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Drug delivery and therapeutic lenses application

Authors:
Ana Alves (FCUP)
Daniela Jordão (FCTUC)
Duarte Carregueiro (FCUP)
Gonçalo Saraiva (FCTUC)
Iria Seoane (FMUSC)
Ricardo Santos (FCUP)

Coordinator:
Professor José Augusto Ferreira (CMUC)

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1 Introduction

Glaucoma is a group of eye diseases that cause optic nerve damage. The eye pressure plays a role in harm the fibres of the optic nerve. When significant number of fibres are damaged, blind spots develop in the field of vision. Once this occurs, visual loss is permanent.

In a healthy eye, the aqueous humor is continuously produced and drained from the ciliary body through the trabecular mesh and leave through the Schlemm canal. In the Figure 1 we can see the anatomy of the human eye.

In glaucoma, the trabecular mesh become inflamed and the circulation of aqueous humor is not possible. This causes an increase of the ocular pressure.

Diseases associated with anterior part of the eye are treated mainly by topic administration of eye drops in the anterior conjuntival fornix. However, the process is extremely inefficient since, once the eye drop is in the eye, the drug stays in the conjuntival sac a short period of time, less than 5 minutes. Furthermore, the amount of drug that penetrates in the cornea and reaches the intra-ocular tissues is just about 1-5% (See [1]).

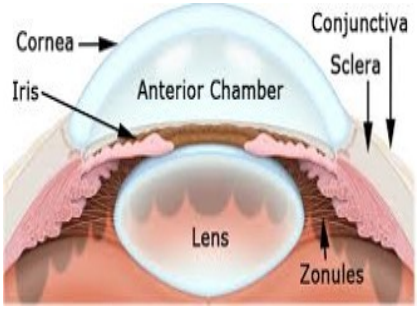

Figure 1: Anatomy of the eye ([2]).

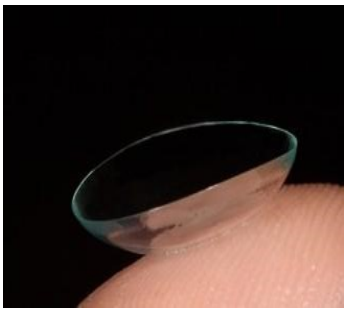

Figure 2: Lenses ([3]).

For avoiding the inconveniences of topic administration, therapeutic lens (Figure 2) are designed for improve the ocular drugs distribution. Polymers are combined with the drug to obtain a predefined drug release profile (See [1]).

There are several types of lens: simple polymeric membranes with disperse drug, polymeric platforms containing disperse particles that encapsulate drug; and multilayer lens.

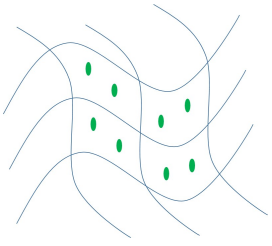

Figure 3: Unbound particles to the polymer chain.

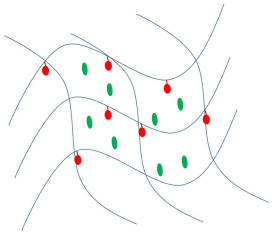

Figure 4: Unbound and bound particles to the polymer chain.

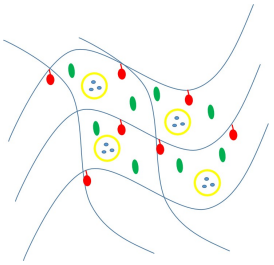

Figure 5: Unbound, bound and encapsulated particles to the polymer chain.

The main objective of this work is to study the evolution of drug in the

anterior chamber using different types of polymeric platforms to distribute the drug (Figures 3-5).

2 Initial considerations and some concepts

Let us suppose that the lens and the cornea are isotropic medias.

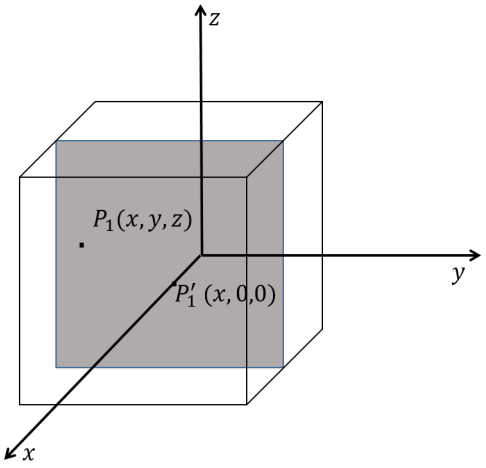

Figure 6: Reference element.

