Mathematics for Industry Modelling Week - Medical Devices

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1 The experiment of interest

A literature review provided many examples of drug release from either proposed device designs or from materials from which the device would be manufactured or from coatings, such as biodegradable polymers. It was decided that the experiments which we would attempt to model, were the ones conducted by Argarate et al. [1]. The experiments concerned were centred on combining different mixtures of the biodegradable polymer PLLA and two drugs, Dexamethasone (DG) and Eugenol (EG), being applied to disks of PLDL and carrying out drug release experiments. Within the publication, the following cumulative release plots are given, which we sought to replicate through mathematical modelling.

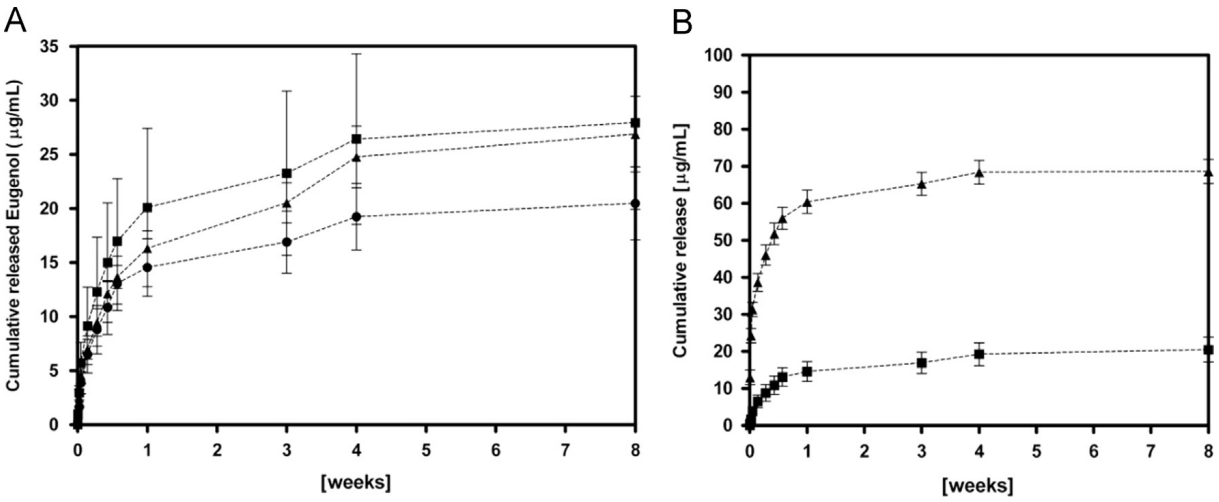

Figure 1: (A) Cumulative release in mg/ml of EG from PLDL disk coated with: direct coating of EG (square), one layer PLLA and EG coating (triangle) and one layer PLLA and EG coating with a second layer of PLLA and DM coating (circle), in PBS for 8 weeks. (B) Cumulative release in mg/ml of (square) EG and (triangle) DM from two layer coated disks in PBS for 8 weeks.

1.1 A Drug Release Experiment

In the drug release experiment, the drug diffuses through the polymer and releases into the overlaying medium (Figure 2) (typically water-dominated). The rate at which the drug releases is evaluated by periodically measuring the amount of drug in the release medium.

1.2 Formulating a well-posed problem

Defining x and t to be the spatial and time variables respectively, we assume that the polymer is initially uniformly loaded with drug, so the initial condition is defined as:

$$c = c_0 \quad \text{at} \quad t = 0,\ 0 < x < L.$$

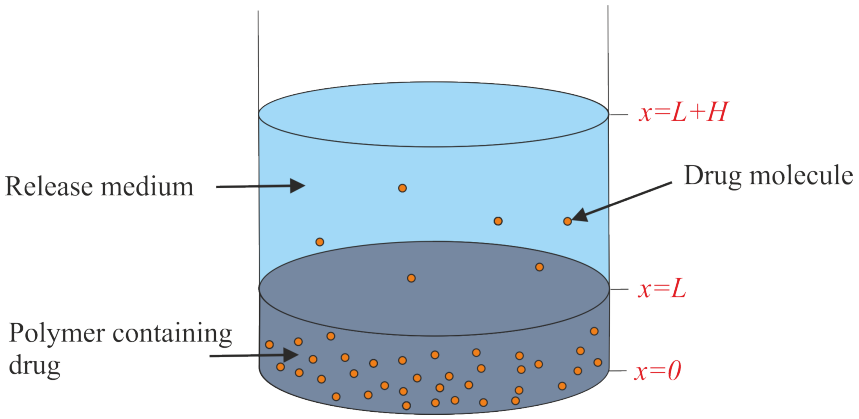

Figure 2: Schematic showing the experimental setup which gives an idea of the geometry.

Assuming that the release medium is well-stirred, we get the following well-posed initial boundary value problem:

$$\begin{aligned}
&\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \quad \text{for} \quad 0 < x < L,\\
&-D\frac{\partial c}{\partial x} = 0 \quad \text{on } x = 0,\\
&c = 0 \quad \text{on } x = L,\\
&c = c_0 \quad \text{at} \quad t = 0,\ 0 < x < L\ .
\end{aligned}$$

1.3 The solution of the mathematical model

It is assumed that the 1D form of the diffusion equation is sufficient to model the release of drug, which is justified in that the release of drug is mainly in one direction and it is also assumed that the dissolution of drug is instantaneous and that all the drug is instantly fully wetted. In the model, D is the diffusion constant which is assumed to be isotropic, this parameter can be determined via comparing the results with the data and thus will allow the model to fit the data more accurately. The model can be solved in numerous ways, in this case Separation of Variables was used and produced the following analytical solution:

$$c(x,t) = \frac{4c_0}{\pi}\sum_{n=1}^{\infty}\frac{(-1)^{n+1}}{(2n-1)}\cos\left(\frac{(2n-1)\pi x}{2L}\right)\exp\left(\frac{-D(2n-1)^2\pi^2 t}{4L^2}\right). \tag{1}$$

1.4 The Drug Release Profile

We introduce notation as follows:

$$\begin{aligned}
M(t) &= \text{(the drug in the release medium at time } t)\\
&= \text{(drug in polymer at } t = 0) - \text{(drug left in polymer at time } t)\\
&= ALc_0 - A\int_0^L c(x,t)dx
\end{aligned}$$

where A is the cross-sectional area of the polymer face.

