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A decade of modelling drug release from arterial stents

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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

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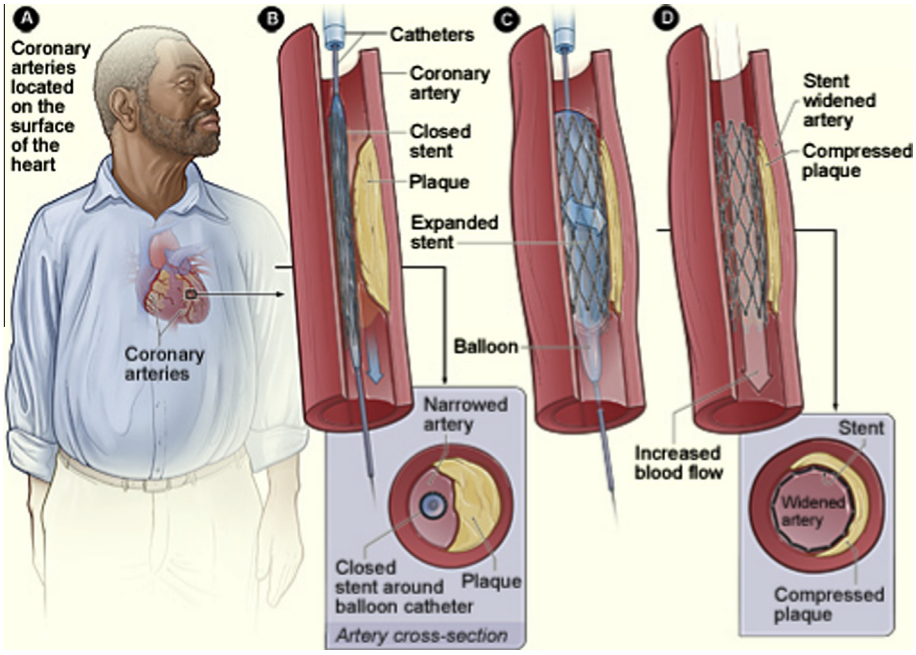

Fig. 1. Illustration of a stent being inserted at the site of a blocked artery. *Source:* National Heart, Lung and Blood Institute; National Institute of Health; U.S. Department of Health and Human Services.

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

unlikely to replicate the *in vivo* situation, it is nonetheless an important step in the development process. From the modelling perspective it makes sense to start with simple models, and in particular, it seems sensible to firstly consider modelling release in a controlled *in vitro* environment before embarking on the highly complex *in vivo* situation.

A number of authors have focussed specifically on modelling the release of drug from DESs, electing to put to one side the range of complexities that are observed in the *in vivo* situation (including flowing blood, pulsatility, wound healing, proliferation, migration of cells and complex uptake/binding). This approach has proven to be useful in helping to address the question of what mechanism(s) are behind the release of drug from a number of stent systems and also in allowing estimates of parameter values (e.g. diffusion coefficients) to be made. Of course, modelling drug release is not an area of research exclusive to DESs. In fact, scientists have been devising models which describe the release of drug from tablet formulations and drug delivery devices for decades. It is therefore not a surprise that the early models of drug release from DESs incorporated well-established ideas from other applications.

2.1. Drug release from non-erodible polymer coated stents

Drug release from DESs comprising non-erodible polymers has been modelled as a diffusion dominated process (see for example [6–8]), with the drug concentration in the polymer C_p satisfying a diffusion equation with drug diffusion coefficient D_p. The geometry can be assumed to be that of a thin film of thickness L_p with no edge effects so that the modelling may be simplified to one dimension:

$$\frac{\partial C_p}{\partial t}(x,t) = D_p \frac{\partial^2 C_p}{\partial x^2}(x,t), \quad x \in (0, L_p), t > 0. \tag{1}$$

In this one-dimensional setting, a zero-flux condition is normally imposed since the stent is impermeable and the initial drug concentration is taken to be uniform. McGinty et al. [9] impose perfect sink conditions ($C_p = 0$) where the drug meets the release medium (these are conditions which can be controlled in the *in vitro* experiment). Zhao et al. [10] presented a similar model, albeit in a cylindrical geometry, when describing the experimental drug release of everolimus from a Dynalink-E polymer coated stent:

$$\frac{\partial C_p}{\partial t}(r,t) = D_p \left(\frac{\partial^2 C_p}{\partial r^2}(r,t) + \frac{1}{r}\frac{\partial C_p}{\partial r}(r,t) \right), \quad r \in (a,b), t > 0, \tag{2}$$

where, here, a is the inner radius (the boundary with the metal stent), b is the outer radius (the boundary with the release medium) and the same initial and boundary conditions as in the McGinty et al. model are supposed. Each of these models admits an analytical solution and has shown favourable results when compared with *in vitro* experimental data. McGinty et al. and Zhao et al. provide the respective solutions for the cumulative fraction of drug released (M_{frac}):

$$M_{frac}(t) = 1 - \frac{8}{\pi^2}\sum_{n=1}^{\infty} \frac{1}{(2n-1)^2} \exp\left\{ \frac{-(2n-1)^2 \pi^2 D_p t}{4L_p^2} \right\}, \tag{3}$$

$$M_{frac}(t) = 1 - \frac{4}{(2a+L_p)L_p}\sum_{n=1}^{\infty} \frac{\exp\{-D_p \alpha_n^2 t\}}{1 - J_0^2(b\alpha_n)/J_1^2(a\alpha_n)}, \tag{4}$$

where α_n is the nth positive root of $J_1(a\alpha_n)Y_0(b\alpha_n) - Y_1(a\alpha_n)J_0(\alpha_n) = 0$ with $J_0(x)$ and $J_1(x)$ Bessel functions of the first kind of orders 0 and 1, and $Y_0(x)$ and $Y_1(x)$ are Bessel functions of the second kind of orders 0 and 1, respectively. In each model the diffusion coefficient is assumed to be constant. McGinty et al. demonstrated that *in vitro* sirolimus release from the Cypher stent was well described by (3) indicating that diffusion was the dominant release mechanism. They estimated the diffusion coefficient to be of $\mathcal{O}(10^{-17})$ m^2 s^{-1} via a best fitting process. Zhao et al. also confirmed diffusion dominated release from the Dynalink stent and they found that their model solution could be fitted to both *in vitro* and *in vivo* release data simply by varying the coating diffusion coefficient. But it is not clear why the coating diffusion coefficient should be different in the two cases. They found that for the *in vivo* release a diffusion coefficient approximately ten times smaller than the *in vitro* release was required ($\mathcal{O}(10^{-17})$ and $\mathcal{O}(10^{-16})$ m^2 s^{-1}, respectively).

