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Mathematical modelling of variable porosity coatings for controlled drug release

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ABSTRACT

In this paper we investigate the extent to which variable porosity drug-eluting coatings can provide better control over drug release than coatings where the porosity is constant throughout. In particular, we aim to establish the potential benefits of replacing a single-layer with a two-layer coating of identical total thickness and initial drug mass. In our study, what distinguishes the layers (other than their individual thickness and initial drug loading) is the underlying microstructure, and in particular the effective porosity and the tortuosity of the material. We consider the effect on the drug release profile of varying the initial distribution of drug, the relative thickness of the layers and the relative resistance to diffusion offered by each layer's composition. Our results indicate that the contrast in properties of the two layers can be used as a means of better controlling the release, and that the quantity of drug delivered in the early stages can be modulated by varying the distribution of drug across the layers. We conclude that microstructural and loading differences between multi-layer variable porosity coatings can be used to tune the properties of the coating materials to obtain the desired drug release profile for a given application.

1. Introduction

The topic of drug delivery is a truly multi-disciplinary research area and has been attracting the interest of engineers, mathematicians, chemists and life scientists for decades. In particular, *controlled* drug delivery has received much attention, particularly concerning the design of tablets [1–3] and local drug delivery devices such as stents [4], transdermal patches [5], contact lenses [6] and orthopaedic implants [7] (Fig. 1). Controlled release of drug from each of these vehicles can in principle be obtained by varying system design parameters. Some of the most common include the device geometry and materials; the physico-chemical properties of the drug and; the drug loading configuration. In the case of experimental studies, it is often *demonstrated* that different drug release profiles can be obtained by either varying the experimental conditions (e.g. in-vitro versus in-vivo) or physical delivery system properties, whilst in the case of mathematical and computational modelling, it is usual for a sensitivity analysis of the underlying model parameters to be conducted, and release profiles subsequently *simulated*. Both approaches are useful and indeed can be complementary in the quest for device design optimisation. In the case of tablets, there is a body of literature concerning multi-layer systems (see e.g. [1–3]), where the individual layers contain either different drugs or chemicals, or contrasting material properties from which the same drug or chemical is released in a bi- or multi-modal fashion. However, the literature concerning drug release from multi-layer coatings is lacking somewhat, particularly in relation to mathematical modelling (see [12] as a rare exception). This will be the focus of the current manuscript.

Much of the research concerned with drug-eluting medical devices is focussed on developing sophisticated computational models which accurately simulate drug release and the subsequent distribution in the biological environment. The complexity of these models is increasing, with more and more realistic features being accounted for, including accurate 3D geometrical representations of the device and anatomical features; anisotropic and spatially-varying drug transport properties within the body and; complex features such as nonlinear binding reactions. If, on the one hand, these models are indeed necessary to accurately simulate drug transport within the device and in the biological environment, on the other hand it is clear that device manufacturers cannot intervene on the underlying biology. What they can control, however, are the properties of the device platform to ensure an optimal release [13]. Therefore, in this paper, we take a step back from the

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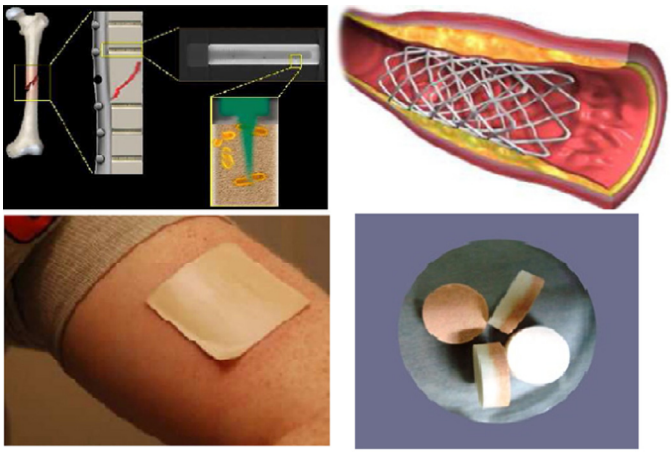

Fig. 1. Examples of drug-delivery devices for different applications. From left to right: an orthopaedic implant [8], a coronary stent [9], a transdermal patch [10] and multi-layer tablets [11].

fully coupled computational models (see e.g. [14]) and focus instead solely on the properties of the drug-containing coating.

As a result of our focus on the coating, we consider only in-vitro drug release, which excludes the biological environment. We justify this as follows: firstly, it is routine for device manufacturers to perform in-vitro drug release testing during the design stage to establish the range of release profiles that can be obtained, and to test the repeatability. This typically involves placing the drug-eluting device in a test tube containing release medium and measuring the mass of drug released under infinite sink conditions. Secondly, to incorporate equations for transport in a particular type of tissue or specific biological environment (e.g. the arterial wall in the case of drug-eluting stents [9,14,18,19]) would be to detract from the generality of the models. We therefore consider multi-layer drug-eluting coatings generally, rather than focussing on a particular device.