The fraction of total drug released from the device by time t is

$$M_{frac} = \frac{M(t)}{ALc_0} = 1 - \frac{1}{Lc_0}\int_0^L c(x,t)dx$$

from (1) it is clear that $c(x,t) \to 0$ as $t \to \infty$ so $M_{frac} \to 1$.

1.5 Estimation of Diffusion Constant D

The experimental results of Argarate et al. [1] were extracted from their plot and compared to our analytical and numerical solution with $L = 30 \times 10^{-6}$m. We estimated D such that the experimental and analytical results are in agreement with each other (Figure 3) and D was estimated to be:

$$D = 5.21 \times 10^{-12} \frac{\text{cm}^2}{\text{s}}.$$

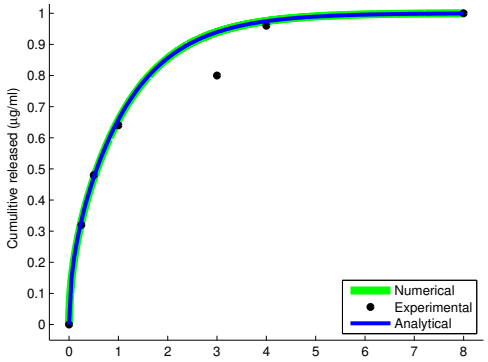

Figure 3: The release profile obtained using the calculated value of D. A numerical approximation of the model was also computed to compare with the analytical solution.

2 Modelling Drug Dissolution

One of the initial assumptions was that drug dissolution is instantaneous. This would not be a valid assumption for drugs with a low solubility, so the drug dissolution process is considered here. An implant is coated with a layer of pure drug. When the system is placed in a release medium, the drug dissolves at its surface interface with the medium. The dominant mechanism of drug release here is dissolution rather than diffusion and we shall assume here that the release medium is well-stirred.

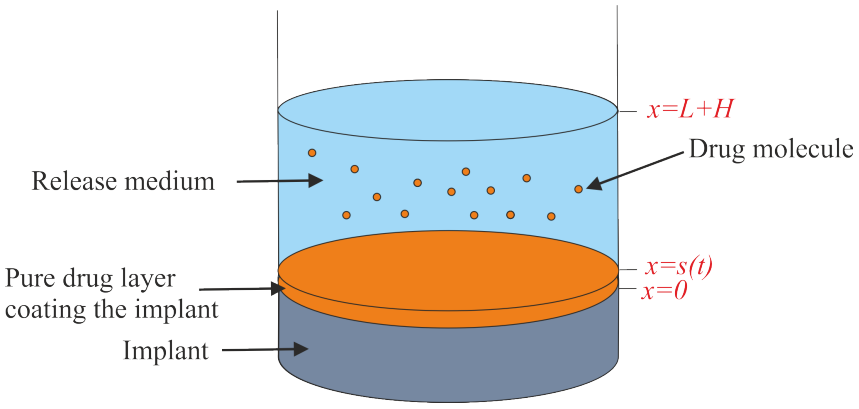

Figure 4: Schematic showing the implant with a pure drug layer.

2.1 Schematic of dissolution release profile

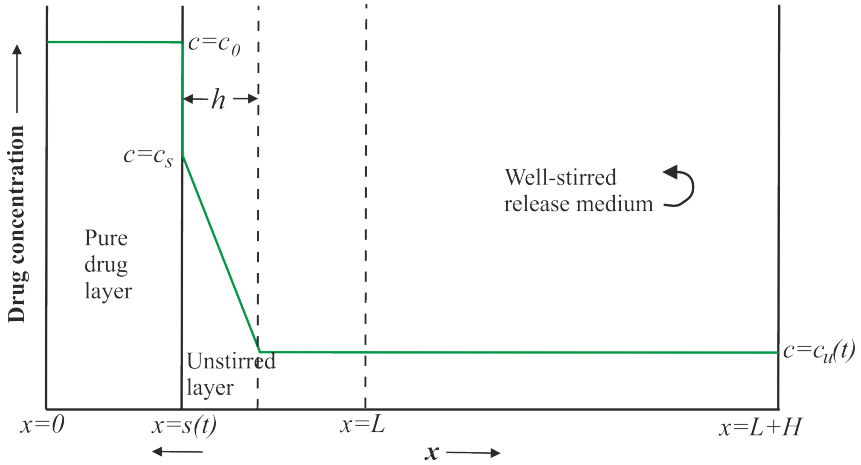

Figure 5: Illustration of how drug concentration will vary under the dissolution process.

2.2 Dissolution ODE model

As the drug layer dissolves we must consider the moving boundary $x = s(t)$ so,

$$\frac{ds}{dt} + \frac{k}{H}\frac{c_0}{c_0 - c_s}s \approx \frac{k}{H}\frac{Lc_0 - Hc_s}{c_0 - c_s},$$

where, c_s is the solubility limit of the drug in the release medium, H is the depth of the release medium above the drug layer and k is a fitting parameter that arises from the derivation of the ODE. The above ODE is subject to $s = L$ when $t = 0$, which gives the solution:

$$s = L + \frac{Hc_s}{c_0}\left(\exp\left(-\frac{kt}{H}\left[\frac{c_0}{c_0 - c_s}\right]\right) - 1\right).$$

To estimate the parameter k we make use of the timescale t_f,

$$k = -\frac{H(c_0 - c_s)}{t_f c_0}\log\left(1 - \frac{Lc_0}{Hc_s}\right),$$

where t_f is the time at which the drug is fully dissolved. The release profile M_t/M_∞ can be obtained from:

$$\frac{M_t}{M_\infty} = 1 - \frac{s(t)}{L} = \frac{Hc_s}{Lc_0}(1 - e^{-at}),$$

where a is the coefficient of s in above ODE, i.e.,

$$a = \frac{k}{H}\frac{c_0}{c_0 - c_s}.$$

2.3 ODE model solution vs experiment

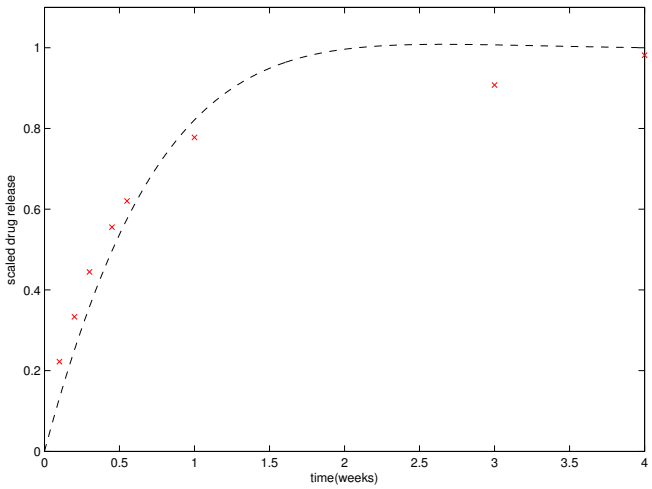

Figure 6: Comparison of the ODE dissolution model with the experimental data.

