Mathematical Modeling of Cardiovascular Drug Delivery

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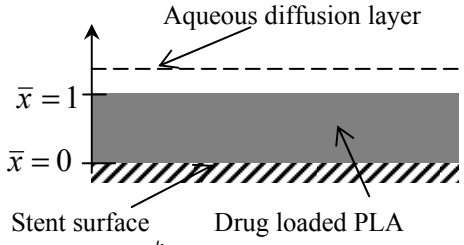
INTRODUCTION

Mathematical modeling of the various aspects of cardiovascular drug delivery plays an important role in the design of device concepts for treating atherosclerosis. Models that can be used for predicting the drug release from devices such as stents and the subsequent transport of these drugs in the arterial ultra-structure are presented in this paper

METHODS

Mathematical models pertaining to drug release from biodurable and biodegradable coating will be presented. A model describing the drug distribution into the arterial wall after a catheter based drug delivery will also be presented. However, for the sake of brevity, in this abstract only the method and results for the modeling of drug release from a biodegradable coating will he presented.

A simultaneous transport-reaction model predicting the release of the drug from a biodegradable poly(lactic acid) [PLA] based stent coating was developed [1]. A schematic of the drug loaded PLA matrix configuration is shown in Fig.2. When device is immersed in a liquid (such as blood or saline buffer) it initiates the physical mass transport processes and a series of chemical reactions that are responsible for the degradation of the matrix and the release of the drug. Water *W* partitions at the surface of the hydrophobic PLA matrix and diffuses into the matrix under the influence of a concentration gradient. As illustrated in Figure 1, Reaction 1 is the hydrolysis of the PLA resulting in oligomers with molecular weight M_w, greater than 20K (indicated by *O*) but less than that of the unhydrolyzed PLA (which about 120K). It is assumed the all these oligomers have similar diffusivities as they diffuse through the matrix. Reaction 2 is the hydrolysis of the oligomers C_2 into lactic acid. The lactic acid generated by this reaction is assumed to have a catalytic effect on the degradation of the PLA.



Reaction 1: $P + W \xrightarrow{k_{PW}} O + L$

Reaction 2: $O + W \xrightarrow{k_{2W}} L$

P – PLA

W – Water

O – Oligomers with molecular weights less than that of PLA but greater than 20K

L – Lactic acid

Figure 1 Schematic of the mathematical model

RESULTS AND DISCUSSION

Figure 2 shows the fractional amount of the different species in the coating as a function of time, obtained from the model. Also, shown in the figure is the experimentally determined fraction of PLA in the coating as a function of time. The fit between the experimentally and computationally determined fractions of PLA in the coating is illustrated in the figure. Also, as illustrated in the Fig. 2, the degradation process can be broken into three regions indicating three distinct phases of the degradation process. The first phase corresponds to the rapid uptake of water by the polymer and occurs within the first 12 hours. The second phase corresponds to the hydrolysis of the polymer and lasts for about 7.5 months. This is the phase where the generation and build up of lactic acid takes place in the polymeric matrix thereby resulting in an autocatalytic effect. This autocatalytic effect, which accelerates the degradation of the PLA, is illustrated by the rapid decrease in the slope of the curve corresponding to the fractional amount of PLA in the coating, as indicated in Figure 9. Most of the drug is released during this phase of the degradation process. The third phase corresponds to the rapid breakdown of the polymer. In this phase, the rate of generation of lactic acid in the matrix is lower than the rate at which the lactic acid is expelled into the aqueous media. This results in a reduction of the concentration of the lactic acid in the polymeric matrix.

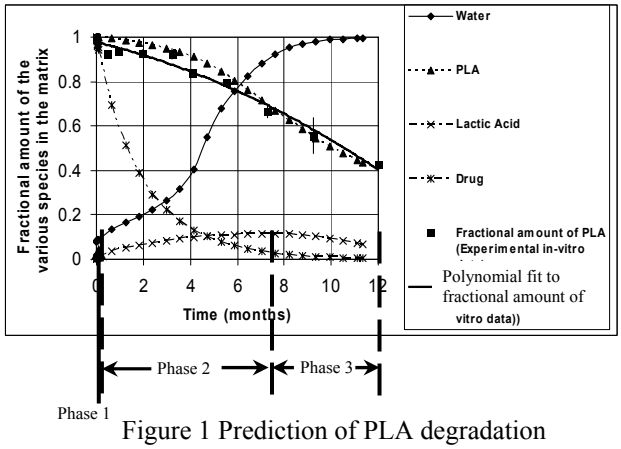


Figure 1 Prediction of PLA degradation

CONCLUSIONS

A simultaneous transport-reaction model has been developed that takes into account the dominating mechanisms for the degradation of PLA. The model can be used to predict the degradation of the PLA and drug release.

REFERENCE

1. Prabhu S, Hossainy S. Modeling of Biodegradation and Drug Release from a PLA based stent coating. To appear in Journal of Biomedical Materials Research Part A.