Let V represented in Figure 6 a reference element in one of these medium and let c be the drug concentration in (x, y, z) at time t. Let $\mathcal{A}$ be a cross section with fixed area A. We suppose that

$$c(x, y, z, t) = c(x, 0, 0, t)$$

for all $(x, y, z) \in \mathcal{A}$. We represent by $c(x, t)$ the concentration $c(x, 0, 0, t)$.

In the reference element V we have a diffusion process whose evolution is described by Fick's law. If we represent by $J(x, t)$ the drug mass flux at x at time t, then

$$J(x, t) = -D\frac{\partial c}{\partial x}(x, t),$$

where D represents the diffusion coefficient (See [4]).

We establish in what follows the diffusion equation, that has a central role in this work. Let $M(t)$ be the drug mass in a sector defined by $x_{\min} < x_1 \leq x_2 < x_{\max}$ then

$$M(t) = A\int_{x_1}^{x_2} c(x, t)\ dx,$$

and the time variation of $M(t)$ is given by

$$M'(t) = A\int_{x_1}^{x_2} \frac{\partial c}{\partial t}(x, t)\ dx \tag{2.1}$$

We remark that $M'(t) = AJ(x_1,t) - AJ(x_2,t)$, and using Fick's law we get

$$M'(t) = -A\ D\ \frac{\partial c}{\partial t}(x_1,t) + A\ D\ \frac{\partial c}{\partial t}(x_2,t) = \\ = A\int_{x_1}^{x_2} \frac{\partial}{\partial x}\Big(D\frac{\partial c}{\partial x}\Big)\ dx. \tag{2.2}$$

From (2.1), (2.2) we conclude that

$$A\ \int_{x_1}^{x_2} \left[\frac{\partial c}{\partial t}(x,t) - \Big(D\ \frac{\partial c}{\partial x}(x,t)\Big)\right]\ dx = 0. \tag{2.3}$$

As x_1, x_2 are arbitrarily and if c, $\dfrac{\partial c}{\partial t}$, $\dfrac{\partial c}{\partial x}$, $\dfrac{\partial^2 c}{\partial x^2}$ are continuous in $[x_{\min}, x_{\max}]$, then from (2.2) we obtain

$$\frac{\partial c}{\partial t}(x,t) - \frac{\partial}{\partial x}\Big(D\ \frac{\partial c}{\partial x}(x,t)\Big) = 0, \qquad \forall x \in]x_{\min}, x_{\max}[. \tag{2.4}$$

Equation (2.4), called diffusion equation, plays a crucial role in what follows.

It must be observed that if a reaction defined by R occurs in the sector $[x_1, x_2]$ then (2.2) is replaced by

$$M'(t) = -A\ D\ \frac{\partial c}{\partial t}(x_1,t) + A\ D\ \frac{\partial c}{\partial t}(x_2,t) + A\int_{x_1}^{x_2} R(x)\ dx = \\ = A\int_{x_1}^{x_2} \frac{\partial}{\partial x}\Big(D\frac{\partial c}{\partial x}\Big) + R(x)\ dx. \tag{2.5}$$

Thus, we obtain

$$\frac{\partial c}{\partial t}(x,t) - \frac{\partial}{\partial x}\Big(D\ \frac{\partial c}{\partial x}(x,t)\Big) + R(x) = 0, \qquad \forall x \in]x_{\min}, x_{\max}[, \tag{2.6}$$

which is called diffusion-reaction equation.

3 A coupled model for the drug distribution

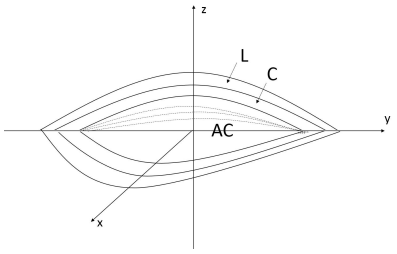

Figure 7: 3D simplified geometry.

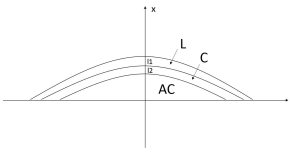

Figure 8: Cross section of the 3D model.

In Figure 7 we represent a simplified geometry of the lens L, the cornea C, and the anterior chamber S, and in Figure 8 a correspondent cross section.

We suppose that the therapeutical lens is composed by a polymeric matrix where the drug has 3 different states: free that is allowed to diffuse, bound that is linked with the polymeric structure and encapsulated in polymeric particles dispersed in the lens.

