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COMBINING MATHEMATICAL MODELLING WITH IN-VITRO EXPERIMENTS TO PREDICT IN-VIVO DRUG-ELUTING STENT KINETICS

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SUMMARY

In this paper we describe a combined in-vitro experimental and mathematical modelling approach to predict in-vivo drug-eluting stent kinetics. We coated stents with a mixture of sirolimus and a novel acrylic-based polymer in two different ratios. Our results indicate differential release kinetics between low and high drug dose formulations. Furthermore, mathematical model simulations of target receptor saturation suggest potential differences in efficacy.

Key words: *Drug-eluting stents, drug delivery, coupled partial differential equations, in-vivo experiments*

1 INTRODUCTION

Mathematical and computational modelling is increasingly being used in the design and testing of medical implants. In particular, modelling of drug-eluting stents (DES) for the treatment of Coronary Heart Disease (CHD) has received much attention in the literature [1]. Many aspects of these devices have been modelled, including deployment, structural and fluid mechanics, and drug-delivery. A common theme has been to use modelling to try to infer the optimal design of a DES [2, 3]. Some authors have focussed on a single feature such as the geometry (e.g. strut thickness), materials, or drug loading, whilst others have considered multi-objective optimisation. Regarding the drug delivery aspect, there exist studies which have used modelling *retrospectively* to demonstrate agreement with in-vivo drug release and tissue uptake data [4, 5]. Usually this involves a fitting procedure, where an algorithm is used to determine the model parameter set which best fits the data. These studies are limited in the fact that they cannot be used in a predictive sense. To the best of our knowledge, there exists no published studies which have attempted to validate and parameterise a model using in-vitro data before using the parameterised model to predict in-vivo kinetics. This is precisely the focus of of the current study.

2 METHODOLOGY

2.1 Drug release

We verified experimentally that a novel acrylic-based polymer (accelerate™AT, Biomer Technology Ltd, UK) could be combined with sirolimus to produce a coating which releases drug at clinically relevant concentrations, initially by coating glass coverslips and then Flash stents (Conic Vascular,

Santiago de Compostella). The stents were coated with *low* and *high* doses of sirolimus/polymer (in ratios 25:75 and 75:25, respectively) using a Sono-Tek Ultrasonic Spray system (Milton, NY, USA). Two coats were applied. The stents were assessed for release of sirolimus over a period of 28 days by immersing in 1.5 ml of release medium (phosphate buffered saline:ethanol 90:10), and transferring to fresh release medium at regular sampling points to maintain sink conditions. The amount of sirolimus in release medium was determined by ultraviolet spectroscopy.

Our previous mathematical modelling of drug release from the Cypher stent revealed that in-vitro release was well described by a relatively simple one-dimensional diffusion model [7], whereas in-vivo release was captured by a diffusion-dissolution model, indicating that differences in drug solubility between the in-vitro and in-vivo release medium may be important [5]. We therefore fit the drug release data for each coating formulation to the diffusion model, and separately to the diffusion-dissolution model.

2.2 Coupled drug release and tissue uptake

The parameterised model of drug release from Section 2.1 was then coupled with a model of drug transport in the arterial wall accounting for diffusion, advection and two modes of binding (specific receptor and non-specific extracellular matrix binding), utilising porcine arterial tissue transport parameters from the literature [4, 5, 6]. As well as providing the opportunity to predict the uptake and retention of drug in the arterial wall, this model allowed us to simulate spatial wall drug concentration and receptor saturation, which have been linked with DES efficacy yet are difficult to measure experimentally.

An in-vivo experimental study was subsequently conducted. Briefly, low and high dose stents were deployed in male Landrace pig coronary arteries with drug release and mass of drug in tissue quantified at 1 day, 7 days and 28 days. Animal care and all procedures conformed to the requirements of the U.K. Animals (Scientific Procedures) Act 1986.