Hossainy and Prabhu [11], in an attempt to predict the release of everolimus from a biodurable fluoropolymer-based DES coating, also adopted a diffusion based approach, but they assumed a bimodal lumped-parameter model. Differently from the models of McGinty et al. and Zhao et al. the assumption is made that the dispersed drug phase contributes to two discrete modes of drug transport through the coating. The first mode is the fast one in which drug is released from a highly percolated structure and the second mode is the slow one where drug is released from a non-percolated polymer encapsulated phase. Although Robin-type boundary conditions are proposed, the parameter values chosen by the authors are such that sink conditions are supposed. The result is Eq. (1) for each mode of transport, with the same zero flux and infinite sink boundary conditions. The difference between the two modes is captured by a different diffusion coefficient. A further parameter, α, which defines the ratio of drug in the first mode to the total drug, is defined. The authors numerically obtain estimates of the diffusion coefficients and α by way of a numerical error minimisation process. They utilise *in vivo* experimental data from a porcine animal study. Good agreement between the model and experiments is observed with the mode 1 and 2 diffusion coefficients predicted to be of order $\mathcal{O}(10^{-13})$ and $\mathcal{O}(10^{-14})$ m^2 s^{-1}, respectively. The parameter α is calculated to be 0.22 and is found to reduce as the initial drug density is increased, i.e. as more drug is loaded initially, a larger fraction of drug exists in the non-percolated phase. The authors also attempt to predict the release of a combination of drugs from a stent coating. They use the same minimisation technique, this time requiring to find six fitting parameters. The authors conclude that the validation of their model with experimental data confirms the mechanistic behaviour of the mass transport phenomena within the coating and their assumption of a biphasic state of drug phase within the coating. Interestingly, the authors also show a plot which compares their model prediction with Cypher release data and claim that the model can be used to predict drug release from the Cypher stent. However, they do not specify the values of diffusion coefficients and α they use to generate their plots. Given that these values are unlikely to be known *a priori* it seems that a numerical algorithm approach has been adopted to find the parameter values which best fit the data. It is interesting that the models of Hossainy et al. and McGinty et al. have both demonstrated good agreement with Cypher release profiles, albeit McGinty et al. compared with *in vitro* data, while Hossainy compared with *in vivo* data. Thus a warning must be issued: a good fit to experimental data does not necessarily confirm that the model is correct. With certain parameter values, it may be possible to show that a set of experimental data is fitted well by several different models.

While not focussing specifically on DESs, Siepmann and Siepmann [12] in their review on modelling of diffusion controlled drug delivery provide a series of analytical solutions for drug release from reservoir and monolithic drug delivery systems, some of which may be applied to DESs under certain assumptions. Many of their solutions are early or late time approximations, and in some cases steady state solutions. The reader is referred to [12] for full details.

Whilst the release of drug from the aforementioned types of stents seems to be well described by diffusion alone, this is not the case for all DESs. Realising that the release mechanism may not be as simple as pure diffusion, Tzafriri et al. [2] chose to write down a two-part equation to describe drug release from the Cypher and NEVO stents and, using a best fitting process, found the values of the parameters of the model. Their approach was of interest to industry since it aimed to compare and contrast the release kinetics of two different types of stent platforms, by way of experimentation coupled with modelling. With similarity to Hossainy et al., their equation assumes that these stents contain two pools of dispersed drug, one that is surface-connected and elutes through a percolating network of drug filled pores, and another that is embedded within the matrix and diffuses more slowly through the percolating polymer phase. Thus they utilised the following equation for the mass of drug released from the Cypher and NEVO stents:

$$M_{stent}(0) - M_{stent}(t) = M_{f_0}\left(1 - e^{-K_{f_0}t}\right) + Q_{sus}\sqrt{t}, \tag{5}$$

where $M_{stent}(0)$, M_{f_0}, K_{f_0} and Q_{sus} denote, respectively, the initial load of drug, the initial pool of first order eluting drug, rate constant and Higuchi rate constant. This equation, however, is empirically-based and does not satisfy mass conservation principles: the mass of drug released eventually tends to infinity as time increases. As a result, while their data is well-fitted to this equation for this set of experiments, it is unlikely that their model may be used in a predictive capacity. It is noteworthy that Tzafriri et al. found that the Nevo release data fit (5) best when $M_{f0} = 0$, suggesting that for this stent there is only one mode of elution.

Building on the idea that drug coated on stents may exist in two distinct forms (dissolved and undissolved), McGinty et al. [9] provided a series of diffusion–dissolution based models which all admitted analytical solutions. Their intention is that these analytical solutions, when used in conjunction with appropriate experimental data, may be easily utilised by researchers or industrialists to help clarify the release mechanism (s) and thus aid in the development of DESs. The first model they present couples diffusion with instantaneous dissolution and is based on the early works of Higuchi [13]. The model assumes that drug is initially present at a concentration (C^0) exceeding solubility (C_s) in the coating and that the drug is dissolved instantly on a moving front which penetrates into the coating. They provide the solution (under sink conditions) in two parts. The first part describes the mass of drug released up until the time ($t^\star$) where the drug concentration throughout the coating falls below solubility. The second part describes the duration of the release:

$$M_{frac}(t) = \frac{\sqrt{t}}{L_p C^0}\left\{\theta\left(C^0 - C_s\right) + \frac{2\sqrt{D_p}C_s\left(1 - \exp\left\{-\frac{\theta^2}{4D_p}\right\}\right)}{\sqrt{\pi}\,\mathrm{erf}\left(\frac{\theta}{2\sqrt{D_p}}\right)}\right\},\quad t < t^\star. \tag{6}$$

$$M_{frac}(t) = 1 - \left\{\frac{\frac{8C_s}{C^0\pi^2\,\mathrm{erf}\left(\frac{\theta}{2\sqrt{D_p}}\right)}}{\times\sum_{n=1}^{\infty}\frac{\exp\left\{\frac{-D_p(2n-1)^2\pi^2}{4L_p}t\right\}\Re\left\{\mathrm{erf}\left(\frac{(2n-1)i\pi D_p t^\star + L_p^2}{2L_p\sqrt{D_p t^\star}}\right)\right\}}{(2n-1)^2}}\right\} t > t^\star \tag{7}$$

where $t^\star = (L_p/\theta)^2$ and θ is found by solving

$$2\sqrt{\frac{D_p}{\pi}}\frac{C_s}{C^0 - C_s} = \theta\,\mathrm{erf}\left(\frac{\theta}{2\sqrt{D_p}}\right)\exp\left\{\frac{\theta^2}{4D_p}\right\}. \tag{8}$$

The error function, erf, is a standard mathematical function and is discussed in, for example, Crank [14]. McGinty et al. also provide an analytical solution for the case of release governed by diffusion and dissolution involving a linear first order reaction. The drug is assumed to exist in two forms: dissolved (or free) (C_f) and undissolved (or bound) (C_b). The drug can dissolve into the free form via the forward reaction rate K_1 and then transform back into bound drug via the backward reaction rate K_2:

$$\frac{\partial C_f}{\partial t}(x,t) = D_P\frac{\partial^2 C_f}{\partial x^2}(x,t) + K_1 C_b(x,t) - K_2 C_f(x,t),\quad 0 < x < L_p,\quad t > 0, \tag{9}$$

$$\frac{\partial C_b}{\partial t}(x,t) = -K_1 C_b(x,t) + K_2 C_f(x,t)\quad 0 < x < L_p,\quad t > 0. \tag{10}$$

