kloet, J., van der Giessen, W. J., Serruys, P. W., and Slager, C. J., 2001, "Relationship Between Neointimal Thickness and Shear Stress After Wallstent Implantation in Human Coronary Arteries," *Circulation*, 103(13), pp. 1740-1745.
- [25] Berry, J. L., Santamarina, A., Moore, J. E., Roychowdhury, S., and Routh, W. D., 2000, "Experimental and computational flow evaluation of coronary stents," *Annals of Biomedical Engineering*, 28(4), pp. 386-398.
- [26] Tesfamariam, B., 2007, "Local vascular toxicokinetics of stent-based drug delivery," *Toxicology Letters*, 168(2), pp. 93-102.
- [27] Yang, C., and Burt, H. M., 2006, "Drug-eluting stents: Factors governing local pharmacokinetics," *Advanced Drug Delivery Reviews*, 58(3), pp. 402-411.
- [28] Lovich, M. A., Philbrook, M., Sawyer, S., Weselcouch, E., and Edelman, E. R., 1998, "Arterial heparin deposition: role of diffusion, convection, and extravascular space," *American Journal of Physiology-Heart and Circulatory Physiology*, 44(6), pp. H2236-H2242.
- [29] Creel, C. J., Lovich, M. A., and Edelman, E. R., 2000, "Arterial Paclitaxel Distribution and Deposition," *Circulation Research*, 86(8), pp. 879-884.
- [30] Levin, A. D., Vukmirovic, N., Hwang, C.-W., and Edelman, E. R., 2004, "Specific binding to intracellular proteins determines arterial transport

- properties for rapamycin and paclitaxel," Proceedings of the National Academy of Sciences, 101(25), pp. 9463-9467.
- [31] Lovich, M. A., Creel, C., Hong, K., Hwang, C. W., and Edelman, E. R., 2001, "Carrier proteins determine local pharmacokinetics and arterial distribution of paclitaxel," Journal of Pharmaceutical Sciences, 90(9), pp. 1324-1335.
- [32] Lovich, M. A., and Edelman, E. R., 1995, "Mechanisms of Transmural Heparin Transport in the Rat Abdominal Aorta After Local Vascular Delivery," Circulation Research, 77(6), pp. 1143-1150.
- [33] Lovich, M. A., and Edelman, E. R., 1996, "Tissue average binding and equilibrium distribution: An example with heparin in arterial tissues " Biophysical Journal, 70(3), pp. 1553-1559.
- [34] Elmalak, O., Lovich, M. A., and Edelman, E., 2000, "Correlation of transarterial transport of various dextrans with their physicochemical properties," Biomaterials, 21(22), pp. 2263-2272.
- [35] Hwang, C.-W., Wu, D., and Edelman, E. R., 2003, "Impact of transport and drug properties on the local pharmacology of drug-eluting stents," International Journal of Cardiovascular Interventions, 5(1), pp. 7-12.
- [36] Baldwin, A. L., Wilson, L. M., Gradus-Pizlo, I., Wilensky, R., and March, K., 1997, "Effect of Atherosclerosis on Transmural Convection and Arterial Ultrastructure : Implications for Local Intravascular Drug Delivery," Arteriosclerosis, Thrombosis, and Vascular Biology, 17(12), pp. 3365-3375.
- [37] Hwang, C.-W., Levin, A. D., Jonas, M., Li, P. H., and Edelman, E. R., 2005, "Thrombosis Modulates Arterial Drug Distribution for Drug-Eluting Stents," Circulation, 111(13), pp. 1619-1626.
- [38] Hwang, C.-W., Wu, D., and Edelman, E. R., 2001, "Physiological Transport Forces Govern Drug Distribution for Stent-Based Delivery," Circulation, 104(5), pp. 600-605.
- [39] Hose, D. R., Narracott, A. J., Griffiths, B., Mahmood, S., Gunn, J., Sweeney, D., and Lawford, P. V., 2004, "A Thermal Analogy for Modelling Drug Elution from Cardiovascular Stents," Computer Methods in Biomechanics and Biomedical Engineering, 7(5), pp. 257-264.