2.4 Mathematical model considering an unstirred medium

The work so far has considered that the release medium is well-stirred during the experiments. Here we examine what the concentration profile of the dissolving drug would be in an infinite, unstirred medium. We consider the front of the moving boundary to be $s(t)$ and c_s to be the solubility limit of the drug at this boundary. The dimensional model is as follows:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2},$$

$$c = c_s, \quad x = s(t), \quad s(t) < x < \infty,$$

$$\frac{ds}{dt}(c_s - c_0) = -D\frac{\partial c}{\partial x}, \quad x = s(t),$$

$$c = 0, \quad x \to \infty, \quad s(0) = 0.$$

We can non-dimensionalise the model with the following scalings:

$$c = c_s c', \quad x = Lx', \quad s = Ls', \quad t = \frac{L^2}{D}t'.$$

2.5 Non-dimensionalised model

The non-dimensional equations are then (dropping the primes for clarity),

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2},$$

$$s(t) < x < \infty\ , \quad c = 1, \quad x = s(t),$$

$$(1-\lambda)\,\frac{ds}{dt} = -\frac{\partial c}{\partial x}, \quad x = s(t),$$

$$c = 0, \quad x \to \infty, \quad s(0) = 0,$$

where $\lambda = c_0/c_s$ is a fitting parameter and these equations are defined until $s(t) = -1$.

2.6 Unstirred model solution

The model can be solved by introducing a similarity variable, transforming $c(x,t) \to f(\eta)$ where $\eta = x/\sqrt{t}$ and the moving boundary can be shown to behave like $\theta = s/\sqrt{t}$. The model then reduces to the second order ODE with BCs,

$$\frac{d^2 f}{d\eta^2} + \frac{\eta}{2}\frac{df}{d\eta} = 0, \quad f(\theta) = 1, \quad \theta < \eta < \infty,$$

$$\frac{df}{d\eta} = \frac{\theta}{2}(\lambda - 1), \quad \eta = \theta, \quad f(\infty) = 0.$$

The solution to this system, when written back in terms of the original variables is,

$$c(x,t) = \frac{\text{erf}(\frac{x}{2\sqrt{t}}) - 1}{\text{erf}(\frac{\theta}{2}) - 1}, \quad s = \theta\sqrt{t},$$

where the value θ comes from solving the following non-linear equation,

$$\sqrt{\pi}\theta(1-\lambda)\left[\text{erf}(\theta/2) - 1\right] + 2\exp(-\theta^2/4) = 0.$$

The fraction of drug released is given by:

$$\frac{M(t)}{M(\infty)} = \begin{cases} \theta\sqrt{t}/L & \text{for} 0 \le t \le L^2/\theta^2 \\ 1 & \text{for } t > L^2/\theta^2 \end{cases}$$

3 Numerical Model of Single Layer Problem

The framework applied is multi-layered and is primarily governed by diffusion but also allows for a coupled secondary state which can be chosen within each layer. The approach is analogous to the linear reversible binding two-phase equations, presented by McGinty and Pontrelli [2]. The governing equations within layer α are thus:

$$\frac{\partial C_{U,\alpha}(x,t)}{\partial t} = \frac{\partial}{\partial x}\left(D_\alpha \frac{\partial C_{U,\alpha}(x,t)}{\partial x}\right) + k_{1,\alpha} C_{B,\alpha}(x,t) - k_{2,\alpha} C_{U,\alpha}(x,t)$$
$$\frac{\partial C_{B,\alpha}(x,t)}{\partial t} = -k_{1,\alpha} C_{B,\alpha}(x,t) + k_{2,\alpha} C_{U,\alpha}(x,t)$$

where D_α is the diffusion coefficient and $k_{1,\alpha}$ and $k_{2,\alpha}$ are release and binding rate constants, which for this case are set to 0. The concentrations $C_{U,\alpha}$ represents unbound free flowing drug concentration and $C_{B,\alpha}$ represents bound stationary concentration. Between layers α and $\alpha+1$, interlayer boundary conditions:

$$-D_\alpha \frac{\partial C_{U,\alpha}}{\partial x}\bigg|_{x=x_\alpha^-} = -D_{\alpha+1}\frac{\partial C_{U,\alpha+1}}{\partial x}\bigg|_{x=x_\alpha^+}$$
$$= K_\alpha(C_{U,\alpha}(x_\alpha,t) - P_\alpha C_{U,\alpha+1}(x_\alpha,t))$$

where P_α is the partition coefficient and K_α is the mass transfer coefficient. On outer boundaries we have the following conditions:

$$-D_1 \frac{\partial C_{U,1}(x,t)}{\partial x}\bigg|_{x=x_0} = K_0(C_{b,0} - P_0 C_{U,1}(x_0,t))$$
$$-D_N \frac{\partial C_{U,N}(x,t)}{\partial x}\bigg|_{x=x_N} = K_N(C_{U,N}(x_N,t) - P_N C_{b,N})$$

here, $C_{b,0}$ and $C_{b,N}$ are concentration in the surrounding medium. Initial concentrations for both phases in each layer must be chosen, $C_{U,\alpha}(x,0)$ and $C_{B,\alpha}(x,0)$.