In deriving their solution they assume that all of the drug is initially in undissolved form and they impose a zero-flux condition at the impermeable stent and a sink condition at the boundary with the release medium. The solution is

$$\begin{aligned} M_{frac}(t) = {} & 1 - \exp\{-K_1 t\} + \frac{2K_2K_1D_p}{L_p^2} \\ & \times\sum_{j=1}^{2}\sum_{n=1}^{\infty}\frac{\left(s_{j_n}+K_1\right)^2\left(\frac{\exp\{s_{j_n}t\}-\exp\{-K_1t\}}{K_1+s_{j_n}} + \frac{\exp\{-(K_2+K_1)t\}-\exp\{-K_1t\}}{K_2}\right)}{s_{j_n}\left(s_{j_n}^2 + 2K_1s_{j_n} + K_1(K_2+K_1)\right)\left(K_2+K_1+s_{j_n}\right)} \\ & + \frac{2K_1D_p}{L_p^2}\sum_{j=1}^{2}\sum_{n=1}^{\infty}\frac{\left(s_{j_n}+K_1\right)^2\left(\exp\{s_{j_n}t\} - \exp\{-(K_2+K_1)t\}\right)}{s_{j_n}\left(s_{j_n}^2 + 2K_1s_{j_n} + K_1(K_2+K_1)\right)\left(K_2+K_1+s_{j_n}\right)} \end{aligned}$$

where

$$\begin{aligned} 2s_{1_n} = {} & -\left(K_2 + K_1 + \frac{D_p}{4L_p^2}\pi^2(2n-1)^2\right) \\ & + \sqrt{\left(K_2 + K_1 + \frac{D_p}{4L_p^2}\pi^2(2n-1)^2\right)^2 - \frac{K_1D_p}{L_p^2}\pi^2(2n-1)^2} \\ 2s_{2_n} = {} & -\left(K_2 + K_1 + \frac{D_p}{4L_p^2}\pi^2(2n-1)^2\right) \\ & - \sqrt{\left(K_2 + K_1 + \frac{D_p}{4L_p^2}\pi^2(2n-1)^2\right)^2 - \frac{K_1D_p}{L_p^2}\pi^2(2n-1)^2}. \end{aligned} \tag{11}$$

They show that by taking the limit as $K_2 \to 0$, the equivalent expression for a non-reversible reaction can be derived:

$$\begin{aligned} M_{frac}(t) = {} & 1 - \exp\{-K_1 t\} \\ & - \frac{8K_1}{\pi^2}\sum_{n=1}^{\infty}\frac{\exp\left\{\frac{-D_p}{4L_p^2}(2n-1)^2\pi^2 t\right\} - \exp\{-K_1 t\}}{(2n-1)^2\left(K_1 - \frac{D_p}{4L_p^2}(2n-1)^2\pi^2\right)}. \end{aligned} \tag{12}$$

They argue that, when compared with appropriate experimental data, the solutions can readily confirm the release mechanism(s) and further, allow estimation of the various parameters of the system via the inverse problem. Pontrelli et al. [15] have adopted a similar approach to modelling drug release from the coating. They too assume that drug within the coating exists in two phases. They neglect diffusion within the solid phase so that their equations are essentially (9) and (10) albeit with their parameters defined differently to include the effects of partitioning of drug between the two phases and the porosity of the coating.

2.2. Drug release from stents with biodegradable and erodible coatings

Up until now we have focussed on models which describe the drug release from first and second generation DESs. Newer generation DESs which have focussed on biodegradable polymers and polymer-free modified surface designs are likely to have more complicated mechanisms of release, and so it is of industrial relevance to consider these types of stents in their own right. In the case of stents with biodegradable polymeric coatings, the drug release may involve diffusion, erosion and possibly dissolution and/or swelling [16,17]. However, in the case of polymer-free stents, it is less clear how the sustained release is obtained and how this may be modelled. Because of the complexities involved in systems which degrade as they release drug, a model which is shown to be accurate for one system may be useless for another. Nevertheless, we discuss here some of the published models in the literature, but invite the reader to refer to the specific articles for full details. Before doing so, it is useful to clarify what is meant by some of the common processes which appear in these models: hydration, degradation and erosion. Hydration is simply the process of combining with water. Degradation is a chain scission process which involves the breaking of polymeric chains by free radicals. On the other hand, erosion is material loss from a system and can be either surface erosion or bulk erosion. With surface erosion, water intrusion into the polymer is slow compared with the rate of degradation, thus the polymer is 'eaten away' from the outside to the inside. With bulk erosion, the rate of degradation is slow compared with the rate of water uptake and so the entire system is rapidly hydrated and degradation occurs throughout the whole material equally.

Prabhu and Hossainy [18] focused specifically on the degradation and release of everolimus from a polylactic (PLA) stent coating and validated their compartmentalised model using *in vitro* data. The model considers two non-linear reactions: the hydrolysis (by water intrusion) of PLA to produce oligomers and lactic acid and the hydrolysis of oligomers to produce lactic acid. Five reaction diffusion equations are presented to describe the temporal and spatial evolution of the concentrations of water, PLA, oligomers, lactic acid and everolimus. The model equations were solved using an iterative finite difference approach which updates estimates of the various parameters via comparison with the experimental data. They indicate that autocatalysis (i.e. a reaction where the reaction product itself is the catalyst of the reaction) is important and cannot be ignored. While not directly focussing on DESs, Siepmann and Gopferich [19] provided a review of the mathematical modelling of bioerodible polymeric drug delivery devices. They consider only systems where the drugs are physically immobilized within a water insoluble polymeric matrix. They stress that accurate physiochemical characterisation of the investigated system is an absolute pre-requisite for the appropriate mathematical modelling of the device, and as such they detail techniques to experimentally characterise degradation and erosion. These can help identify whether the erosion is surface or bulk and assist in clarifying the time-dependence of the diffusion coefficients. Among the models presented are those of Heller and Baker [20] which involves modification of the Higuchi equation to include a time-dependent permeability as a result of bulk erosion, the model of Lee [21] which lends itself to an approximate analytical solution for drug release from thin eroding films and the models of Joshi and Himmelstein [22,23] which accounts for acid producing species that accelerate matrix hydrolysis. The authors comment that modelling efforts should try to take into account the *in vivo* conditions since, for example, cellular tissue reactions can affect the degradation process. Again, not referring specifically to DESs, Rothstein et al. [24] present a unified model for the prediction of controlled release from surface and bulk eroding polymer matrices which also accounts for the transition from surface eroding to bulk eroding behaviour during the course of degradation. Soares and Zunino [25] introduced a mixture model for water uptake, degradation, erosion and drug release from polydisperse polymeric networks. Each constituent of the model represents chains of an average size. A multiscale description of degradation and erosion is proposed, combining the molecular description of scission with Fick's macroscopic laws of diffusion. The approach adopted here describes degradation by means of the time evolution of weight fractions of polymeric constituents of average degree of polymerisation. They argue that the key advantage of their model is the fact that polymer degradation is described as an individual chemical reaction. Rossi et al. [26] modelled a bioresorbable DES based on detailed constitutive equations and taking into account the main physical and chemical mechanisms involved in coating degradation, drug release and restenosis inhibition. Their results were verified against selected *in vitro* and *in vivo* data available in the literature. Formaggia et al. [27] considered a two dimensional dissolution–diffusion model which also included surface erosion. Similarly to McGinty et al. [9], they too realised that as a result of the industrial manufacturing coating process, the drug may exist in the coating in a form which needs to dissolve before it can diffuse. They consider the drug in polymer as two separate phases: a dissolved phase and a solid phase with concentrations C_f and C_b, respectively. Only dissolved drug is permitted to diffuse. Thus they include a source term in the diffusion equation to account for the solid phase dissolution. The dissolution term is non-linear and is based on a reformulation of the empirical Noyes–Whitney equation [28] with the dissolution coefficient, K_1, possibly space and time dependent. The resulting equations in the polymer coating are

