Modelling Simple Experimental Platform for In Vitro Study of Drug Elution from Drug Eluting Stents (DES)

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Abstract. We present a simple model of experimental setup for in vitro study of drug release from drug eluting stents and drug propagation in artificial tissue samples representing blood vessels. The model is further reduced using the assumption on vastly different characteristic diffusion times in the stent coating and in the artificial tissue. The model is used to derive a relationship between the times at which the measurements have to be taken for two experimental platforms, with corresponding artificial tissue samples made of different materials with different drug diffusion coefficients, to properly compare the drug release characteristics of drug eluting stents.

Key words: model reduction, asymptotic expansion, drug eluting stents, experimental measurements

1. Introduction
Drug Eluting Stents (DES) are widely used for treating coronary artery disease; compared to bare metal stents DES represent more advanced medical devices that are intended to reduce the tissue damage and to speed up the healing of artery walls after stent implantation / expansion within the blocked region of an artery. Modelling of drug elution from DES is a widely expanding area of research. A large number of publications address modelling of drug elution from stents of different geometry, the effect of artery wall conditions, such as, e.g., thrombosis, on drug propagation within vessel wall, etc. (see, e.g., [1] – [13]). In addition to in vivo drug release models for DES the comparison of different possible experimental platforms for study of in vitro release setups, which may mimic the in vivo release processes for their future use in product quality control, regulatory documents filing, etc., is of current interest. One of the ideas is related to using the “artificial tissue” samples, made, e.g., of collagen, or some porous polymer, and shaped as a blood vessel, for modelling and analysis of drug release into real vessels; some materials on “artificial tissue” fabrication for studying drug release and other medical application may be found, e.g., in [14], [15].

In this paper we briefly discuss the basic ideas behind comparison of drug release measurement results obtained for two in vitro release experiments where two “artificial tissue” materials are characterized by different diffusion coefficients for a particular drug. Here we formulate and analyse a simple model addressing some important general features of the process omitting certain details which are not easily quantifiable in real in vivo experiments (such as the difference between propagation of

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lipophilic and hydrophilic drugs, the effect of drug partition coefficient of characteristics of drug elution and propagation, the actual tissue constitution which is highly non-uniform, etc.).

The main question that is addressed in this paper is formulated as follows. Assume that we have an experimental system #1 that measures the percentage of drug remnant on stent at an instant of time \( t^* \) during drug release from DES into an “artificial tissue” sample, that is a substitution for a real blood vessel, characterized by a drug diffusion coefficient \( D_1 \). We want to design an experimental system #2 to check the properties of the same type of DES release, but we now use a different type of an “artificial tissue” sample, playing the role of a real blood vessel, that is characterized by the diffusion coefficient \( D_2 \). Once again, we measure the percentage of drug remnant on stent, but now at an instant of time \( t^{**} \). We want to look at a measurement obtained using experimental system #2 and make a conclusion on expected outcome of the measurement (actual or potential) obtained using the experimental system #1. In fact, ideally, if the stents are absolutely the same we want the measured percentages of drug remnant on stent be the same in the case #1 and in the case #2. Here is the question that we address: if for the two experimental systems the measurements are performed at the same instants of time, i.e., \( t^{**} = t^* \), will it be possible to get the same results for the percentages of drug remnant on stents? The answer to this question is NO. It is, however, possible to choose the time of measurement \( t^{**} \) for the experimental system #2 in such a way that the measurement result will be absolutely the same as that obtained from experimental system #1 at time \( t^* \). The formula that relates the choice of the measurement time \( t^{**} \) to the original measurement time \( t^* \) for particular experimental platform geometry is presented below (see section 4, formula (40)). Thus, one of the conclusions may be formulated as follows: for the same type of DES to obtain the same measurement results on two different experimental systems, the measurements collected using these systems must be taken at different time points (e.g., if for system #1 we originally take the measurements at \( t = 1 \) day, 3 days, 7 days, etc., for system #2 corresponding measurements must be taken at \( t = t_1 \) days, \( t_2 \) days, \( t_3 \) days, etc., where, in general, \( t_1 \neq 1, t_2 \neq 2, t_3 \neq 3 \) may be computed for particular choice of experimental system geometry, choice of materials, etc.).