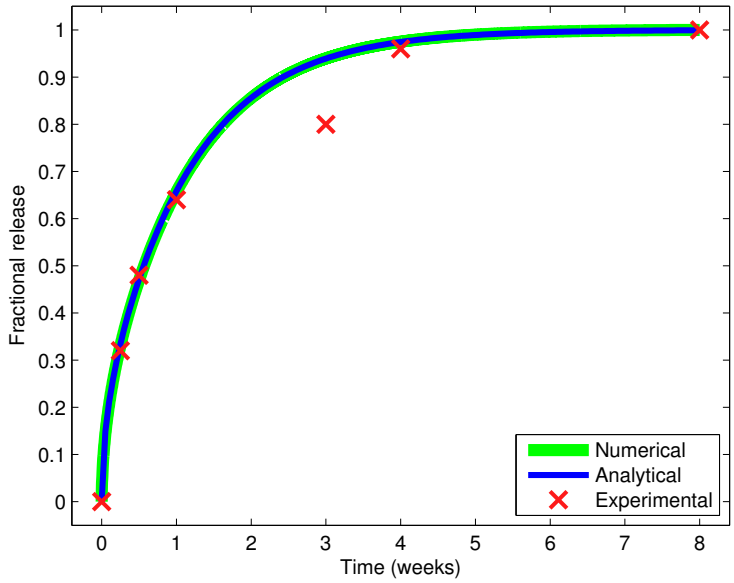

Figure 7: Comparison of the numerical and analytical solutions with experimental data.

3.1 Case 1

To compare the framework to an analytical solution we solve a drug loaded single layer diffusion system with zero flux and infinite sink boundary conditions. In this case we have $N = 1$ as the number of layers is 1

To recreate the boundary conditions, we set K_0 to zero to enforce a no flux condition at the PLDL/PLLA boundary. For the PLLA/release medium boundary we assign a large value to K_1 assuming no surface barrier effects. In this case the partition coefficients P_0 and P_1 are irrelevant but are nevertheless set to 1. Setting $C_{b,1}$ to 0 introduces the sink condition. Results from this case compare favourably with analytical solutions as numerical and analytical solutions overlap. An interesting aspect of the release curves (Figure 7) is that the initial concentration of the system is irrelevant. This is can be noted when looking at the analytical solution as initial concentration does not factor in and so some homogeneous $C_{U,\alpha}(x, 0) > 0 \ \forall x$ was chosen.

3.2 Case 2

In this case we will incorporate the concentration of the surrounding release medium, $C_R(t)$, which is assumed to be constant in space. Here we signify the concentration within the single PLLA layer simply with C. We apply the mass conservation formula

$$A \int_0^L C(x,t)\ dx + C_R(t) H A = ALc_0,$$

where A is the cross-sectional area of the PLLA surface and H is the height of release medium, obtained from $V = H \cdot A$. The area is $A = \pi \cdot (0.6 \text{ cm})^2$ and volume is $V = 1$ ml (Note that the actual volume of the release medium is 2 ml, however, using a symmetry argument we can focus on one side and halve the volume). Taking the time derivative we have

$$\int_0^L \frac{\partial C(x,t)}{\partial t}\ dx + H \frac{\partial C_R(t)}{\partial t} = 0.$$

Instead of the temporal derivative we insert the second spatial derivative times the diffusion coefficient and solve the integral

$$D \frac{\partial C}{\partial x}\bigg|_{x=L} + H \frac{\partial C_R(t)}{\partial t} = 0.$$

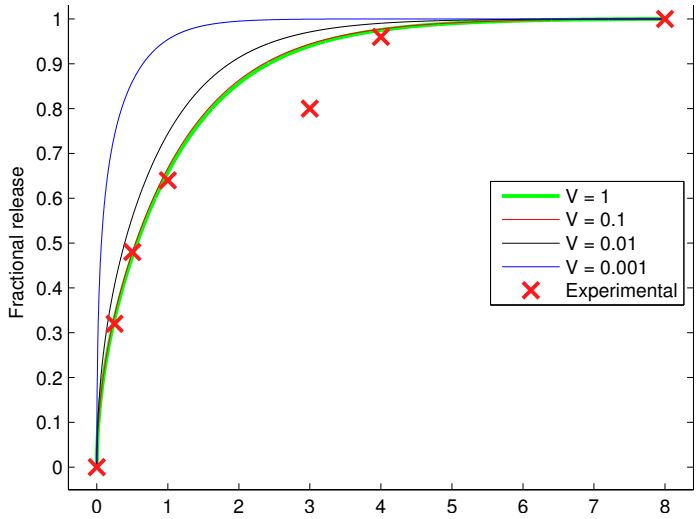

Figure 8: Comparison of the effects of different release media volumes on the solution of the model and hence the release profile.

So to summarize, we use the same system as above but instead of the sink condition on the PLLA/release medium (at L) we have (where x_N is the final spatial node):

$$C_{U,1}(L,t) = C_R(t)$$
$$H\frac{\partial C_R(t)}{\partial t} = -D\frac{\partial C(x,t)}{\partial x}\bigg|_{x=x_N}$$

3.3 Discretisation

We use the following notation to represent the nodal coefficients $c_1^{t_i}, c_2^{t_i}, \ldots, c_{N-1}^{t_i}, c_N^{t_i}$ for the finite element discretisation of C at timestep t_i. Similarly, we use $c_R^{t_i}$ as the temporal discretisation of C_R at timestep t_i. Applying finite differences to the above equation gives

$$H\frac{c_R^{t_{i+1}} - c_R^{t_i}}{\triangle t} = -D\frac{c_N^{t_i} - c_{N-1}^{t_i}}{\triangle x}.$$

Isolating $C_R(t_{i+1})$ gives

$$C_R(t_{i+1}) = C_R(t_i) - \frac{\triangle t}{H}\frac{D}{\triangle x}\frac{C_N(t_i) - C_{N-1}(t_i)}{\triangle x}.$$

3.4 Results

It is interesting to see that the release medium (RM) does not take effect until the RM volume is reduced to $V = 0.01$ml (black curve). It seems that the appropriate volume (of $V = 1$) for this system replicates the sink conditions on the PLLA/RM boundary.

4 Two-layer model of drug-eluting implant

Simplified same polymer problem

List of assumptions:

1. 1D problem
2. PLDL impermeable for the drug transport
3. Well stirred solution with infinite release medium volume

4. Two different drugs do not react with each other or with the polymer and do not degrade

5. Each drug has the same diffusion coefficient D in each layer, although these coefficients may be different for either drug.