$$\frac{\partial C_f}{\partial t} - \nabla \cdot (D_p \nabla C_f) = K_1 C_b^{2/3} (C_s - C_f), \tag{13}$$

$$\frac{\partial C_b}{\partial t} = -K_1 C_b^{2/3} (C_s - C_f). \tag{14}$$

3. Modelling drug transport through the arterial wall

Modelling the release of drug from arterial stents is only one part of the story. What happens to the drug after it is released *in vivo* is of more clinical interest and certainly more difficult to model. Clinicians advise that a uniform drug concentration should be attained across the arterial wall, and the concentration should be maintained within some therapeutic window. Thus an understanding of the structure and components of the arterial wall is crucial. The arterial wall is a porous heterogeneous structure, consisting of three distinct layers (see Fig. 2). Closest to the lumen is the intima, followed by the media and finally the adventitia [29]. The intima consists of the sub-endothelial space and the endothelial layer of cells, known as the endothelium. This layer is crucial to the control of the normal function of the artery, through its mediation of relaxation and contraction and via its control of smooth muscle cell proliferation within the underlying media layer. The internal elastic lamina forms the outermost part of the intima. The media region comprises smooth muscle cells, collagen and elastin. Finally, the outermost layer of the arterial wall is the adventitia. The adventitia tethers the artery to perivascular tissue, and contains cells known as fibroblasts as well as a network of small blood vessels, called vasa vasorum, which act as a blood supply to the adventitia and provide a clearance mechanism for drugs released into the artery wall.

3.1. The advection–diffusion–reaction equation

The processes that govern mass transport through the arterial wall are diffusion, convection and binding (reaction). If the arterial

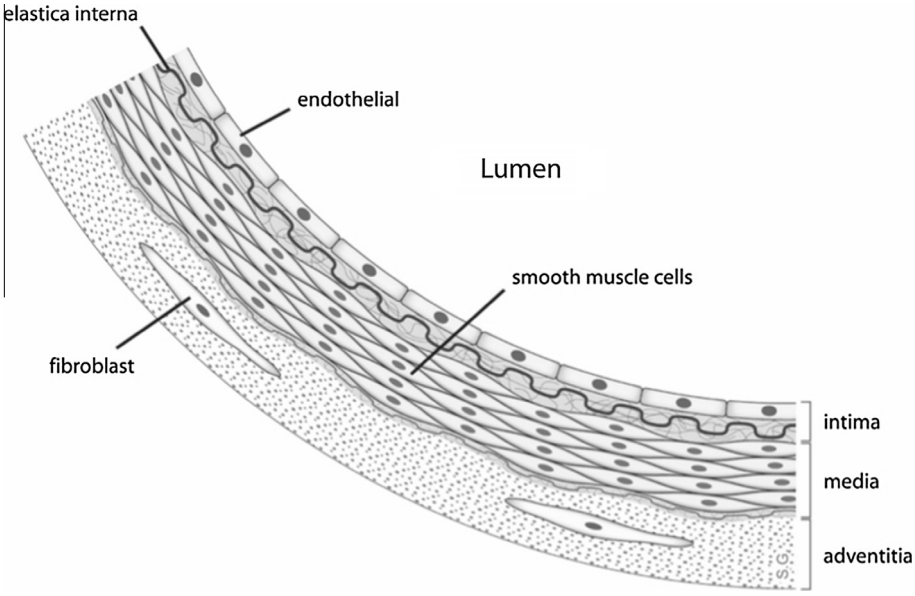

Fig. 2. The structure of the arterial wall.

wall was a single layer, then the drug transport could be described by an advection–diffusion–reaction equation of the form:

$$\frac{\partial C}{\partial t} + \mathbf{v} \cdot \nabla C = \mathbf{D}\nabla^2 C - R, \tag{15}$$

where, here, C is the concentration of drug in the wall, $\mathbf{v}$ is the transmural convection (as a result of the pressure difference across the wall), $\mathbf{D}$ is the diffusivity tensor and R represents the binding 'reaction', which may take several forms. For a derivation of the transport equation the reader is referred to, for example, de Monte et al. [30]. Actually, we require an equation of the form (15) for each layer of the arterial wall since the material properties are different in each layer. In particular, the different composition of each layer results in differing porosities, diffusion coefficients and binding properties. There is evidence that within each layer, anisotropy may be important. For example, diffusion within the tissue has been reported to be anisotropic [31,32] with the diffusion coefficient in the radial direction possibly as much as 100 or 1000 times less than in the circumferential and axial directions. The diffusion coefficients in the following models incorporate the effects of porosity and tortuosity and are sometimes referred to as 'effective' diffusion coefficients.

The first mathematical treatment of arterial drug transport seems to have been by Zunino who built on the earlier experimental works of Creel et al. [33], Hwang et al. [34], Lovich et al. [35], Hwang and Edelman [36] and Lovich and Edelman [37]. The purpose of Zunino's work was to show how mathematical models and numerical simulations can help to identify the physical properties of the stent coating in order to ensure a desired drug release rate. In his model, Zunino assumed the transport was via convection and diffusion with instantaneous reaction. Volume averaged drug concentrations, C, defined as the amount of drug in the fluid phase plus the amount of drug bound with the tissue, divided by the considered control volume, were utilised. Zunino related the fluid phase drug concentration, C_f, to the concentration of drug in a control volume, via $C_f = C/(K\phi)$ where ϕ represents the porosity of the medium and K is the partition coefficient which defines the equilibrium ratio of bound drug within the tissue with respect to drug dissolved in the fluid. He proposed the following equation in two dimensions:

$$\frac{\partial C}{\partial t} + \nabla \cdot \left(-D\nabla C + \frac{\gamma \mathbf{u}}{K\phi} C \right) = 0, \tag{16}$$

where $0 < \gamma < 1$ accounts for possible frictional effects between drug molecules and the pores. Here $\mathbf{u}$ is defined as the filtration velocity. Zunino's most important finding was that drug retention strictly depends on the properties of the drug inside the wall and is not influenced by the characteristics of the carrier.