We note that below we talk about one instant of time at which the measurement is taken (for each experimental system). Since this instant of time is chosen arbitrarily, the same analysis will work for the case where measurements are taken at several time points. Then the analysis just has to be repeated for each individual time point.

The motivation for the current analysis comes from the fact that in numerous practical pharmacokinetics studies performed at pharmaceutical companies the “purely statistical” approach to comparing kinetic drug release curves is used to evaluate different drug eluting devices, where one exponential curve, or a linear combination of exponential curves, are fit to the experimental data. This analysis represents one of the examples where modelling approach allows one to introduce meaningful explanation of where these “exponentials” come from and how they are affected by the parameters in the models describing real experimental setups.

The paper is organized as follows. In section 2 we introduce the description of a simple experimental platform for studying in vitro drug release from DES that is supposed to mimic the in vivo drug release into blood vessel tissue. In section 3 we introduce a model formulation for a simplified version of the experimental setup and perform model reduction. Simplification is needed to clarify the basic ideas and underlying questions that must be addressed when the real experimental systems of this type are built. In section 4 we present the comparison of two experimental setups based on the introduced simplified model formulation. We derive the explicit expressions that relate measurement times for two experimental systems that produce the same measurement results for similar DES. In section 5 we briefly comment on more realistic models and possible extensions of the results derived in sections 3 and 4. Finally, conclusions and discussion of the main results are presented in section 6.
2. Description of a simple experimental platform
We start with the description of a simple (in vitro drug release) experimental platform that is intended to imitate in vivo drug release from DES into a blood vessel. It consists of a hollow cylindrical tube made of collagen or some porous polymer (“artificial tissue”) immersed in a buffer solution. The hollow part of the cylinder representing “artificial vessel’s” lumen is connected by the hoses to a pump that forces a liquid, representing blood, to constantly move through the lumen. The cross-section of a portion of such “artificial vessel” (without hoses and without a container that holds the buffer solution) is shown in figure 1. The DES is expanded inside the luminal part of the artificial vessel. The drug will be entering the “artificial tissue” sample from DES from the coating pressed against the luminal surface of the sample. At a certain instant of time the elution experiment is stopped, the amount of drug remnant on stent is measured, and the percentage of drug remaining on stent is determined (using the original known drug load).

![Figure 1](image1.png)

**Figure 1.** Cross-section of a portion of an in vitro drug release experimental platform.

![Figure 2](image2.png)

**Figure 2.** Transversal cross-section corresponding to the case shown in figure 1.

![Figure 3](image3.png)

**Figure 3.** Cross-section representing a simplified model.
3. Model formulation for a simplified experimental setup and model reduction

We start with the description of a simple (in vitro drug release) experimental platform that is intended to imitate in vivo drug release from DES into a blood. Instead of the situation characterized by the cross-section shown in figure 2 and corresponding to the experimental setup shown in figure 1, we will consider a simplified experimental setup illustrated in figure 2. The main difference between the geometry of the experimental system represented by cross-section shown in figure 2 and that shown in figure 3 is that in the latter case the coating and the “artificial tissue” sample are planar (not cylindrical) which will allow us to use the symmetry of the simplified case to write corresponding model as spatially one-dimensional. We want to reiterate that this simplification is needed to clarify the conclusions following from the analysis, to simplify notations and to make the formulas in the presentation shorter; similar results will hold for the original geometry as well. Also, for the purpose of model simplification, we consider the homogenized drug eluting coating distribution over the luminal surface of the vessel tissue (i.e., we suppress the dependence of drug distribution on the particular local geometry of stent struts). Such approach was used previously (see, e.g., [5]); it allows one to concentrate on the general characteristics of drug elution / propagation omitting details of local drug distribution in the tissue.