- [40] Zunino, P., 2004, "Multidimensional Pharmacokinetic Models Applied to the Design of Drug-Eluting Stents," Cardiovascular Engineering, 4(2), pp. 181-191.
- [41] Balakrishnan, B., Dooley, J. F., Kopia, G., and Edelman, E. R., 2007, "Intravascular drug release kinetics dictate arterial drug deposition, retention, and distribution," Journal of Controlled Release, 123(2), pp. 100-108.

- [42] Mongrain, R., Leask, R., Brunette, J., Faik, I., Bulman-Feleming, N., and Nguyen, T., 2005, "Numerical modeling of coronary drug eluting stents," *Studies in health Technology and Informatics*, 113, pp. 443-458.
- [43] Lovich, M. A., and Edelman, E. R., 1996, "Computational simulations of local vascular heparin deposition and distribution," *American Journal of Physiology-Heart and Circulation Physiology*, 271(5), pp. H2014-2024.
- [44] Sakharov, D. V., Kalachev, L. V., and Rijken, D. C., 2002, "Numerical Simulation of Local Pharmacokinetics of a Drug after Intravascular Delivery with an Eluting Stent," *Journal of Drug Targeting*, 10(6), pp. 507-513.
- [45] Migliavacca, F., Gervaso, F., Prosi, M., Zunino, P., Minisini, S., Formaggia, L., and Dubini, G., 2007, "Expansion and drug elution model of a coronary stent," *Computer Methods in Biomechanics and Biomedical Engineering*, 10(1), pp. 63-73.
- [46] Balakrishnan, B., Dooley, J., Kopia, G., and Edelman, E. R., 2008, "Thrombus causes fluctuations in arterial drug delivery from intravascular stents," *Journal of Controlled Release*, 131(2), pp. 173-180.
- [47] Balakrishnan, B., Tzafriri, A. R., Seifert, P., Groothuis, A., Rogers, C., and Edelman, B. R., 2005, "Strut position, blood flow, and drug deposition: Implications for single and overlapping drug-eluting stents," *Circulation*, 111(22), pp. 2958-2965.
- [48] Rogers, C. D. K., 2004, "Optimal stent design for drug delivery," *Reviews in Cardiovascular Medicine*, 5(SUPPL. 2), pp. S9-S15.
- [49] Serruys, P. W., and Rensing, B., 2002, *Handbook of coronary stents*, Martin Dunitz, London.
- [50] Delfour, M. C., Garon, A., and Longo, V., 2005, "Modeling and Design of Coated Stents to Optimize the Effect of the Dose," *SIAM Journal on Applied Mathematics*, 65(3), pp. 858-881.
- [51] Bertrand, O. F., De Larochellière, R., Joyal, M., Bonan, R., Mongrain, R., and Tardif, J.-C., 2004, "Incidence of Stent Under-Deployment as a Cause of in-Stent Restenosis in Long Stents," *The International Journal of Cardiovascular Imaging (formerly Cardiac Imaging)*, 20(4), pp. 279-284.
- [52] Amin, T. M., and Sirs, J. A., 1985, "The blood rheology of man and various animal species," *Quarterly Journal of Experimental Physiology*, 70(1), pp. 37-49.
- [53] Cho, Y. I., and Kensey, K. R., 1991, "Effects of the non-Newtonian viscosity of blood on flows in a diseased arterial vessel. Part I: Steady flows," *Biorheology*, 28(3-4), pp. 241-262.

- [54] Perktold, K., and Hofer, M., 1999, Mathematical modeling of flow effects and transport processes in arterial bifurcation models. In *The Haemodynamics of Arterial Organs—Comparison of Computational Predictions with In vivo and In vitro Data*, edited by X. Y. Xu and M. W. Collins. Southampton, UK: WIT, pp. 43–84.