Let C_l, C_b, C_e, C_c and C_a denotes the free, bound and encapsulated concentration in the lens, the drug concentration in the cornea, and anterior chamber, respectively. We consider in what follows the evolution of C_l, C_b, C_e and C_c in the spatial domains $]l_1, l_2[$ and $]l_2, l_3[$, respectively.

We remark that the bound and encapsulated drug can be converted into free drug that diffuses through to the polymeric structure and in the cornea reaching the anterior chamber. To simplify the presentation we introduce different models, that describe the drug evolution in different type of lenses:

(i) Lenses with dispersed drug (Figure 3);

(ii) Lenses with bound and dispersed drug (Figure 4);

(iii) Lenses with dispersed, bound and encapsulated drug (Figure 5).

We introduce now several parameters that are needed in the mathematical description of the drug evolution.

Let D_l and D_c represent the drug diffusion coefficients in the lens and cornea, respectively. By δ_1 we denote the unbinding rate coefficient. As the encapsulated drug can be converted in free drug, by δ_2 we represent such rate transference coefficient.

In the anterior chamber the drug can be absorbed by the trabecular mesh or metabolised. The drug degradation rate (also called clearance rate) here is denoted by γ.

We describe now the evolution of the drug in different types of lens.

Model I: Lens with unbound drug particles

According to *mass conservation law* (2.4), the reaction term, $R(c(x,t))$, is null since we do not have bound or encapsulated drug. Hence, the governing diffusion equation that describes the drug dynamics in the lens is

$$\frac{\partial C_l}{\partial t} = D_l \frac{\partial^2 C_l}{\partial x^2}, \qquad x \in (0, l_1)\ , \quad t > 0, \tag{3.1}$$

Dimensional analysis of the Equation 3.1:

$$\left[\frac{\partial C_l}{\partial t}\right] = g \;\; cm^{-3}s^{-1} \quad [D_l] = cm^2 \;\; s^{-1} \quad \left[\frac{\partial^2 C_l}{\partial x^2}\right] = g \;\; cm^{-5},$$

where by $[H]$ we represent the units of the quantity H.

Model II: Lens with free and bound drug

We assume that the drug is in two different states: dispersed in the polymeric matrix and linked to polymeric chain.

In this case, the reaction term, $R(c(x,t))$, in the diffusion equation is not null since connections between drug particles and the polymer will be broken. Hence, the governing diffusion equation that describes the drug dynamics in the lens is,

$$\frac{\partial C_l}{\partial t} = D_l \frac{\partial^2 C_l}{\partial x^2} + \gamma(C_b - C_l), \quad x \in (0, l_1) \;,\; t > 0 \tag{3.2}$$

$$\frac{\partial C_b}{\partial t} = -\gamma(C_b - C_l), \qquad x \in (0, l_1) \;,\; t > 0, \tag{3.3}$$

Dimensional analysis of the Equations 3.2:

$$\left[\frac{\partial C_l}{\partial t}\right] = g \;\; cm^{-3}s^{-1} \quad [D_l] = cm^2 \;\; s^{-1} \quad \left[\frac{\partial^2 C_l}{\partial x^2}\right] = g \;\; cm^{-5}$$

$$[\gamma] = s^{-1} \quad [C_b] = [C_l] = g \; cm^{-3}$$

Dimensional analysis of the Equations 3.3:

$$\left[\frac{\partial C_b}{\partial t}\right] = g \quad [\gamma] = s^{-1} \quad [C_b] = [C_l] = g \; cm^{-3}$$

Model III: Lens with free, bound and encapsulated drug

In this case, we assume that bound and encapsulated drug can be converted into free drug depending such conversation on the difference between free and bound drug, and free and encapsulated drug.

- Free drug concentration:

$$\frac{\partial C_l}{\partial t} = D_l \frac{\partial^2 C_l}{\partial x^2} + \delta_1(C_b - C_l) + \delta_2(C_e - C_l) \qquad x \in (0, l_1) \;, \quad t > 0 \tag{3.4}$$

This equation describes the time and space evolution of the free drug concentration in the polymeric lens. The bound and encapsulated drug have a source role in the evolution of the free drug.