The drug is typically contained within some durable/biodegradable polymeric coating attached to the device platform or embedded within a nanoporous structure. The drug release profile depends on a number of factors including the porosity of the coating or bulk structure; the drug loading and initial distribution; the physico-chemical properties of the drug (e.g. molecule size, solubility, etc.) and; the release medium. A certain level of control is required: an excessive amount of drug delivered too quickly can result in toxicity, but, on the other hand, the therapeutic action vanishes when the drug concentration drops below a given threshold. However, the most desirable release profile is not always known and may in fact be patient-specific and therapy-dependent.

Motivated by today's advances in material fabrication and by the increased capabilities of the miniaturisation of structures offered by micro and nanotechnology, we propose variable porosity multi-layer coatings as an additional means of controlling the drug delivery and tailoring the release profile to the desired application. Our initial goal is to gain a better understanding of the potential benefits of replacing a single-layer with a two-layer drug-eluting coating of identical total thickness and initial drug mass. In our study, what distinguishes the layers (other than their thickness and initial drug loading) is the underlying microstructure, and in particular the effective porosity and tortuosity of the material (Fig. 2). The primary novelty of our work is that whilst some existing drug delivery devices already make use of bi- and multi-layer coatings, to the best of our knowledge, no groups have theoretically investigated and assessed the effect on drug transport of varying the porosity and material microstructure between layers. We are not

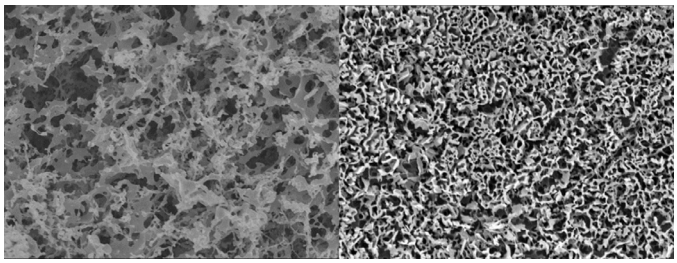

Fig. 2. Example of two adjacent polymer coatings with different microstructural properties. These were prepared from different concentrations of polymer solutions (0.6% left and 0.8% right) [15].

aware of any published experimental work which investigates drug release from variable porosity multi-layer coatings: we believe that our model may inspire and guide such experiments, which in turn could then be used to assess the predictive capacity of the model.

The structure of the paper is as follows. In Section 2 we provide the mathematical formulation of the problem and define a suitable non-dimensionalisation. We then propose, in Section 3, a semi-analytical solution method which makes use of separation of variables and expresses the solution as a Fourier series. A special case which admits an analytical solution is also presented. In the penultimate section we provide our results and investigate the sensitivity of the release profile to variations in the model parameters. Finally, in Section 5, we provide the conclusions of our study.

2. Mathematical formulation

A drug delivery device typically includes a polymeric matrix coating containing drug which is in contact with some release medium. The particular geometry of the device varies between applications, but the drug-eluting coating can usually reasonably be idealised as a slab (*layer*) of some thickness L. In Fig. 2 we display an example of the situation we wish to model in the present work: two adjacent coating layers with different microstructural properties. Since the total thickness of drug-eluting coatings is typically small relative to the lateral coating dimensions, and the net drug transport is along a single direction, we restrict our attention to a one-dimensional model (Fig. 3). The one-dimensional assumption

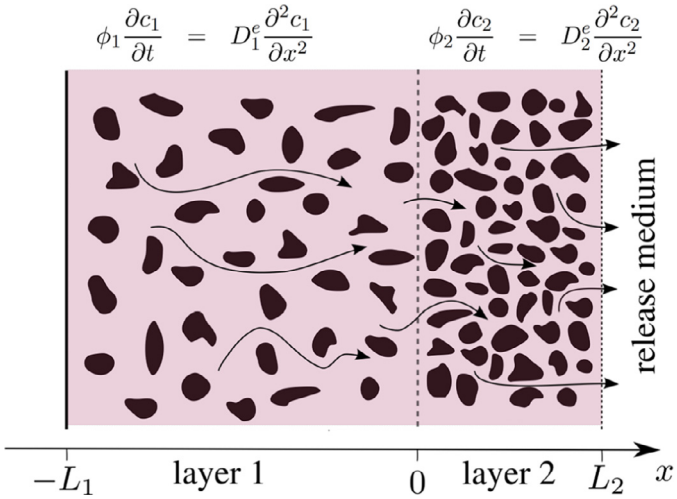

Fig. 3. Schematic showing a simplified one-dimensional configuration of drug release from a medical device coating into a release medium. Two porous layers of different thickness and structure are faced. Due to an initial difference of drug concentrations between the two layers and the release medium, a mass flux is established to the right and drug diffuses through the coating and into the release medium. Figure not to scale.