Although this is a two layer problems, we are treating both layers as being made of the same polymer and essentially there is only one layer. Since there is no interaction between the two drugs, we could consider the problem for each drug separately. Nonetheless, the set of equations remains the same for each drug except for the value of diffusion coefficient D or the function of initial drug concentration.

$$\frac{\partial c_i}{\partial t} = D_i \cdot \frac{\partial^2 c_i}{\partial x^2}, \tag{2}$$

where c_i is the concentration of a drug, and D_i is the diffusion coefficient for that drug in both layers.

The condition of the impermeability of the PLDL layer gives us the condition of no flux at the bottom boundary:

$$\frac{\partial c_i}{\partial x}\Big|_{x=0;\forall t} = 0. \tag{3}$$

The condition of the infinite release medium with combined with good mixing gives us the limit condition for the upper boundary:

$$c_i\Big|_{x=L_1+L_2;\forall t} = 0. \tag{4}$$

The initial condition for this system is the following

$$c_1 = c_{01} \text{ if } x \in (0, L_1) \text{ and } 0 \text{ if } x \in (L_1, L_1 + L_2) \text{ at } t = 0, \tag{5}$$

$$c_2 = 0 \text{ if } x \in (0, L_1) \text{ and } c_{02} \text{ if } x \in (L_1, L_1 + L_2) \text{ at } t = 0, \tag{6}$$

The diffusion equation has an analytic solution with this set of initial and boundary conditions. This equation can be solved using separation of variables, and the generalized time-dependent solution takes the form:

$$c_i(x,t) = \sum_{n=0}^{\infty} (A_{ni} cos(\lambda_{ni} x) + B_{ni} sin(\lambda_{ni} x)) e^{-D_i \lambda_{ni}^2 t} \tag{7}$$

In order to define the parameters λ_{ni} and the coefficients A_{ni} and B_{ni} we use the boundary and initial conditions. Let us first apply the condition (3) to the generalized solution:

$$\frac{\partial c_i}{\partial x}\Big|_{x=0;\forall t} = \sum_{n=0}^{\infty} (-A_{ni}\lambda_{ni} sin(0) + B_{ni}\lambda_{ni} cos(0)) e^{-D_i \lambda_{ni}^2 t} = \sum_{n=0}^{\infty} B_{ni}\lambda_{ni} e^{-D_i \lambda_{ni}^2 t} = 0.$$

$$\Rightarrow B_{ni} = 0. \tag{8}$$

From condition (4) we can obtain the condition on the eigenvalues λ_{ni}:

$$c_i\Big|_{x=L_1+L_2;\forall t} = \sum_{n=0}^{\infty} A_{ni} cos(\lambda_{ni}(L_1 + L_2)) e^{-D_i \lambda_{ni}^2 t} = 0$$

$$\Rightarrow cos(\lambda_{ni}(L_1 + L_2)) = 0 \text{ or } \lambda_{ni} = \frac{\pi(2n+1)}{2(L_1 + L_2)}. \tag{9}$$

Finally, to identify the coefficients A_{ni} for each drug we should calculate the projection of initial concentration on normalized basis functions $cos(\lambda_{ni} x)$:

$$A_{ni} = \frac{\int_0^{L_1+L_2} c_i(t=0)cos(\lambda_{ni}x)dx}{\int_0^{L_1+L_2} cos^2(\lambda_{ni}x)dx}. \tag{10}$$

For the first drug contained initially in the bottom layer of the polymer with the initial concentration given in (5), the integration gives the following expression for A_{n1}:

$$A_{n1} = \frac{4C_{01}}{\pi(2n+1)} sin\frac{L_1\pi(2n+1)}{2(L_1+L_2)}. \tag{11}$$

Similarly, for the drug contained initially only in the upper layer with initial concentration given in (6):

$$A_{n2} = \frac{4C_{02}}{\pi(2n+1)}\Big((-1)^n - sin\frac{L_1\pi(2n+1)}{2(L_1+L_2)}\Big). \tag{12}$$

Knowing the function for the concentration of drugs within polymer layers we can now calculate the normalized release profiles:

$$\frac{M_i(t)}{Q_i(0)} = 1 - \frac{1}{L_i c_{0i}} \int_0^{L_1+L_2} C_i(x,t)dx, \tag{13}$$

where $M(t)$ is quantity of drug released into the medium and $Q(0)$ is quantity of drug initially contained in the polymer. Doing the integration in (13) for the two drugs we obtain the following function of release:

$$\begin{cases} \frac{M_1(t)}{Q_1(0)} = 1 - \sum_{n=0}^{\infty} \frac{8\cdot(-1)^n(L_1+L_2)}{L_1\pi^2(2n+1)^2} sin\frac{L_1\pi(2n+1)}{2(L_1+L_2)} \exp^{\frac{-D_1\pi^2(2n+1)^2t}{4(L_1+L_2)^2}}, \\ \frac{M_2(t)}{Q_2(0)} = 1 - \sum_{n=0}^{\infty} \frac{8(L_1+L_2)}{L_2\pi^2(2n+1)^2}\Big(1-(-1)^n sin\frac{L_1\pi(2n+1)}{2(L_1+L_2)}\Big) \exp^{\frac{-D_2\pi^2(2n+1)^2t}{4(L_1+L_2)^2}}. \end{cases}$$

This theoretical solution for release curves shows that for the second drug we obtain a more "classical" release curve, while for first drug diffusing from the bottom layer, the release profile has a slower ramp in the beginning as there is a certain delay in the release while the drug is diffusion through the upper layer.

Using this theoretical solution to fit the experimental curves, we can conclude that the diffusion coefficient for those two drugs are different. This is not surprising as the two drugs have different molecule sizes. Secondly, in the experiment we do not really observe the delay in release for the bottom drug. Out hypothesis to explain this would be that during the sample manufacturing the bottom drug may already start diffusing in the upper layer. The translation of initial time point could be efficient to explain the difference between the experimental and the theoretical curves as in reality, the diffusion started before the $t = 0$ of the experiment. Indeed, introducing this time translation allowed us to fit the data using $\delta t \approx 3h$. This time shift has the same order of magnitude with the time the sample has spent in a liquid solution while the deposition of the second polymer layer or in a humid state before the actual experiment (1h drying).