3 RESULTS AND CONCLUSIONS

3.1 In-vitro drug release

At the end of the in-vitro experiments, stents were immersed in ethanol to strip any remaining drug. In all cases, we observed that not all of the initial drug mass was released by 28 days, despite the release profiles appearing to asymptote. We therefore assumed that some quantity of drug would never be released (as has been observed with other commercial stents, e.g. TAXUS) and so normalised release data by the cumulative mass of drug released by the final measurement time point. Whilst our low drug dose formulations were very well described by a simple diffusion model, the fit to the high dose formulation data was not so good. In Figure 1 we compare in-vitro drug release from the low and high dose formulations with two applied coats. The best-fitting diffusion coefficient in the high dose case is an order of magnitude less than in the low dose case. This may suggest that drug transport in the high dose case is more complex than diffusion alone, or perhaps that one or more of the model assumptions are not appropriate. Results from fitting to a diffusion-dissolution model essentially reproduced Figure 1, suggesting that the more complex diffusion-dissolution model is no better at capturing the release. Since in the high dose case, the ratio of drug to polymer is 75:25, the validity of the diffusion model (i.e. the dilute species assumption) may be called into question, and multi-species diffusion models may be more appropriate.

3.2 In-vivo drug release

Our preliminary results indicate that for the low dose stents, drug elution is complete by 1 day, in agreement with the in-vitro drug release profile. However, for the high dose stents, whilst the duration of drug release is the same (28 days) for the in vitro and in-vivo cases, the release rate is significantly faster in-vivo: approximately 85% of drug is released within 1 day in-vivo, compared

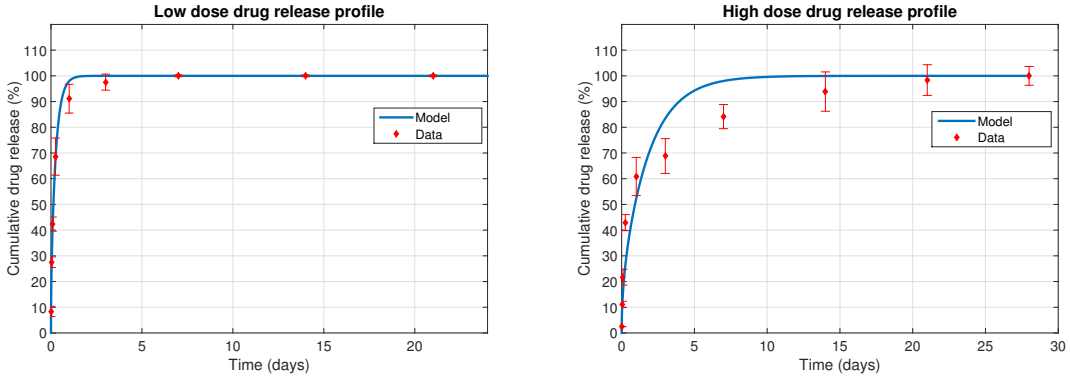

Figure 1: Comparison between experimental in-vitro drug release data (normalised by the cumulative mass eluted by the final measurement time point), and model simulations. LEFT: The low dose stent was well-fitted by a diffusion coefficient of the order of $10^{-16} m^2\ s^{-1}$. RIGHT: The fit between the diffusion model and the data from the high dose stent was not so good. Furthermore, the best-fitting diffusion coefficient was of the order $10^{-17} m^2\ s^{-1}$.

with approximately 60% in-vitro. In agreement with the in-vitro release, the remainder of drug is released at a slower rate over the following 27 days.

