Prediction of Biodegration and Drug Release from a Biodegradable Stent

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INTRODUCTION

A drug-eluting stent generally consists of a metallic stent platform with a polymeric coating that encapsulates a drug. In recent times, a large number of clinical trials have demonstrated that local drug delivery using drug-eluting stents can inhibit several of these processes thereby preventing or minimizing restenosis. However, metallic stent platforms might not be the most ideal means of drug delivery. A metallic stent significantly alters the local compliance of the artery making the stented segment much stiffer than a native artery and there is a potential for the stent to fail under long term fatigue loading. Further, the permanent metallic implants might interfere with future interventional procedures. Therefore, ideally it is desirable to have a stent that provides sufficient support to the arterial wall upon deployment delivers a therapeutic dose of the drug to prevent restenosis and then degrades to non-toxic products either during the drug release process or after the drug delivery is completed. Biodegradable polymers such as Poly(lactic acid) [PLA] have been investigated for stent based drug delivery [1].

Mathematical models can serve as important tools in the development of such biodegradable drug eluting stents. Depending on the nature of the polymer used to design the stent and its interaction with the vasculature, numerous mass transport and chemical reaction kinetics phenomena affect the degradation of the polymer and drug release profile. These phenomena include but are not limited to water absorption by the polymer, micro-environmental pH changes inside polymeric matrix and diffusion of the drug and degradation products in the channels created inside the polymeric matrix. The mathematical model should take into account the dominant physicochemical process responsible for the degradation and drug delivery. In order to prove that the model captures these important processes, it has to be validated with experimental data. This validated model can be used to optimize coating design or to design similar biodegradable coatings. The model can also be used to study the effect of different coating parameters such as size and shape on the degradation and drug release.

MATHEMATICAL MODEL

A diffusion-reaction based model is presented here to predict the degradation of a PLA stent and the release of the drug from the stent. Such models have been developed in the past for PLA based coating on metallic stents [2]. Figure 1 shows the schematic diagram of the mathematical model. The model incorporates governing equations and boundary conditions that couple the phenomena of polymer breakdown, water uptake, and drug diffusion. The model assumes molecular polymeric breakdown of PLA (M_w<120000) into oligomers with molecular weight M_W<20000 (component 2) and into lactic acid. The oligomers with M_W<20000 undergo degradation to produce lactic acid. The time dependence of the diffusivity of the drug and the components resulting from the degradation process are also incorporated in the model. The governing diffusion-reaction equations describing the model are as follows:

1. Transport of the water into the PLA stent

$$\frac{\partial C_W}{\partial t} = \frac{\partial}{\partial x}\left(D_W \frac{\partial C_W}{\partial x}\right) - k_{PW} C_P C_W (1+\alpha C_L) - k_{2W} C_2 C_W (1+\beta C_L)$$

2. Transport of unhydrolyzed PLA

$$\frac{\partial C_P}{\partial t} = \frac{\partial}{\partial x}\left(D_P \frac{\partial C_P}{\partial x}\right) - k_{PW} C_P C_W (1+\alpha C_L)$$

3. Transport of component 2

$$\frac{\partial C_2}{\partial t} = \frac{\partial}{\partial x}\left(D_2 \frac{\partial C_2}{\partial x}\right) + k_{PW} C_P C_W (1+\alpha C_L) - k_{2W} C_2 C_W (1+\beta C_L)$$

4. Transport of lactic acid

$$\frac{\partial C_L}{\partial t} = \frac{\partial}{\partial x}\left(D_L \frac{\partial C_L}{\partial x}\right) + k_{PW} C_P C_W (1+\alpha C_L) + k_{2W} C_2 C_W (1+\beta C_L)$$

5. Transport of the drug

$$\frac{\partial C_D}{\partial t} = \frac{\partial}{\partial x}\left(D_D \frac{\partial C_D}{\partial x}\right)$$

The boundary conditions at the luminal surface of the stent (i.e. surface exposed to the blood flow) and the abluminal (i.e. surface in contact with the arterial wall are $D_i(\partial C_i/\partial x) = k_i(\mathrm{C_{i,tissue}} - \mathrm{C}_i)$ at $x = 0$ and $D_i(\partial C_i/\partial x) = k_i'(\mathrm{C_{i,blood}} - \mathrm{C}_i)$ at $x = l$ for t>0 and *i=P, 2, L* and *D*. The boundary conditions for the transport of water are $C_W(0,t) = kC_0(t)$ and $C_W'(l,t) = k'C_0'(t)$. The initial conditions are given by $C_i(x,0) = 0$ for *i=2,L* and $C_i(x,0) = C_i^0$ for *i=P,D*. Diffusivities of the water, component 2, and Lactic acid and the drug is given by $D_{W,2,1,D} = D^0_{W,2,L,D} \exp\left[\alpha_{W,2,1,D}(C_P|_{t=0} - C_P)/C_P|_{t=0}\right]$ where $D^0_{W,2,L,D}$ is the diffusivity of the respective species in the unhydrolyzed PLA and $C_L|_{t=0}$ of the unhydrolyzed polymer at *t=0*.

The results obtained from the model and its validation with experimental data will be presented

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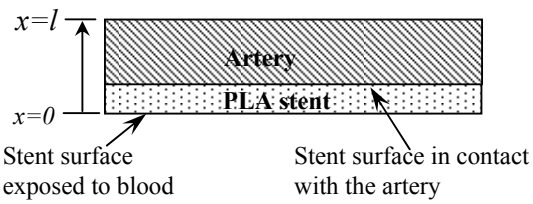

Figure 1 Schematic diagram for model for predicting degradation and drug release.