Let us list / re-iterate the assumptions that we make to formulate the model: (a) The coating is assumed to be uniformly distributed over the luminal surface of the “artificial tissue” sample. (b) We assume that the coating is fully hydrated, so that the entire drug in DES is immediately available for release. Mathematically this condition may be formulated in terms of drug diffusion coefficients \( D_0 \) (in the coating) and \( D_1 \) (in the tissue): \( D_0 \gg D_1 > 0 \). (c) The drug may leave coating only in the direction of the “artificial tissue” sample, e.g., no flux conditions for drug hold at all the boundaries of the coating except for the boundary facing the sample. This condition is quite realistic since the coating is attached to the stent struts made of metal providing impermeable boundary for drug on the side opposite to that corresponding to vessel’s luminal boundary. (d) No membrane slowing down the drug transfer from the coating into the sample is present at the sample’s boundary. (e) The problem is spatially one-dimensional, i.e., only one spatial variable \( x \) enters the model formulation instead of three spatial variables \( x, y \) and \( z \), i.e., we have diffusion present only in one spatial direction. This condition naturally holds in the following situation. We consider originally the “artificial tissue” sample shaped as a parallelepiped with height \( Z \), i.e., \( 0 \leq z \leq Z \), width \( Y \), i.e., \( 0 \leq y \leq Y \), and thickness \( L \), i.e., \( 0 \leq x \leq L \); the coating also has the shape of a parallelepiped with the same height \( Z \), the same width \( Y \), and some other thickness \( -L \leq x \leq 0 \). If the “no flux” boundary conditions (i.e., zero Neumann type boundary conditions) are specified at \( z = Z \), \( y = 0 \) and \( y = Y \) for the drug in the sample, the final formulation of the model will not contain \( y \) and \( z \). (f) Sufficient amount of buffer is present so that the drug concentration in the buffer is far from saturation; in fact, we assume that concentration of drug in the buffer is zero, i.e., as soon as drug molecules enter the buffer solution through the adventitial boundary of the “artificial tissue” sample, they are immediately removed from the vicinity of this boundary. More realistic situations mentioned in section 4 can be considered as well. Here we concentrate on simple explanation of qualitative results using a simple model. For more complex models the results, and related conclusion, will become even more complicated.

The percentage of drug remnant on stent will depend on the geometry of the “artificial tissue” sample, on drug diffusion coefficient of the “artificial tissue” material, on such properties of the DES coating as its porosity, drug content, shape of stent struts as well as on other factors. While the model for the case of geometry shown in figure 1 may be constructed and analysed, in the next section, to make the explanation and qualitative results of analysis as explicit as possible, we will discuss a somewhat simpler model of drug elution from DES (see figures 2 and 3 as well as detailed explanation in section 3 below).

We start with the model describing concentration \( w(x, t) \) of drug in the coating and concentration \( u(x, t) \) of drug in the tissue sample can be written as follows (here we note once again that \( x = 0 \) corresponds to the boundary between drug eluting stent and vessel tissue):
\[
\frac{\partial w}{\partial t} = D_0 \frac{\partial^2 w}{\partial x^2}, \quad -L_0 < x < 0, \tag{1}
\]

\[
\frac{\partial u}{\partial t} = D_1 \frac{\partial^2 u}{\partial x^2}, \quad 0 < x < L_1, \tag{2}
\]

at \( x = 0 \):

\[
w = u, \quad D_0 \frac{\partial w}{\partial x} = D_1 \frac{\partial u}{\partial x}, \tag{3}
\]

at \( x = -L_0 \):

\[
\frac{\partial w}{\partial x} = 0, \tag{4}
\]

at \( x = L_1 \):

\[
u = 0. \tag{5}
\]

At \( t = 0 \):

We rescale the model (1) – (6) using the following changes of variables:

\[
\tau = t \cdot \left( \frac{D_1}{L_1^2} \right), \quad \rho = \frac{x}{L_1}, \quad \frac{w}{w^*} = \frac{u}{u^*}, \quad \frac{\rho}{L_1}.
\]

The non-dimensional model formulation may be written as follows:

\[
\frac{\partial W}{\partial \tau} = \frac{D_0}{D_1} \frac{\partial^2 W}{\partial \rho^2}, \quad -\frac{L_0}{L_1} < \rho < 0, \tag{7}
\]

\[
\frac{\partial U}{\partial \tau} = \frac{\partial^2 U}{\partial \rho^2}, \quad 0 < \rho < 1, \tag{8}
\]

at \( \rho = 0 \):

\[
W = U, \quad \frac{\partial W}{\partial \rho} = D_1 \frac{\partial U}{\partial \rho}. \tag{9}
\]

at \( \rho = -\frac{L_0}{L_1} \):

\[
\frac{\partial W}{\partial \rho} = 0, \tag{10}
\]

at \( \rho = 1 \):

\[
u = 0. \tag{11}
\]

