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A decade of modelling drug release from arterial stents

Sean McGinty

Department of Mathematics and Statistics, University of Strathclyde, Glasgow G1 1XH, UK

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ABSTRACT

Drug-eluting stents have revolutionised the treatment of coronary artery disease. These small medical devices have attracted much interest over the past decade from biologists, clinicians, engineers and mathematicians alike. This article provides a comprehensive review of the modelling of drug release from arterial stents and the subsequent drug transport through arterial tissue, and acts as a useful reference equally for those who are already involved in drug-eluting stents research and for those who are starting out in the field. Assembled in this review are the main models of drug release and arterial drug transport that have been published in the literature to date. Many of the models presented in this paper have evolved from drug transport models in other applications. Furthermore, the ideas presented in this review may also be extended to other drug-delivery applications, such as drug coated balloons, transdermal patches and therapeutic contact lenses.

1. Introduction and Background

Arterial stents have revolutionised the treatment of coronary heart disease (CHD). Acting as a supporting scaffold, these small mesh devices are now routinely inserted into arteries where the blood flow has become dangerously restricted (see Fig. 1). There are many benefits to the patient over more traditional treatment strategies such as open-heart surgery, including a lower incidence of major complications and an expedited recovery time. Furthermore, most patients do not require general anesthesia. Over the past decade, arterial stents have evolved from mere bare metal scaffolds to polymer coated drug-delivery vehicles and, more recently, sophisticated fully biodegradable drug delivery configurations. The driver behind these continuing advances is the desire to improve clinical outcomes. The original bare metal stents, while revolutionary at the time, were soon rendered unsatisfactory due to the relatively quick occurrence of restenosis, the re-narrowing of the lumen. The next wave of arterial stents included a drug designed to prevent the occurrence of restenosis: these are the so-called drug-eluting stents (DESs). The development of these stents threw up all sorts of questions such as: What type of drug should be used? How much drug should be coated on the stent? How will the drug release be controlled? Effective DES design became the priority for many of the top medical device companies, with considerable budgets spent on developing these products. In 2002 the first-generation DESs, Cypher (sirolimus-eluting stent; Cordis Corporation) and Taxus (paclitaxel-eluting stent; Boston Scientific Corporation) arrived. They comprised a stainless steel platform with a drug containing polymer coating attached to the stent struts [1,2]. The philosophy behind this design was to allow the drug to be released gradually so as to avoid toxic levels of drug initially, but also to permit sustained delivery over many weeks. The Cypher stent actually consists of multiple polymer layers designed to enhance the controlled nature of the release. The drugs used (sirolimus and paclitaxel) are both lipophilic and are able to inhibit smooth muscle cell (SMC) proliferation and migration. The second-generation DESs Endeavor (zotarolimus-eluting; Medtronic), Promus (everolimus-eluting; Boston Scientific Corporation) and Xience V (everolimus eluting; Abbott Laboratories) attempted to improve the biocompatibility and reduce the incidence of thrombosis which was associated with first-generation DES [3,4]. These stents were generally designed with thinner struts and utilised cobalt-chromium and platinum chromium platforms. A variety of multi-layer polymer combinations were used on these stents to attempt to control the release. Generally these stents have been shown to exhibit lower thrombosis rates compared with first generation DES [5]. Since the polymer coating in the earlier DES has been associated with a local vascular inflammatory reaction and potentially inducing late stent thrombosis, newer generation stents have focussed on biodegradable polymers (BioMatrix, Biosensors Inc, Nobori, Terumo, and Synergy, Boston Scientific Corporation), where the polymer carries and controls the drug release and then erodes or vanishes, and also coatings which do not contain any polymer at all (Yukon, Translumina and BioFreedom, Biosensors Inc), with the drug being contained on a modified surface of the stent. Perhaps the most sophisticated to date is the completely bioresorbable stent Absorb (Abbott