3.3 Efficacy

It is generally accepted [4] that the fraction of drug bound to target receptors is an indicator of DES efficacy, yet there is currently no straightforward way to measure this in-vivo. We therefore used our mathematical model of coupled drug release and tissue uptake to predict target receptor binding levels for both low dose and high dose stents, using porcine coronary artery wall model parameters from the literature [4, 5, 6]. In Figure 2, we observe that the model predicts target receptor saturation within 1 day for both low dose and high dose stents. Despite drug elution for the low dose stent being complete by 1 day, target receptors remain saturated for approximately the first 3 days, with a declining rate of saturation over the remainder of the 28 days. In contrast, the high dose stent results in near 100% target receptor saturation for the majority of the first 2 weeks, followed by a steady decline for the remainder of the study. Simulations of non-specific extracellular matrix (ECM) binding revealed that neither the low dose nor the high dose stent delivered drug at levels capable of reaching saturation. Histological analysis, important for assessing efficacy experimentally, is ongoing. The results from this analysis will be assessed in conjunction with model predictions of receptor saturation.

4 CONCLUSIONS

In this study we have successfully developed two novel DES with distinct release profiles. By comparing experimental drug release data with our diffusion-based mathematical model, we have shown that the model captures the release of drug from the low dose stent very well and less well for the high dose stent. In an attempt to assess efficacy, we have used our parameterised model to simulate the level of sirolimus bound to target receptors. Our preliminary results indicate differential levels of receptor saturation between low dose and high dose stents, indicating possible differences in efficacy. Experimental analysis of DES efficacy is ongoing.

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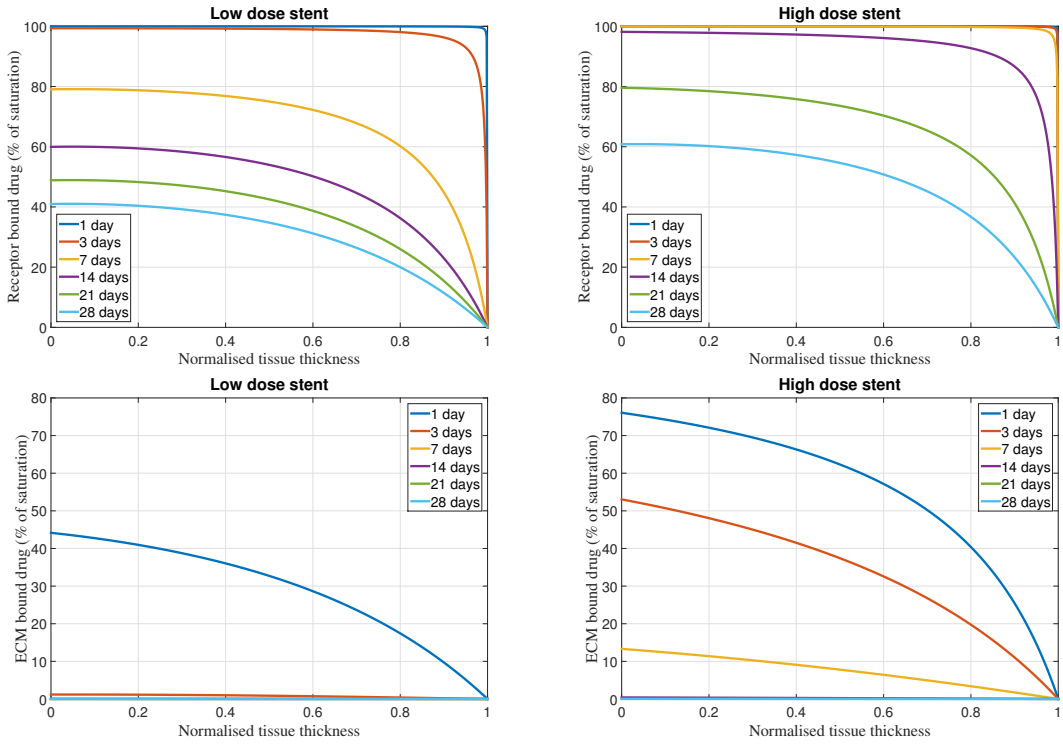

Figure 2: Simulated arterial binding kinetics. LEFT: Low dose stent. RIGHT: High dose stent. In both cases the model predicts target receptor saturation within 1 day. The % of drug bound receptors decreases more rapidly for the low dose stent. Neither low dose nor high dose stents result in ECM non-specific binding site saturation.

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