3.2. Modelling drug binding in arterial tissue

While the convective and diffusive element of the drug transport is well established, the issue of drug binding is more controversial. Some authors have assumed equilibrium models [6,38,39], while others have considered simple loss terms [7,8,40,41]. More recently, non-linear saturable binding models have been utilised [2,42–44].

3.2.1. Models involving linear reaction terms

The simplest form of reaction is a loss term which accounts for consumption of drug in the system (for example, to cells or through *vasa vasorum* blood vessels). If drug is lost from the system in proportion to some parameter, say β, then the reaction term may be written as:

$$R = \beta C. \tag{17}$$

Pontrelli and de Monte [40] proposed a model which incorporated (15) along with binding of the type (17). Their most sophisticated model [41] has the benefit of being multi-layered, although only one-dimension is considered. In each layer, the drug transport is described by

$$\phi \frac{\partial C_i}{\partial t}(x,t) + 2\gamma_i \frac{\partial C_i}{\partial x}(x,t) = D_i \frac{\partial^2 C_i}{\partial x^2}(x,t) - \beta_i C_i(x,t), \tag{18}$$

where the subscript i indicates the ith layer, $2\gamma_i$ represents a constant characteristic convection parameter and D_i represents the effective diffusion coefficient. Pontrelli and de Monte's model has the advantage of admitting an analytical solution.

McGinty et al. [6] utilised a more sophisticated reaction model based on the idea that the drug in the tissue exists in two phases: an extracellular fluid phase and a solid cellular phase. If in equilibrium the concentration of drug in the bound solid phase (C_b) is some constant, say K, times the concentration in the extracellular fluid phase (C), then we may have the following reaction term:

$$R = (1-\phi)\frac{\partial C_b}{\partial t} = \alpha(C - C_b/K), \tag{19}$$

where α is a rate constant. Absorbing the porosity terms into a forward reaction uptake rate k_f and backwards reaction rate k_r, the McGinty model becomes

$$\frac{\partial C_b}{\partial t} = k_f C - k_r C_b, \tag{20}$$

which is identical to the form of reaction considered by Horner et al. [38] and Abraham et al. [39]. Horner et al. conclude in their analysis that a single species drug delivery model cannot accurately predict the distribution of bound drug and so a two-species approach that includes reversible binding is essential.

3.2.2. Models involving non-linear reaction terms

While it is generally appreciated that a reversible reaction is required to describe binding, the form need not be linear. In particular, if we consider the drug binding process as a ligand binding to a receptor to form a complex then we can utilise some ideas from molecular cell biology. Consider the following equilibrium binding for a reversible reaction between a receptor (r) and ligand (l) to form a receptor/ligand complex (c) [45]:

$$l + r \underset{k_r}{\overset{k_f}{\rightleftharpoons}} c,$$

where, here, k_f and k_r are termed the association and dissociation rate constants, respectively. Assuming that each ligand binds only with one binding site (or receptor), Lauffenburger and Linderman present the following first order reversible saturable equation describing the time rate of change of concentration of the complex:

$$\frac{dc}{dt} = k_f r l - k_r c, \tag{21}$$

where here k_f characterises the velocity of the second-order interaction between the receptor and ligand while k_r characterises the velocity of the first-order breakdown of the receptor/ligand complex. It will be convenient to refer to receptors as unoccupied binding sites and receptor/ligand complexes as occupied binding sites. It will also be useful to define a binding site conservation condition:

$$b(t) + a(t) = b_{max}, \tag{22}$$

which states that at any time the number of occupied binding sites, b, plus the number of unoccupied binding sites, a, is equal to the local density of binding sites, b_{max}.

Sakharov et al. [42] seems to be the first group to have applied this type of binding model within a DES setting. They provide the following binding equation which describes the rate of change of concentration of unoccupied binding sites:

$$\frac{dC_a}{dt} = -k_f C C_a + k_r\{b_{max} - C_a\}, \tag{23}$$

where, here, C and C_a denote the concentrations of free drug and unoccupied binding sites, respectively. Tzafriri et al. [43] provide an alternative equation in terms of the rate of change of occupied binding sites.

$$\frac{dC_b}{dt} = k_f C\{b_{max} - C_b\} - k_r C_b, \tag{24}$$

where C_b is the concentration of occupied binding sites (bound drug). It is straightforward to show that (24) is equivalent to (23) by substituting (22) into (23). This type of binding model has also been adopted by other authors [44]. It is well established that in addition to binding to specific receptors, there is also the occurrence of relatively weak non-specific binding caused by association of drug with membrane constituents or by trapping of drug in the extracellular medium [45]. While it is believed that only the receptor (specific) binding is linked to the desired biological effect, binding to non-specific sites will nevertheless, have an impact on drug distribution. Taking this into account, Tzafriri et al. [2] in their most recent work include two equations for drug binding in arterial tissue: one for specific binding to receptors (24) and another for non-specific binding to general extracellular matrix (ECM) sites:

$$\frac{dC_{b_{ns}}}{dt} = k_{f_{ns}} C\{b_{max_{ns}} - C_{b_{ns}}\} - k_{r_{ns}} C_{b_{ns}}, \tag{25}$$

where here the subscript *ns* indicates non-specific. While determining which type of binding model is most appropriate is not within the remit of this review, it is worth stating that Tzafriri et al. [43] found that while a non-saturable linear model of the type (20) agrees with a saturable model of the type (24) in simulating the predicted arterial distribution of heparin, this is not the case for more lipophillic drugs like paclitaxel and sirolimus. They argue that the nonsaturable binding model significantly underestimates the depth of paclitaxel and sirolimus penetration while overestimating the total arterial deposition. However, no experimental results are presented to compare with the simulations. On the other hand, Zhu et al. [46] considered a compartmental model of the type (20) to describe uptake of drug into SMCs and demonstrated good agreement with experiments. It is certainly true that the drug will bind to binding sites in the tissue and on/in cells [2,47,48] although the strength of the affinity will likely vary substantially with the particular drug under consideration. Furthermore, it is not clear how the density of the binding sites may be easily measured *in vivo*. Thus it may be that this binding model is specific to a particular class of drugs and not suitable for more general compounds. A greater understanding of the binding process would undoubtedly assist with model development.