4.1 Numerical Solution for the Simplified same polymer problem

To solve the simplified same polymer problem numerically, we use the finite difference method. Assuming again the problem as one dimensional, we discretise the space occupied by the layers into 100 nodes along the x direction. Using a forward difference scheme to approximate the first order time derivative, and a central difference approximation to model the second order space derivative, equation (2) is written as:

$$\frac{C_i^{t+1} - C_i^t}{\delta t} = D\frac{C_{i+1}^t - 2C_i^t + C_{i-1}^t}{\delta x^2} \tag{14}$$

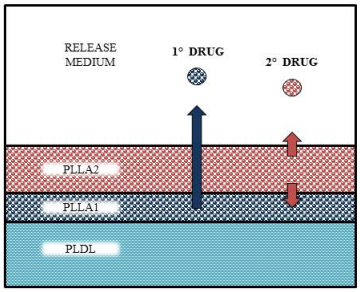

Figure 9: Graphical representation of generalized two layers problem with different polymers.

where i refers to the node index, C_i^t is the concentration at node i at time t, δt is the timestep, δx is the distance between two consecutive nodes ($\delta x = \frac{L_1+L_2}{100}$), and D is the polymer diffusion coefficient.

The timestep δt is assigned a value that ensures drug mass conservation in the domain, and consequently, the stability of the scheme. Therefore, δt is calculated as follows:

$$\delta t = \frac{\delta x^2}{2D} \tag{15}$$

After each time step t, the concentration at each node i is updated according to:

$$C_i^{t+1} = C_i^t + \frac{D\delta t}{\delta x^2}\left(C_{i+1}^t - 2C_i^t + C_{i-1}^t\right) \tag{16}$$

As the expression of concentration is not valid for the nodes at the extremities of the space domain, we use the boundary conditions to deduce the values of C_{-1}^t and C_{101}^t as shown below:

$$\begin{cases} \frac{\partial C}{\partial x} = 0; x = 0 \Rightarrow \frac{C_i^t - C_{i-1}^t}{\delta x} = 0 \Rightarrow C_{-1}^t = C_0^t & i = 0 \\ C = 0; x > L1 + L2 \Rightarrow C_{101=0} & i = 100 \end{cases} \tag{17}$$

We use the parameters in table 1 to solve the finite difference scheme using an in-house C++ code. Sensitivities were made to deduce the value of diffusion coefficient that leads to the best match between simulated and experimental data. This was achieved (see Figure 10 and 11) for a diffusion coefficient value equal to:

$$D = 7 * 10^{-15} m^2/s \tag{18}$$

It is worth noting that the numerical solution deployed here matches exactly the analytical solution.

Table 1: Value of model parameters employed in Finite Difference Simulations

Parameter	Symbol	Value
PLLA1 layer thickness	L_1	0.41 mm
PLLA2 layer thickness	L_2	0.47 mm

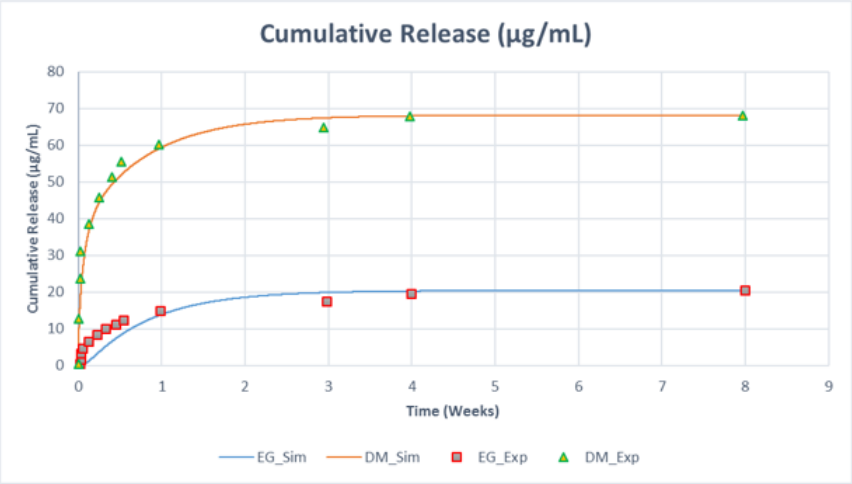

Figure 10: Release profile of the two drugs obtained with Finite Difference Method

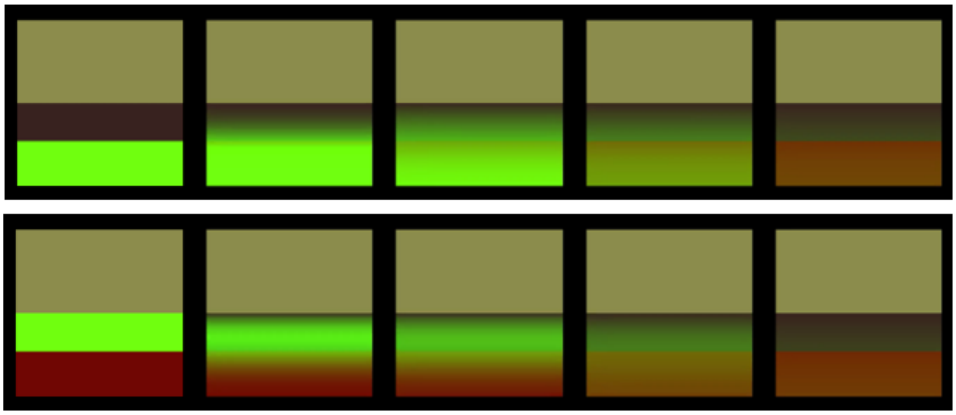

Figure 11: Visualisation of the drugs evolution in both layers. Drug is colored as bright green. Top row: EG drug. Bottom row: DM drug.