At \( \tau = 0 \):

\[
W = 1, \quad U = 0. \tag{12}
\]
Taking into account condition (b), $D_0 \gg D_1 > 0$, we can introduce a small parameter $0 < \varepsilon = D_1 / D_0 \ll 1$, and use asymptotic approximation

\[
W = \bar{W} + \varepsilon \cdot \tilde{W} + \ldots, \quad U = \bar{U} + \varepsilon \cdot \tilde{U} + \ldots
\]  

(13)

to derive a simplified (reduced) formulation of the model; see, e.g., [16] for more detailed description of one of the asymptotic algorithms, the Boundary Function Method, that may be used to construct corresponding approximation. The functions used in the expansions (13) do not contain sub-indices; this is done intentionally to simplify the notation. Also, the resulting rescaled problem turns out to be singularly perturbed. However, in (13) we use the, so-called, “regularly perturbation” ansatz since the experimental data in the experimental setups characteristic for this problem is usually collected on the time scales which are much longer compared to the “fast” mixing time over which the drug is re-distributed within the DES coating. For such “long” characteristic times the, so-called, boundary functions describing the exponentially fast adjustment of the solution to the comparatively slowly varying leading order terms of the regular expansion (13) do not need to be taken into consideration.

We substitute the series (13) into (7) – (12), where equation (7) now has the form

\[
\varepsilon \cdot \frac{\partial W}{\partial \tau} = \frac{\partial^2 W}{\partial \rho^2},
\]  

(14)

and the second boundary condition in (9) has the form

\[
\rho = 0: \quad \frac{\partial W}{\partial \rho} = \varepsilon \cdot \frac{\partial U}{\partial \rho},
\]  

(15)

and determine consecutively the terms of the asymptotic series in the standard way. In the leading order approximation, we obtain:

\[
0 = \frac{\partial^2 \bar{W}}{\partial \rho^2},
\]  

(16)

\[
\frac{\partial \bar{U}}{\partial \tau} = \frac{\partial^2 \bar{U}}{\partial \rho^2},
\]  

(17)

at $\rho = 0$:

\[
\bar{W} = \bar{U}, \quad \frac{\partial \bar{W}}{\partial \rho} = 0,
\]  

(18)

at $\rho = -L_0 / L_1$:

\[
\frac{\partial \bar{W}}{\partial \rho} = 0,
\]  

(19)

at $\rho = 1$:

\[
\bar{U} = 0.
\]  

(20)

At $\tau = 0$:

\[
\bar{W} = 1, \quad \bar{U} = 0.
\]  

(21)
It follows from (16), the second condition in (18) and (19) that $\tilde{W} = \tilde{W}(\tau)$ is, yet unknown, function of only one variable, non-dimensional time $\tau$. In the first order approximation we obtain:

\[
\frac{\partial \tilde{W}}{\partial \tau} = \frac{\partial^2 \tilde{W}}{\partial \rho^2},
\]

\[
\frac{\partial \tilde{U}}{\partial \tau} = \frac{\partial^2 \tilde{U}}{\partial \rho^2},
\]

at $\rho = 0$:

\[\tilde{W} = \tilde{U}, \quad \frac{\partial \tilde{W}}{\partial \rho} = \frac{\partial \tilde{U}}{\partial \rho},\]

at $\rho = -L_0/L_1$:

\[\frac{\partial \tilde{W}}{\partial \rho} = 0,\]

at $\rho = 1$:

\[\tilde{U} = 0.\]

At $\tau = 0$:

\[\tilde{W} = 0, \quad \tilde{U} = 0.\]

From solvability condition of equation (22) with the second condition in (24) and condition (25) we obtain the equation for $\tilde{W} = \tilde{W}(\tau)$:

\[
\frac{\partial \tilde{W}}{\partial \rho}(\rho = 0) - \frac{\partial \tilde{W}}{\partial \rho}(\rho = -L_0/L_1) = \frac{\partial \tilde{U}}{\partial \rho}(\rho = 0) = \int_{-L_0/L_1}^{0} \frac{\partial \tilde{W}}{\partial \tau}(\tau)d\rho = \frac{L_0 \partial \tilde{W}}{L_1 \partial \tau},
\]

and thus,

\[
\frac{\partial \tilde{W}}{\partial \tau} = \frac{L_1 \partial \tilde{U}}{L_0 \partial \rho}(0, \tau).
\]