4. Modelling the coupled stent-wall system

So far we have reviewed the modelling of drug release from DESs and drug transport through arterial tissue, both of which are important problems in their own right. In reality, of course, the stent and arterial wall are a coupled system. Thus, to accurately model the *in vivo* situation we are obliged to consider the interaction between the stent and the tissue. The coupled problem has received much attention in the literature, with most of the models necessarily requiring to be solved numerically due to the complexity of the problem. One exception is the model due to Pontrelli and de Monte [40] who consider diffusion based drug release from a non-erodible polymer-coated stent (Eq. (1)) coupled with a convection–diffusion equation in the arterial wall which also accounts for drug consumption via a linear reaction (Eq. (18)). They assume that where the polymer rests against the bare metal of the stent there is zero flux and that the initial concentration within the polymer is some constant C_0. At the polymer/tissue interface the total flux is assumed to be continuous, and a top-coat on the polymer is allowed for:

$$D_p \frac{\partial C_p}{\partial x} = D\frac{\partial C}{\partial x} - 2\gamma C, \tag{26}$$

$$-D_p \frac{\partial C_p}{\partial x} = P\left(\frac{C_p}{K_p \phi_p} - \frac{C}{K\phi}\right), \tag{27}$$

where, here, P denotes a parameter with units m s^{-1} and the subscript p denotes parameters associated with the polymer. At the perivascular end of the tissue they assume that $C = 0$. The significance of Pontrelli and de Monte's work is that they were able to obtain an analytical solution for the drug concentration in the polymer and the media tissue region (through separation of variables), allowing drug concentrations to be readily computed.

They were able to show that the presence of a relatively small advection lowers the observed wall concentration curves due to the convective velocity sweeping away drug from the wall and that at intermediate and later times, a more uniform concentration is guaranteed. In addition they found that increasing the drug consumption rate diminishes the concentrations but preserves the profile shapes. The drug diffusivity in the wall was shown to greatly influence the residence time of the drug. The relevance of this finding is that drugs which exhibit a smaller diffusivity in the arterial wall will be retained longer. Their work has been extended to multi-layers [41].

While the models of Pontrelli and de Monte are an important contribution to the field, they are unable to model the spatial and temporal concentration of bound drug. Indeed, the drugs used in DESs are usually targeted to bind to specific receptors on/in SMCs. One of the first stent/tissue models which encompassed convection, diffusion and uptake into SMCs within the porous media was presented by McGinty et al. [6]:

$$\frac{\partial C_p}{\partial t}(x,t) = D_p \frac{\partial^2 C_p}{\partial x^2}(x,t), \quad x \in (0, L_p), t > 0, \tag{28}$$

$$\phi \frac{\partial C}{\partial t} + v \frac{\partial C}{\partial x} = D \frac{\partial^2 C}{\partial x^2} - \alpha \left(C - \frac{C_b}{K} \right), \quad x \in (L_p, L_p + L), t > 0, \tag{29}$$

$$(1-\phi) \frac{\partial C_b}{\partial t} = \alpha \left(C - \frac{C_b}{K} \right), \quad x \in (L_p, L_p + L), t > 0, \tag{30}$$

where C and C_b denote the volume averaged concentration of drug in the extracellular and cellular regions, respectively [6]. The parameters ϕ, v, D, α, K and L denote the porosity, magnitude of effective transmural convection, effective drug diffusion coefficient in the media, drug uptake rate constant, partition coefficient and thickness of the media region. Eq. (30) expresses the rate of uptake of drug by the cells: it is initially proportional to the free drug C but that proportionality diminishes with increasing C_b until the carrying capacity (or partition coefficient) of the drug is reached at which point the uptake becomes zero. This system of equations allows for an exchange of drug between the extracellular phase and the cells which is dependent on the concentration in the extracellular phase. The boundary conditions they adopted at the interface between the polymer coating and the arterial tissue were continuity of the relative fluxes (Eq. (26) with v replacing 2γ) and continuity of fluid drug concentration. They assumed that the flux of drug out of the media was proportional (via some parameter δ) to the concentration at the interface between the media and adventitia to provide the final boundary condition:

$$-D \frac{\partial C}{\partial x} + vC = \delta C. \tag{31}$$

Their model was also extended to include the adventitia region (where fibroblast cells were modelled in a similar way to SMCs), a topcoat of polymer to slow the release of the drug, and one of the first models of atherosclerotic plaque (modelled using an equilibrium model in the same way as SMCs uptake).

McGinty et al. simulated the problem using a finite difference scheme and conducted a thorough sensitivity analysis which allowed them to infer the importance of the parameters in their model. They found that the results were particularly sensitive to fluctuations in the magnitude of the transmural velocity, and to changes in the drug uptake rate and partition coefficient. Small changes in these parameters were found to result in a large large variation in clinically significant indicators such as uniformity of the concentration profile, maximum cellular drug concentrations and therapeutic period (the time period over which the cells are exposed to drug levels within a clinically relevant therapeutic window). The significance of this finding is that it is important that reliable measurements/estimates of these parameters are obtained. In line with the findings of Pontrelli and de Monte, they found that as the magnitude of the transmural velocity was increased, the wall concentration profile became more uniform but they also noted that the therapeutic period was significantly reduced while the maximum cellular concentration attained was increased. Increasing the drug uptake rate can reduce the therapeutic period, while increasing the partition coefficient can significantly increase the therapeutic period. Their simple model of plaque suggested that the plaque could act as a reservoir for the drug, ensuring that patients with a higher degree of atherosclerosis may receive therapeutic levels of drug for longer than those with a lesser degree of plaque. This finding is in contrast to an experimental study in the literature [49] where it was concluded that drug concentration was inversely correlated to lipid concentrations. The McGinty et al. model did, however, neglect the intimal region of the arterial wall and the endothelium layer of cells (as indeed have several other authors). Their justification for this is that the endothelium is severely damaged when a stent is inserted and in some cases is completely removed; and indeed the properties of the intima may not be too different from those in the media. In a subsequent paper, McGinty et al. [50] combined their earlier work [6] with that of Pontrelli and de Monte [40] to obtain an analytical solution for the drug concentration both in the target cells (C_b) and the interstitial region of the tissue (C) in terms of the drug release concentration at the interface between the polymer and the tissue. They showed that when the polymer region and the tissue region are considered as a coupled system, under certain assumptions, the drug release concentration satisfies a Volterra integral equation which must be solved numerically in general. The drug concentrations, both in the cellular and extracellular regions, are then determined from the solution of this integral equation and then used in deriving the mass of bound drug in the cells.