Dimensional analysis of the Equation 3.4:

$$\left[\frac{\partial C_l}{\partial t}\right] = g \;\; cm^{-3}s^{-1} \quad [D_l] = cm^2 \;\; s^{-1} \quad \left[\frac{\partial^2 C_l}{\partial x^2}\right] = g \;\; cm^{-5} \quad [\delta_1] = s^{-1}$$

$$[\delta_2] = s^{-1} \quad [C_b] = g \;\; cm^{-3} \quad [C_l] = g \;\; cm^{-3} \quad [C_e] = g \;\; cm^{-3}$$

- Bound drug concentration:

$$\frac{\partial C_b}{\partial t} = -\delta_1(C_b - C_l) \quad x \in (0, l_1)\ , t > 0 \tag{3.5}$$

This equation describes the evolution in time and space of the bound drug concentration. As this drug does not diffuse, this equation do not have a diffusion term. We remark that while the term $(C_b - C_l)$ works as a source in equation (3.4), in equation (3.5) this term has a sink role.

Dimensional analysis of the Equation 3.5:

$$\left[\frac{\partial C_b}{\partial t}\right] = g\ \ cm^{-3}s^{-1} \quad [\delta_2] = s^{-1} \quad [C_e] = g\ \ cm^{-3} \quad [C_l] = g\ \ cm^{-3}$$

- Encapsulated drug concentration:

$$\frac{\partial C_e}{\partial t} = -\delta_2(C_e - C_l) \quad x \in (0, l_1)\ , t > 0 \tag{3.6}$$

We observe that the encapsulated drug is not allowed to diffuse and while the term $(C_l - C_e)$ works as a source in equation (3.4), in last equation this term has a sink role.

Dimensional analysis of the Equation 3.6:

$$\left[\frac{\partial C_e}{\partial t}\right] = g\ \ cm^{-3}s^{-1} \quad [\delta_1] = s^{-1} \quad [C_b] = g\ \ cm^{-3} \quad [C_l] = g\ \ cm^{-3}$$

Drug evolution in cornea:

The free drug diffuses through the lens entering in the cornea where it also diffuses. We do not consider the possible links between the drug and the cornea tissue and its degradation. Consequently, the evolution of the drug in the cornea is described by the simple diffusion equation

$$\frac{\partial C_c}{\partial t} = D_c \frac{\partial^2 C_c}{\partial x^2} \quad x \in (l_1, l_2)\ , t > 0. \tag{3.7}$$

Cornea can be seen as a transfer layer since its properties may slow down or speed up the drug admission into anterior chamber, according to a higher or lower dilution level.

Dimensional analysis of the Equation 3.7:

$$\left[\frac{\partial C_c}{\partial t}\right] = g\ \ cm^{-3}s^{-1} \quad [D_c] = cm^2\ \ s^{-1} \quad \left[\frac{\partial^2 C_c}{\partial x^2}\right] = g\ \ cm^{-5}$$

Drug evolution in the anterior chamber:

The drug that diffuses in the cornea enters in the anterior chamber by the involving surface. So the time evolution of the concentration depends on the drug success flux entering by this surface as well as on its degradation. Consequently, we consider the following differential equation

$$\frac{\partial C_a}{\partial t} = \frac{1}{V_a}(-SD_c \frac{\partial C_c}{\partial x}(l_2, t)) - \gamma C_a, \quad t > 0 \tag{3.8}$$

where V_a denotes the volume of the anterior chamber, S the area of the surface which is the limit of the cornea that is in contact with the aqueous humour and γ represents the degradation rate.

Dimensional analysis of the Equation 3.8:

$$\left[\frac{\partial C_a}{\partial t}\right] = g \;\; cm^{-3}s^{-1} \quad \left[\frac{1}{V_a}\right] = cm^{-3} \, [D_c] = cm^2 \;\; s^{-1} \left[\frac{\partial C_c}{\partial x}\right] = g \;\; cm^{-4}$$
$$[\delta] = s^{-1} \quad [C_a] = g \;\; cm^{-3}$$

The drug evolution in the lens, cornea and anterior chamber when only dispersed drug is considered in the lens is described by Model I which is composed by equations (3.1), (3.7) and (3.8). Equations (3.2), (3.3), (3.7) and (3.8) define Model II where the drug in the lens has two different states: free and bound. Finally, Model III is defined by equations (3.4), (3.5), (3.6), (3.7) and (3.8). In this model we consider that the drug is dispersed, bound and encapsulated. We remark that Model III has as particular cases Models I and II. In fact if we take in (3.4) $\delta_1 = \delta_2 = 0$ then Model III is reduced to Model I and to model II if we take $\delta_2 = 0, \delta_1 \neq 0$.