The reduced model in the final form can now be written as (here, without loss of generality, we omit tildes to make notations shorter):

\[
\frac{\partial U}{\partial \tau} = \frac{\partial^2 U}{\partial \rho^2},
\]

\[
\frac{\partial W(\tau)}{\partial \tau} = \frac{L_1 \partial U}{L_0 \partial \rho}(0, \tau),
\]

at $\rho = 0$:

\[W(\tau) = U(0, \tau),\]

at $\rho = 1$:

\[U(1, \tau) = 0.\]
At \( \tau = 0 \):

\[
W(0) = 1, \quad U(\rho, 0) = 0.
\]  

(33)

The original model solution has to be considered in a finite time interval \( 0 < t \leq t^* \), which corresponds to a non-dimensional time interval \( 0 < \tau \leq \tau^* = t^* \cdot \left( \frac{D_1}{L_1^2} \right) \). The non-dimensional spatial domain for (29) is \( 0 < \rho < 1 \). In the next section we compare the measurements taken for two different experimental setups using the reduced model formulation (29) – (33).

Remark: The theorem on the passage to the limit or the theorem on estimation of the remainder term, which relates the reduced model formulation (29) – (33) to the original model formulation (14) – (21) can be proved using standard approaches (see, e.g., [16]). These results will be published later elsewhere.

4. Comparison of results obtained for two different “artificial tissue” materials

In the previous section we discussed the model for experimental setup for which “artificial tissue” sample is characterized by the diffusion coefficient \( D_1 \) (experimental system #1). Now consider an “artificial tissue” sample made of a different material and characterized by a different diffusion coefficient \( D_2 \) associated with drug propagation through this material (experimental system #2). We want to address the following question: If DES used in both experiments are similar, and if the shape of the “artificial tissue” sample in the second experimental setup is the same as that in the first experimental setup, at which instant of time \( t^{**} \) the measurement of the total drug remnant on stent must be taken for the experimental system #2 to produce the same result as that obtained in on experimental system #1 at the instant of time \( t^* \)?

To answer this question let us first write down the model system and additional conditions that describe the second experimental setup. Since the stents and the coating are the same, the diffusion coefficient in the coating, \( D_0 \), is the same for both experimental systems. We have:

\[
\frac{\partial w}{\partial t} = D_0 \frac{\partial^2 w}{\partial x^2}, \quad -L_0 < x < 0,
\]  

(34)

\[
\frac{\partial u}{\partial t} = D_2 \frac{\partial^2 u}{\partial x^2}, \quad 0 < x < L_1,
\]  

(35)

at \( x = 0 \):

\[
w = u, \quad D_0 \frac{\partial w}{\partial x} = D_2 \frac{\partial u}{\partial x},
\]  

(36)

at \( x = -L_0 \):

\[
\frac{\partial w}{\partial x} = 0,
\]  

(37)

at \( x = L_1 \):

\[
u = 0.
\]  

(38)

At \( t = 0 \):

\[
w = w^*, \quad u = 0.
\]  

(39)

Now we rescale the model (34) – (39) using the following changes of variables:
\[ \tau = t \cdot \left( \frac{D_2}{L_1^2} \right), \quad W = w/w^*, \quad U = u/w^*, \quad \rho = x/L_1. \]

In the new non-dimensional variables the model formulation for experimental system #2 will have the form \((7) - (12)\) with one exception: the non-dimensional time interval will now be

\[ 0 < \tau \leq \tau^{**} = t^{**} \cdot \left( \frac{D_2}{L_1^2} \right). \]

We assume that for experimental system #2 the condition (b), \(D_0 \gg D_2 > 0\), holds. This means that we can introduce the small parameter \(0 < \varepsilon = D_1/D_0 \ll 1\), use asymptotic approximation \((13)\) and apply the analysis similar to that presented in section 3 to obtain the reduced model formulation \((29) - (33)\) with a different expression for the non-dimensional time \(\tau\).