Building upon their earlier works, Pontrelli et al. [15] presented a semi-analytical expression for the drug concentration and mass in each layer of the arterial wall for the case where the drug must dissolve in the polymer before it can diffuse. The equations for drug transport through the tissue layers were identical to their earlier models [40] but now the equations for the drug in the coating were similar to (9) and (10):

$$\frac{\partial C_f}{\partial t}(x,t) = D_p \frac{\partial^2 C_f}{\partial x^2}(x,t) + \frac{K_p \phi_p}{t_f} \left(C_b - \frac{C_f}{K_p \phi_p} \right), \tag{32}$$

$$\frac{\partial C_b}{\partial t}(x,t) = -\frac{\rho_f}{t_f} \left(C_b - \frac{C}{K_p \phi_p} \right). \tag{33}$$

Here t_f is a function of the physio-chemical properties of the substance and of the microstructure of the porous material and ρ_f is the ratio of non-solid volume to solid volume. In their analysis, Pontrelli et al. exploit a perturbation solution method (noting that the coating thickness is much less than the penetration distance) as an alternative to numerical integration. They conclude that the solid–liquid mass transfer time can have a significant influence on the time taken for drug to be released from the coating as well as the on the drug mass distribution in the wall.

The coupled models discussed so far, all being one-dimensional, have allowed for analytical or semi-analytical solutions due to the particular simplifications that were made. However, in general, analytical solutions are extremely difficult to obtain, especially when two or three dimensions are considered. Zunino [8], in his early model, considered a two-dimensional geometry and solved the diffusion equation in two dimensions coupled with an advection diffusion Eq. (16) for the drug concentration in the arterial wall. Zunino obtained the velocity field by consideration of Darcy's Law and applied a finite element approach to solving the resulting equations. Zunino was able to show that a significant

amount of drug may be lost from the lumen (up to 70% for heparin and 60% for paclitaxel) and this is related to the binding and diffusion properties of drug in the tissue. This has implications for stent manufacturers when considering the type of drug to include on their stent. Due to the zero-flux conditions imposed by McGinty et al. [6] and Pontrelli and de Monte [7,40] in their one-dimensional setting, this is a feature that they neglect and may well lead to over-prediction of drug concentrations in the arterial wall. Two-dimensional models in simplified geometries were also computed by [32,51], among others.

A number of three-dimensional models have also been devised. Moving to three dimensions opens up the possibility of considering more realistic geometries than the simplified cases considered in the lower dimensional models. However, these models require to be solved numerically and often make a number of assumptions to facilitate quick computation or to reduce the complexity of the numerical code. Weiler et al. [52] provided a broad generalization of the works of [53–55]; a three-dimensional model of drug transport in the lumen and the arterial wall. Laminar steady flow was assumed in the lumen and the steady diffusion equation (no convection or reaction) in the arterial wall. Through numerical simulation using commercial finite element software, they found that the highest rates of mass transfer occurred at the forward portion of the stent and the rate of drug delivery to the lumen was greater than that to the tissue. The implication is that not all of the drug on the stent will actually reach the tissue. Indeed many commercially available stents now only coat drug abluminally. While not the focus of this review, a number of studies have considered the interaction of blood flow and drug release. Zunino et al. [56] found that a significant fraction of the drug that is released into the blood flow resides into the recirculation downstream of the struts, where it can be absorbed into the arterial wall. They also found that the interaction between the blood flow and the struts can result in very complex flow patterns [57]. Borghi et al. [58] also considered the interaction with flow in their model, which also included a nonlinear model of binding in the tissue as well as a degradable polymer matrix. The reader is referred to these articles for further details.

Horner et al. [38] appear to be one of the first authors to provide a three-dimensional reaction–diffusion–convection model in a realistic geometry. They stress the importance of considering two phases of the drug (bound and unbound) and use a first order reaction kinetics model to describe the transfer of drug between the two phases. They utilise ABAQUS (commercial finite element analysis software) to obtain a realistic geometry of a deformed stent and vessel wall and then employ FLUENT (commercial software with flow modelling capabilities) to solve their transport equations. Their three-dimensional setting allows for the consideration of anisotropic diffusion in the arterial wall. They do, however, make three significant simplifications. Firstly, they model the arterial wall as a linear homogeneous solid and do not distinguish between the intima, media and adventitia. Secondly, despite calculating the transmural velocity field, they assume this is fixed when solving the transport equations. Perhaps the most unrealistic assumption is that the drug concentration on the stent remains constant and does not deplete. They find that deposition patterns tend to follow the pattern of the stent struts and that the drug is able to penetrate deep into the arterial wall. The pattern of bound drug becomes less uniform as the Peclet number is increased, eventually becoming restricted to areas adjacent to the struts, as convection dominates over diffusion. Feenstra and Taylor [59], in their earlier work, utilize a sequential porohyperelastic transport approach and do not apply any of these assumptions. In particular, they calculate the interstitial fluid velocity field using a stent deployment simulation, rather than assuming it is known *a priori*. A common difficulty with turning to higher dimensional models is the increased computational cost associated with accounting for multiple space scales. To overcome this, Vergara and Zunino [60] proposed a model reduction strategy to derive approximate boundary conditions that significantly reduce the computational burden.

Only two groups thus far have attempted to model the coupled problem of drug release from DESs and arterial deposition which involves a nonlinear saturable binding model. Tzafriri et al. use the formula (5) to describe the release of drug from two types of non-erodible stents (Cypher and Nevo) and from this the rate of change of mass is easily derived:

$$\frac{dM_{stent}}{dt} = -K_{f_0} M_{f_0} \exp\{-K_{f_0} t\} - \frac{Q_{sus}}{2\sqrt{t}}. \tag{34}$$

Within the media layer of the tissue they utilise the one-dimensional convection–diffusion–reaction equation (in a cylindrical co-ordinate system)

$$\frac{\partial C}{\partial t} + \frac{\partial C_b}{\partial t} + \frac{\partial C_{b_{ns}}}{\partial t} = D\frac{\partial^2 C}{\partial r^2} + \frac{D}{r}\frac{\partial C}{\partial r} - v\frac{\partial C}{\partial r} \tag{35}$$

and couple the release to the tissue equation through the following flux boundary condition:

$$-D\frac{\partial C}{\partial r} + vC = -\frac{f_{wall}}{S_{lumen}A_{drug}}\frac{dM_{stent}}{dt} \tag{36}$$

$$= Flux_{in}, \tag{37}$$

where f_{wall}, S_{lumen} and A_{drug} are the efficiency factor for delivery into the arterial wall, the surface area of the blood wall interface and the drug's molecular weight, respectively. The time rate of change of the concentrations of specifically bound drug ($\partial C_b/\partial t$) and of the non-specifically bound drug ($\partial C_{b_{ns}}/\partial t$) are given by (24, 25). They assumed $C = 0$ at the perivascular end and simulated the solution numerically. In addition to this, by assuming that once drug concentrations have traversed the thickness of the arterial wall, concentration gradients in the wall quasi-statically track the declining rate of drug elution, they solved the steady-state version of the model and also neglected the curvature term. They find that once quasi-steady state is established, the content of free drug in coronary tissue should proportionally track the rate of drug elution:

$$C_{free}(t) = \frac{A_{drug} Flux_{in}(t)}{\rho_{tissue} v}\left(1 - \frac{1 - \exp\{-Pe\}}{Pe}\right), \tag{38}$$

where ρ_{tissue} and Pe are the density of wet arterial tissue and the Peclet number, respectively. By probing their analytical solution they conclude, in conjunction with the numerical results, that the persistence time of receptor saturation and effect is more sensitive to duration of elution than to eluted amount. Consequently, dose escalation is inefficient at compensating for sub-optimal duration of elution, so that stent manufacturer's efforts should be concentrated on sustaining elution rather than elevating the load. Interestingly, by comparison with experiments, they find that f_{wall} is approximately 0.06 and 0.16 for Cypher and Nevo stents, respectively, suggesting that a significant portion of drug is lost.