E-mail address: s.mcginty@strath.ac.uk

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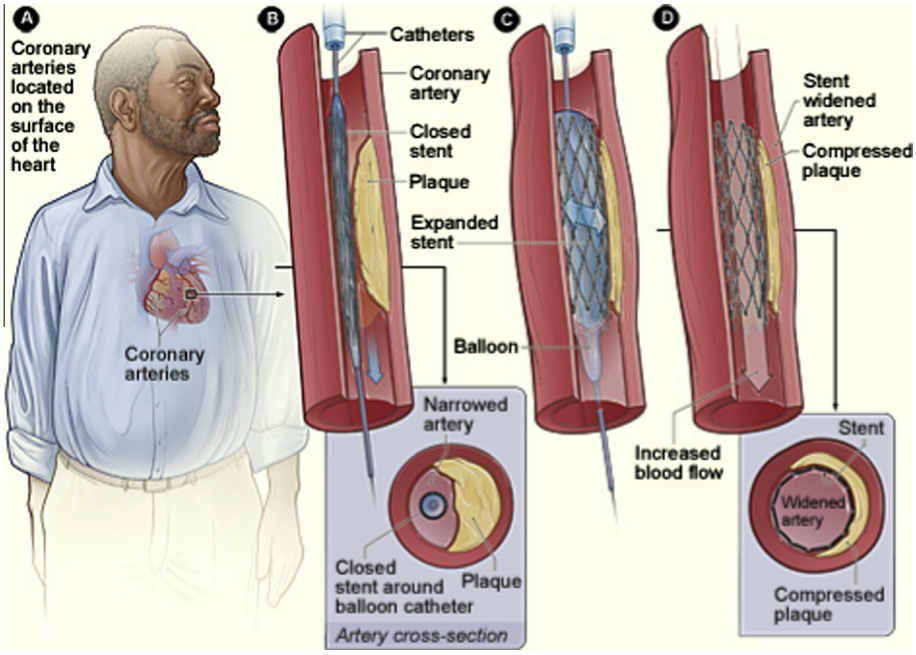

Fig. 1. Illustration of a stent being inserted at the site of a blocked artery. *Source:* National Heart, Lung and Blood Institute; National Institute of Health; U.S. Department of Health and Human Services.

Laboratories). This stent elutes everolimus in a similar way to Xience V and then resorbs naturally into the body leaving no permanent scaffold.

A significant amount of research has gone into the development of arterial stents. Countless experiments have been performed (many of which involving animals), not to mention the need for clinical trials before accreditation is finally granted. The long treacherous and costly road from a good stent design idea to regulatory approval has led many to question whether modelling could be better used to try to make this path an easier one. Indeed, only those stents which show promising results in laboratory and clinical trials are retained and those that do not are discarded – often after considerable investment. Mathematicians and engineers, realising that this complex problem is amenable to modelling, have become increasingly interested over the years. In the early years the drug release mechanism was very poorly understood, but through mathematical modelling approaches, combined with experiments, researchers have helped identify the dominant mechanisms of release in a number of stents. While release experiments alone can give information regarding the release profile and the duration of release, the data generated is for one particular set of parameters (e.g. coating thickness, drug type and concentration) and the experiment needs to be repeated for each new parameter considered. Once verified, mathematical models have the advantage of allowing several parameters to be varied and the release profiles compared without the need to repeat the experiments. The ability of a mathematical model to help identify the important parameters that govern the drug release is invaluable. Modelling can also play an important role when an understanding of the drug distribution within arterial tissue is required. Cardiologists will often stress that uniform drug concentrations across the wall are desired, and that these concentrations should be maintained within some minimum therapeutic and toxic levels. Obtaining this kind of information from experiments is extremely challenging, yet free and bound drug concentration profiles can readily be output from a mathematical model. But experiments and modelling must go hand in hand: the accuracy of the model results can only ever be as good as the quality of the inputs, especially when the model is sensitive to changes in one or more of the parameters. Indeed, the accurate determination of system parameters remains one of the biggest challenges in the field due to the natural variation between species and the complexity involved in making the required measurements, especially in the *in vivo* situation. However, some recent progress has been made by combining *in vitro*/*ex vivo* experiments with simple mathematical models, and this approach may continue to yield useful results in the future. As we shall see, the conclusions which can be drawn from modelling have provided useful insights, some of which are counter-intuitive. Among the many other benefits of adopting a modelling approach include the potential to indicate at an early stage the designs that are doomed to failure, to design stents that are optimised and to result in a reduction in the number of experiments required.

In this paper we provide a comprehensive review of the modelling of drug-release from arterial stents and the subsequent arterial drug redistribution. We firstly present the models which have been developed to describe drug release from DESs. Then, we consider how drug uptake into arterial tissue has been modelled. Thirdly, models which treat the stent and the arterial wall as a coupled system are reported. The benefits and drawbacks of each model are discussed. We have attempted to unite the various different notations in the literature. With this in mind, the models presented here may differ in notation from the original work.

2. Modelling the release of drug from arterial stents

An important aspect in the performance of any DES is the drug release profile. If too much drug is delivered then toxicity can arise, whereas if too little drug is delivered then it may have no effect at all. Of course, this "therapeutic window" varies between drugs and between patients and most probably with time after implantation too. Stent manufacturers routinely test the release of drug from their stents in an *in vitro* environment to gain an understanding of the shape of the release profile and to compare the release profile of different devices. This allows the manufacturers to ascertain the repeatability of the release profile. Whilst the *in vitro* release is

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