5 Generalized two layers problem with different polymers

Analytical solution

List of assumptions:

1. 1D problem
2. PLDL impermeable for the drug transport
3. Well stirred solution with infinite release medium volume
4. Two different drugs do not react with each other or with the polymer and do not degrade
5. Polymer layers are different thus having different drug specific coefficients (D_{1i} is the diffusion coefficient for drug i in the bottom layer whereas D_{2i} will be the coefficient in the upper layer)

In contrary to the previous problem let the $x = 0$ level be positioned at the boundary between two polymers. For each drug we need to solve the set of equations separately as there is no coupling between them, but the procedure is very similar for the both of them as we have seen in the simplified version of the problem. Here we will consider the drug in the bottom layer. We will define the function c_1 as the concentration of this drug in the bottom layer and

c_2 as the concentration of the drug in the upper layer. In this case we obtain the following set of equation:

$$\begin{cases} \frac{\partial c_1}{\partial t} = D_1 \cdot \frac{\partial^2 c_1}{\partial x^2}, \\ \frac{\partial c_2}{\partial t} = D_2 \cdot \frac{\partial^2 c_2}{\partial x^2}. \end{cases}$$

Similarly to the previous case, we have a zero flux condition on the bottom boundary, and due to perfect stirring the concentration on top is equal to zero:

$$\begin{cases} \frac{\partial c_1}{\partial x}\Big|_{x=-L_1;\forall t} = 0, \\ c_2\Big|_{x=L_2;\forall t} = 0. \end{cases}$$

Finally, we need to introduce a condition at the boundary between two polymer layers. The flow across the boundary should be the same. We also assume that the flow is proportional to the difference of concentration with a certain coefficient of mass transfer p:

$$D_1 \frac{\partial c_1}{\partial x}\Big|_{x=0} = D_2 \frac{\partial c_2}{\partial x}\Big|_{x=0} = p(c_2 - c_1). \tag{19}$$

Having in mind the general solution of the diffusion equation (7), we obtain from (19) that:

$$\frac{T_1(t)}{T_2(t)} = \frac{D_2 X_2'(0)}{D_1 X_1'(0)} = const, \tag{20}$$

$$\Rightarrow \exp^{(D_1\lambda_{n1}^2 - D_2\lambda_{n2}^2)t} = 1 \;\Rightarrow \lambda_{n1} = \lambda_{n2}\sqrt{\frac{D_2}{D_1}}, \tag{21}$$

where $c_i(x,t) = T_i(t)X_i(x)$.
From (19) we can also obtain the relation between the coefficients for X_i function:

$$D_1\lambda_{n1}B_{n1} = D_2\lambda_{n2}B_{n2} = p(A_{n2} - A_{n1}). \tag{22}$$

The condition on the bottom boundary gives us the following relation between A_{n1} and B_{n1}:

$$\frac{\partial c_1}{\partial x}\Big|_{x=-L_1} = 0 = \lambda_{n1}(A_{n1}sin(\lambda_{n1}L_1) + B_{n1}cos(\lambda_{n1}L_1)),$$

$$A_{n1} = -B_{n1}\frac{cos(\lambda_{n1}L_1)}{sin(\lambda_{n1}L_1)} = -B_{n1} \cdot ctg(\lambda_{n1}L_1). \tag{23}$$

From the upper boundary condition we obtain:

$$c_2\Big|_{x=L_2} = 0 = A_{n2}cos(\lambda_{n2}L_2) + B_{n2}sin(\lambda_{n2}L_2)),$$

$$A_{n2} = -B_{n2} \cdot tan(\lambda_{n2}L_2). \tag{24}$$

(22), (23) and (24) give us a system of linear equations:

$$\begin{cases} A_{n1} + B_{n1} \cdot cot(\lambda_{n1}L_1) = 0, \\ A_{n2} + B_{n2} \cdot cot(\lambda_{n2}L_2) = 0, \\ B_{n1}D_1\lambda_{n1} - p(A_{n2} - A_{n1}) = 0, \\ B_{n2}D_2\lambda_{n2} - p(A_{n2} - A_{n1}) = 0. \end{cases}$$

$$\mathbf{C} \cdot (A_{n1}, B_{n1}, A_{n2}, B_{n2})^T = 0, \tag{25}$$

where $\mathbf{C}$ is the matrix of coefficients. The non-trivial solution exists if the $det\mathbf{C} = 0$. This gives the condition on the eigenvalues:

$$\sqrt{D_1D_2^2}\lambda_{n2} + p(\sqrt{D_1}tan(\lambda_{n2}L_2)) - \sqrt{D_2}cot\left(\lambda_{n2}L_1\sqrt{\frac{D_2}{D_1}}\right) = 0. \tag{26}$$

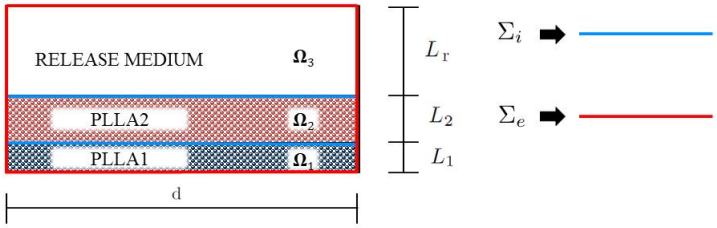

Figure 12: Representation of 2D domain of model

This equation cannot be solved analytically. We could numerically solve this equation to identify the eigenvalues, then we can identify the coefficients for spatial functions and thus obtain the concentration profile. As this procedure is similar to a simpler case described earlier, we won't go through it in details.

In the limit of $D_1 = D_2 = D$ we obtain the same condition on eigenvalues as calculated for a simplified problem. First, the mass transfer parameter $p \to \infty$ because there is no contrast of material. Equation (26) takes the form:

$$\frac{\sqrt{D^3}\lambda_{n2}}{p} + \sqrt{D}(tan(\lambda_{n2}L_2) - cot(\lambda_{n2}L_1)) = \sqrt{D}(tan(\lambda_{n2}L_2) - cot(\lambda_{n2}L_1)) = 0$$

$$tan(\lambda_{n2}L_2) = cot(\lambda_{n2}L_1) \Rightarrow cos(\lambda_{n2}(L_1 + L_2)) = 0. \tag{27}$$

We would like to note, that this model can also be used for a one-layer polymer containing the drug if we want to calculate the solution in case where the mixing is not ideal and there is a certain boundary layer of the release medium where the medium is not stirred and the drug is transported only by diffusion.

Numerical solution

Hypotheses list:

1. 2D problem;
2. PLDL impermeable for the drug transport;
3. Well stirred solution;
4. Two different drugs do not react with each other or with the polymer and do not degrade;
5. Polymer layers have different physical properties thus having different diffusion coefficients that is independent of the drug.