Most recently, Bozsak et al. [44] attempted to answer three key questions of industrial and clinical interest: Why do some drugs coated on stents perform differently from others when their properties appear to be similar? How important is the inclusion of a multi-layered structure of the arterial wall? Which type of reaction (saturable nonlinear two species model or non-saturable one species model) captures the binding effect in the tissue? The authors consider a two-dimensional model where drug transport in the drug coating is governed by diffusion only and drug transport through the arterial wall is governed by the convection–diffusion reaction Eq. (15) where the reaction takes the form (24), i.e. a non-linear saturable binding model. In addition, Bozsak

et al. model the drug transport in the lumen with a convection–diffusion equation where the blood flow is assumed steady. Kedem–Katchalsky membrane conditions are utilised to describe the concentration discontinuity across the thin endothelium and internal elastic lamina and continuity of flux conditions are also employed (essentially the two-dimensional equivalent of (26) and (27)). Three different conditions are considered at the far adventitia, these being infinite sink, zero flux and Robin-type conditions. It was found that the choice of boundary condition had no significant effect on the results. The governing equations were discretized by means of the finite element method (FEM) using the commercial software package COMSOL Multiphysics 4.3. They conclude that the one layer model (which includes only the medial layer and neglects the sub-endothelial space) is incapable of predicting the observed backflow that enters the sub-endothelial space in the two layer model. Furthermore, the peak tissue concentration is underestimated by 30% and as the thickness of the sub-endothelial space increases (representing diseased arteries) the difference between the one and two layer models become more pronounced. Comparing the two different binding models, the authors note they are comparable at very early times but the peak concentration predicted by the equilibrium model occurs considerably later and is significantly higher. Matching the prediction of drug accumulation by the equilibrium model to that of the saturable model requires a reduction in partition coefficient while matching drug residence time requires an increase. Clearly, both cannot be achieved simultaneously. Finally the authors conclude that the difference in binding properties between paclitaxel and sirolimus are due to the greater convection-dominated transport of paclitaxel compared with sirolimus. For paclitaxel, the drug is initially predominantly in the free state and invades the media driven by plasma flow in the arterial wall since the timescale for convection is faster than that for binding. With rising levels of free drug in the wall, the binding rate increases. Once all binding sites are saturated any excess drug is washed out and when the stent polymer is empty and the wall is devoid of excess drug, the transport becomes dominated by unbinding. However, for sirolimus, the initial dominating process is binding and so the binding sites become very rapidly occupied. Once they become exhausted, a more convection-driven phase takes over.

5. Discussion

In this article we have attempted to provide a comprehensive review of the modelling approaches adopted to study the release of drug from arterial stents and the redistribution in arterial tissue. Despite the high level of complexity involved, over the past decade real progress has been made in attempting to understand the mechanism(s) governing the release of drug from DESs and also in understanding the transport and binding properties of drugs in arterial tissue. Stimulated by early experimental works [33–37] researchers from across the globe have become increasingly interested in attempting to model these processes. A combination of approaches have been adopted. Some authors have focussed on trying to accurately characterise the release of drug from DES in controlled *in vitro* experiments while others have applied simple models to the *in vivo* situation. A number of groups have focussed specifically on drug transport through arterial tissue and in trying to understand the complex binding process that takes place as well as the relative importance of convection, diffusion and reaction.

While simplified one-dimensional models can provide useful insights into this problem, ultimately three-dimensional models which capture the full complex geometry of the stent and the arterial wall may be required. The existing three-dimensional models in the literature all make certain simplifying assumptions, whether it be in idealising the stent geometry, or in neglecting convection, diffusion or binding, or in considering only single or bi-layer arterial walls. Thus there is an opportunity to increase the sophistication of the three-dimensional models, whether it be incrementally or all at once. However, caution must be exercised to ensure that the results of the simulations are not subject to high uncertainty, in which case the fidelity of the results may be called into question. Thus there is still a role for simplified models, especially those which can admit analytical solutions, in helping to ascertain the numerous parameters of the increasingly complex models. Many of the parameters of the most involved models are extremely difficult (or impossible) to measure experimentally in the living system and thus new methods for approximating these parameters should be developed by modellers and experimentalists working in tandem. Some progress has been made on this issue with experimental data complemented with values from fiber matrix and pore theory [57,44].

Presently, the stent manufacturers are predominantly concerned with mechanical integrity of the device and as such the stent design is usually the first consideration. The stent must be flexible and expandable and stay in situ after deployment. During the expansion process the stent should undergo minimum shortening and after implantation should conform to the natural geometry of the vessel without any unnatural straightening [5]. Circumferential strength is another key component; without this the stent will collapse under the strain of the artery. Furthermore, the materials used must be bio-compatible and must not fracture. But it is no good having a stent which is mechanically sound but does not elute drug in a favourable fashion. The release of the drug must be controlled so that it elutes over a defined period of time and, furthermore, the drug concentration in the arterial wall should ideally be maintained between therapeutic and toxic levels over and beyond the period of release. Taking this into account, it would seem that the drug release and uptake is intrinsically linked to the stent design. Ideally the stent should be optimised, both in terms of the mechanical design as well as drug loading so that the required clinical outcomes are realised. This optimisation is further complicated by the observed variation in lesion composition and other underlying health conditions of the patient. Thus a single optimised stent design is simply unrealistic, but it may well be possible to develop an optimised stent for a set of different situations. Certainly, in light of increased understanding of the drug release and arterial binding processes there is an opportunity to design stents to achieve desired clinical outcomes.

Stent manufacturers have demonstrated consideration of clinical outcomes in recent stent designs which have included biodegradable polymers, fully biodegradable structures and polymer free designs. Whilst these tackle the problem of having a permanent polymer in situ, the clinical outcomes have been observed to be largely equivalent to their non-erodible polymer coated counterparts [61]. To date there appears to be limited mathematical modelling of these more advanced stents which couples drug release with arterial transport: the only example seems to be the work of Borghi et al. [58]. Such modelling may shed light on how these devices may be improved to realise the desired clinical outcome.

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