Mathematical Modeling and Simulation of Intravascular Drug Delivery from Drug-Eluting Stents with Biodegradable PLGA Coating

by

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ABSTRACT

Drug-eluting stents (DES) are commonly used in coronary angioplasty procedures. A DES elutes drug compounds from a thin polymeric coating into the surrounding coronary artery tissue to reduce in-stent restenosis (a significant lumen loss due to growth of vascular tissue). Biodegradable (non-erodible) polymers are often used in the current DES coatings, which stay permanently in the patients. While promising treatment results were obtained, in-stent restenosis remains an issue and late in-stent thrombosis, which is associated with hypersensitivities to the polymer coatings, is also reported. Increasing interests have been raised towards the design of a more biocompatible coating, in particular a poly(lactic acid-co-glycolic acid) (PLGA) coating, for DES applications to improve the drug delivery and reduce adverse outcomes in patients.

This dissertation aims to develop a mathematical model for describing the process of drug release from a biodegradable PLGA stent coating, and subsequent drug transport, pharmacokinetics, and distribution in the arterial wall. A model framework is developed in the first part of the dissertation, where a biodegradable stent coating is considered, and the intravascular delivery of a hydrophobic drug from an implanted DES in a coronary artery is mathematically modeled. The model integrates drug diffusion in the coating with drug diffusion and reversible drug binding in the arterial wall. The model was solved by the finite volume method. The drug diffusivities in the coating and in the arterial wall were investigated for the impact on the drug release and arterial drug uptake. In particular, anisotropic vascular drug diffusivities result in slightly different average arterial drug levels but can lead to very different spatial drug distributions, and is likely related to the reported non-uniform restenosis thickness distribution in the artery cross-section.

The second part of the dissertation focuses on modeling drug transport in a biodegradable poly(D,L-lactic-co-glycolic acid) (PLGA) coating. A mathematical model for the PLGA degradation, erosion, and coupled drug release from PLGA stent coating is developed and validated. An analytical expression is derived for PLGA mass loss. The drug transport model incorporates simultaneous drug diffusion through both the polymer solid and the liquid-filled pores in the coating, where an effective drug diffusivity model is derived taking into account factors including polymer molecular weight change, stent coating porosity change, and drug partitioning between solid and aqueous phases. The model predicted in vitro sirolimus release from PLGA stent coating, and demonstrated
the significance of the developed model by comparing with existing drug transport models.

An integrated model for intravascular drug delivery from a PLGA-coated DES is developed in the last part of the dissertation. The integrated model describes the processes of drug release in a PLGA coating and subsequent drug delivery, distribution, and drug pharmacokinetics in the arterial wall. Model simulations first compared a biodegradable PLGA coating with a biodurable coating for stent-based drug delivery. The simulations further investigated drug internalization, interstitial fluid flow in the arterial wall, and stent embedment for impact on the drug release and arterial drug distribution of a PLGA-coated stent. These three factors greatly change the average drug concentrations in the arterial wall. Each factor leads to significant and distinguished alterations in the arterial drug distribution that can potentially influence the treatment outcomes.

The developed model here provides the basis of a design tool for evaluating and studying a PLGA coating for stent applications. Simulations using the model helped to provide insights into the potential impacts of various factors that can affect the efficacy of drug delivery. With the developed model, optimization of the model parameters can also be performed for future exploration on the design of PLGA-coated drug-eluting stents.

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