If \(\tau^* = \tau^{**}\), then the non-dimensional model formulations for experimental systems #1 and #2 will be absolutely the same. So, if the measurements on the two systems are performed for the same DES, then the drug remnant on stent values must be the same at the same non-dimensional instants of time \(\tau^* = \tau^{**}\). This means that for identical DES the experimental data values must be the same if the measurements are obtained for the original dimensional instants of time \(t^*\) and \(t^{**}\) satisfying the following relationship:

\[ \tau^* = t^* \cdot \left( \frac{D_1}{L_1^2} \right) = t^{**} \cdot \left( \frac{D_2}{L_1^2} \right) = \tau^{**}, \]

or

\[ t^{**} = t^* \cdot \left( \frac{D_1}{D_2} \right). \tag{40} \]

We illustrate this result qualitatively in figure 4.

\[ \text{Figure 4. Qualitative illustration of formula (40): the case for which } D_1 > D_2. \]
5. Comments on more realistic models
Let us discuss possible extensions of the simple model presented above to more realistic cases and make several important comments.

- In the above model the assumptions were made that the entire drug in the coating is immediately available for release (after instantaneous hydration of coating polymer), the diffusion (drug mixing) within the coating is infinitely fast, and the release is modulated by the finite diffusion within the “artificial tissue” sample. The natural extension of this model is related to introduction of fast release and slow release compartments in the coating. The model will then still be formulated as a partial differential (diffusion) equation for the drug concentration in the sample and two ordinary differential equations describing drug concentrations in “fast” and “slow” release compartments. Within each compartment the drug mixing is fast, however the drug transfer between the compartments is slow (e.g., due to finite rate of coating polymer hydration). It is still assumed that the coating and the “artificial tissue” sample are in direct contact with each other.

- The spatially one-dimensional model (1) – (6) is derived under no flux (zero Neumann type) boundary conditions for drug at the boundaries of the “artificial tissue” sample corresponding to \( z = 0, z = Z, y = 0, \) and \( y = Y \) (in other words, we have a translational symmetry in the two spatial directions corresponding to \( z \) and \( y \)). If the Neumann type boundary conditions at these boundaries are substituted by Dirichlet type conditions (e.g., describing drug washout) or by Robin type conditions (describing, e.g., drug exchange between the sample and the buffer through these boundaries), the model will become spatially three-dimensional.

- The dependence of drug concentration in the coating not only on time but also on spatial variable(s) may be taken into account in case the coating polymer is not fully hydrated. We then must use the original partial differential (diffusion) equation for description of drug concentration in the coating (in addition to diffusion equation describing drug distribution in the “artificial tissue” sample) instead of using the reduced model.

- In the presence of a membrane between the coating and the “artificial tissue” sample, the boundary conditions between the coating domain and the tissue sample domain will change (from Dirichlet type to Robin type). Also, depending on whether the concentration of the drug in a buffer is close to saturation or not, the conditions at the boundary of the sample exposed to the buffer may change. These new assumptions will make the model more complicated.

- Other extensions of the above mentioned models are related to possible differences in drug partition in the coating and in the “artificial tissue” sample, presence of drug binding in the sample, as well as different mobility properties of hydrophilic and lipophilic drugs that may be loaded in the coating.

- Different shapes of the “artificial tissue” samples may also be considered (e.g., cylinder shown in figure 1) together with changing in time volume of DES coating (volume changes due to coating polymer degradation).

- Numerical implementations of the model extensions mentioned above may be used for design of particular experiments, estimation of parameters from data, etc.

6. Conclusions
Let us discuss possible extensions of the simple model presented above to more realistic cases and make several important comments. We considered some basic ideas behind the comparison of measurement results (representing percentage of drug remnant on stent) obtained for two experimental setups corresponding to in vitro release from DES into “artificial tissue” samples. In vitro release experiments are usually intended to mimic in vivo release into the real blood vessels. It turns out that for a particular experimental platform that we discussed in this paper the difference in diffusion coefficients between
the two “artificial tissue” samples of the same shape makes it necessary to take measurements for the two experimental setups at different instants of time to produce comparable percentage of drug remnant of stent results. The explicit formula connecting the dimensional (real) instants of time when the measurements must be taken for proper comparison of DES characteristics using two experimental systems was derived; see (40).

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