Differently from previous cases the domain of the problem is 2D. In this model the domain is composed from three layers:

1. PLLA1 layer with uniformly distributed drug 1 (Ω_1),
2. PLLA2 layer with uniformly distributed drug 2 (Ω_2),
3. release-medium layer (Ω_3).

For further detail about the problem domain see the graphic representation in figure 9. We will define the function $c_{1,i}$ as the concentration of the drug 1 in layer i and $c_{2,i}$ as the concentration of the drug 2 in layer i. In this case we obtain the following set of equation:

$$\begin{cases} \frac{\partial c_{1,i}}{\partial t} = D_i \cdot \nabla^2 c_{1,i} \\ \frac{\partial c_{2,i}}{\partial t} = D_i \cdot \nabla^2 c_{2,i} \end{cases} \qquad \text{with} \qquad i = 1, 2, 3. \tag{28}$$

Table 2: Value of model parameters employed in numerical applications.

Parameter	Symbol	Value
PLLA1 layer thickness	L_1	$0.41\ mm$
PLLA2 layer thickness	L_2	$0.47\ mm$
Release-medium layer thickness	L_r	$8\ mm$
Domain width	d	$12\ mm$
PLLA1 diffusion coefficient	D_1	$4 \times 10^{-15}\ m^2/s$
PLLA2 diffusion coefficient	D_2	$7 \times 10^{-15}\ m^2/s$
Release-medium diffusion coefficient	D_3	$1 \times 10^{-5}\ m^2/s$
Kedem-Katchalsky constant value	p	$5 \times 10^{-6}\ cm/s$

where D_i is the diffusion coefficient of layer i. In this case we have no-flux condition on external boundary Σ_e (red line in figure 12) and continuity flux coupled with Kedem-Katchalsky condition on internal boundary Σ_i (light-blue line in figure 12):

$$\begin{cases} D_i \nabla c_{1,i} = 0 \\ D_i \nabla c_{2,i} = 0 \end{cases} \quad \text{on} \quad \Sigma_e \tag{29}$$

$$\begin{cases} D_1 \nabla c_{1,1} = D_2 \nabla c_{1,2} = p(c_{1,2} - c_{1,1}) \\ D_2 \nabla c_{1,2} = D_3 \nabla c_{1,3} = p(c_{1,3} - c_{1,2}) \\ D_1 \nabla c_{2,1} = D_2 \nabla c_{2,2} = p(c_{2,2} - c_{2,1}) \\ D_2 \nabla c_{2,2} = D_3 \nabla c_{2,3} = p(c_{2,3} - c_{2,2}) \end{cases} \quad \text{on} \quad \Sigma_i \tag{30}$$

where i is referred to the layer and p is a constant value. We solve the problem-governing-equation with Finite Element Method (FEM) using COMSOL software. In particular the rectangular domain of generalized two layers problem is discretized by means of isoparametric 6-nodes 2D-triangular elements with quadratic shape functions on concentration. The COMSOL libraries allows to obtain the concentration field of the two drug $c_{1,i}$ and $c_{2,i}$ in the three layer through concentration nodal values and shape-functions. The result obtained is shown in figure 13, in terms of time-dependent variation of concentration $c_{1,3}$ and $c_{2,3}$ in one fixed point of the release-medium-layer. In addition we compare our result model with the release profile obtained in experimental study of [1]. The good fit was obtained via an empiric optimisation of the diffusion coefficient D_1 (PLLA1 layer) and D_2 (PLLA2 layer) while in agreement with the condition of well stirred solution D_3 is much larger when compared to D_1, D_2. The value of model parameters employed is reported in Table 2.

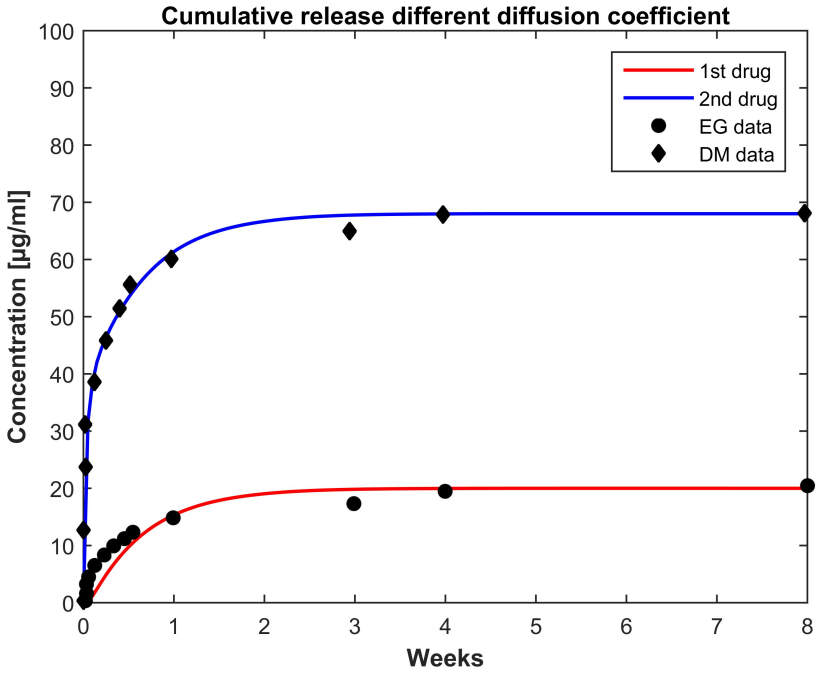

Figure 13: Concentration profile of the two drugs obtained with FEM in domain point $P1 = (d/2, L_1 + L_2 + L_r/2)$

References

[1] N. Argarate, B. Olalde, G. Atorrasagasti, J. Valero, S. C. Cifuentes, R. Benavente, M. Lieblich, and J. L. González-Carrasco, "Biodegradable Bi-layered coating on polymeric orthopaedic implants for controlled release of drugs," *Materials Letters*, vol. 132, pp. 193–195, 2014.

[2] S. McGinty and G. Pontrelli, "A general model of coupled drug release and tissue absorption for drug delivery devices," *Journal of Controlled Release*, vol. 217, pp. 327–336, 2015.