- [55] Kaazempur-Mofrad, M. R., and Ethier, C. R., 2001, “Mass transport in an anatomically realistic human right coronary artery,” *Annals of Biomedical Engineering*, 29(2), pp. 121-127.
- [56] Liu, Y., Lai, Y., Nagaraj , A., Kane, B., Hamilton, A., Greene, R., McPherson, D. D., and Chandran, K. B., 2001, “Pulsatile flow simulation in arterial vascular segments using intravascular ultrasound images,” *Medical Engineering & Physics*, 23, pp. 583–595.
- [57] Myers, J. G., Moore, J. A., Ojha, M., Johnston, K. W., and Ethier, C. R., 2001, “Factors influencing blood flow patterns in the human right coronary artery,” *Annals of Biomedical Engineering*, 29(2), pp. 109–120.
- [58] Green, G. W., Jones ,J. E. F., Band , A. G., 2005, "Arterial stents: Modelling drug release andrestenosis", *Proceedings of the 4th Mathematics in Medicine Study Group*.
- [59] Kedem, O., and Katchalsky, A., 1989, "Thermodynamic analysis of the permeability of biological membranes to non-electrolytes," *Biochimica et biophysica acta*, 1000, pp. 413-430.
- [60] Nanfeng, S., Nigel, B. W., Alun, D. H., Simon, A. M. T., and Xu, X. Y., 2006, "Fluid-Wall Modelling of Mass Transfer in an Axisymmetric Stenosis: Effects of Shear-Dependent Transport Properties," *Annals of Biomedical Engineering*, V34(7), pp. 1119-1128.
- [61] Yang, N., and Vafai, K., 2006, "Modeling of low-density lipoprotein (LDL) transport in the artery--effects of hypertension," *International Journal of Heat and Mass Transfer*, 49(5-6), pp. 850-867.
- [62] Hwang, C. W., and Edelman, E. R., 2002, "Arterial ultrastructure influences transport of locally delivered drugs," *Circulation Research*, 90(7), pp. 826-832.
- [63] Cho, Y. I., Back, L. H., Crawford, D. W., and Cuffel, R. F., 1983, "Experimental study of pulsatile and steady flow through a smooth tube and an atherosclerotic coronary artery casting of man," *Journal of Biomechanics*, 16(11), pp. 933-946.
- [64] Welkowitz, W., 1987, *Engineering hemodynamics : application to cardiac assist devices*, New York University Press, New York.

- [65] Whale, M. D., Grodzinsky, A. J., and Johnson, M., 1996, "The effect of aging and pressure on the specific hydraulic conductivity of the aortic wall," *Biorheology*, 33(1), pp. 17-44.
- [66] COMSOL multiphysics user's guide. Version 3.3, August 2006.
- [67] Deuflhard, P., 1974, "A modified Newton method for the solution of ill-conditioned systems of nonlinear equations with application to multiple shooting," *Numerische Mathematik*, 22(4), pp. 289-315.
- [68] Peter, N. B., Alan, C. H., and Linda, R. P., 1994, "Using Krylov methods in the solution of large-scale differential-algebraic systems," *The SIAM Journal on Scientific Computing*, 15(6), pp. 1467-1488.
- [69] Borghi, A., Foa, E., Balossino, R., Migliavacca, F., and Dubini, G., 2008, "Modelling drug elution from stents: effects of reversible binding in the vascular wall and degradable polymeric matrix," *Computer Methods in Biomechanics and Biomedical Engineering*, 11(4), pp. 1-11.
- [70] Qiu, Y., and Tarbell, J. M., 2000, "Numerical simulation of pulsatile flow in a compliant curved tube model of a coronary artery," *Journal of Biomechanical Engineering*, 122(1), pp. 77-85.
- [71] Wei, L., Wen, G. B., and Tan, W. C., 2006, "Blood flow and macromolecular transport in curved blood vessels," *Applied Mathematics and Mechanics (English Edition)*, 27(9), pp. 1223-1231.