	Parameter δ_1	Parameter δ_2
Model I	0	0
Model II	$\neq 0$	0
Model III	$\neq 0$	$\neq 0$

To complete the definitions of the mathematical problems we need to specify initial, boundary and transition conditions that define the variables at $t = 0$, at the boundary of the spatial domain, and at the interface between the lens and the cornea, and between the cornea and the anterior chamber.

Let C_l^0, C_b^0 and C_e^0 represent the drug concentration at $t = 0$ in the three different states: free, bound and encapsulated. Initially we do not have drug in the cornea and in the anterior chamber. Then

$$\begin{cases} C_l(x,0) = C_l^0 & x \in (0, l_1) \\ C_b(x,0) = C_b^0 & x \in (0, l_1) \\ C_e(x,0) = C_e^0 & x \in (0, l_1) \\ C_c(x,0) = 0 & x \in (l_1, l_2) \\ C_a(0) = 0 \end{cases} \tag{3.9}$$

Boundary conditions:

- At $x = 0$: As the lens surface in contact with air is isolated, the mass flux in the surface is null and this conditions is described by

$$\frac{\partial C_l}{\partial x}(0,t) = 0. \tag{3.10}$$

Transition conditions:

- Lens-Cornea surface: We assume that the mass flux that leaves the lens enters in the cornea, which means that the two mass fluxes are equals

$$- D_l \frac{\partial C_l}{\partial x}(l_1,t) = -D_c \frac{\partial C_c}{\partial x}(l_1,t), \; t > 0. \tag{3.11}$$

Moreover we assume that in the interface between the lens and the cornea we have continuity of the concentrations, this means that

$$C_l(l_1, t) = C_c(l_1, t),\ t > 0. \tag{3.12}$$

- Cornea-Anterior chamber surface: The drug mass flux that enter in the anterior chamber comes from the cornea and it depends on the permeability of the contact surface (α). Moreover we assume that the mass flux depends on the difference between the two concentrations: in the cornea and in the anterior chamber. These assumptions are mathematically described by

$$-D_c \frac{\partial C_c}{\partial x}(l_2, t) = \alpha(C_c(l_2, t) - C_a(t)),\ t > 0. \tag{3.13}$$

Remark. The coupled model: (3.4), (3.5), (3.6), (3.7), (3.8), (3.9), (3.10), (3.11), (3.12) and (3.13) present several challenges in what concerns its mathematical analysis: well-posedness in traditional sense, this means it has unique solution and it is stable, in the sense that if we perturb the initial conditions (3.9) then the correspondent solution is a perturbation of the solution defined by (3.9).

The mathematical analysis of the initial boundary problem (3.4), (3.5), (3.6), (3.7), (3.8), (3.9), (3.10), (3.11), (3.12) and (3.13) will not be included in this work.

As the main motivation of this work is the construction of the mathematical model III and its qualitative behaviour, in what follows we present its numerical simulation.

4 Numerical Simulation

4.1 Introduction

To illustrate the behavior of the different drug concentrations defined by the initial value problem (3.4), (3.5), (3.6), (3.7), (3.8), (3.9), (3.10), (3.11), (3.12) and (3.13) we need to introduce a discretization of this problem.

Different approaches can be used to introduce such discrete model, namely, finite element or finite difference approaches. In what follows, we use the finite difference approach and the discrete model will be implemented in Matlab.

We start by the introduction of the finite difference method that is constructed using an implicit-explicit approach. Finally, we present some numerical experiments that aim to illustrate the qualitative behaviour of the coupled model defined by (3.4), (3.5), (3.6), (3.7), (3.8), (3.9), (3.10), (3.11), (3.12) and (3.13).

4.2 Discrete Method

In the spacial domain $\bar{\Omega} = [0, l_2]$, we introduce the uniform partition $0 = x_0 < x_1 < \cdots < x_I < \cdots < x_{N-1} < x_N = l_2$, $x_I = l_1$. Let be $h = x_i - x_{i-1}$, $i = 1, \ldots, N$ and let $x_{-1} = -h$. By D_2 we denote the second order centred difference operator

$$D_2 u_h(x_i) = \frac{u_h(x_{i-1}) - 2u_h(x_i) + u_h(x_{i+1})}{h^2},$$

by D_{-x} the backward difference operator

$$D_{-x} u_h(x_i) = \frac{u_h(x_i) - u_h(x_{i-1})}{h},$$

and by D_x the progressive difference operator

$$D_x u_h(x_i) = \frac{u_h(x_{i+1}) - u_h(x_i)}{h}.$$

We consider the previous operators in the discretization of spatial derivate present in the equations of the model and let be $C_{l,h}$, $C_{b,h}$, $C_{e,h}$, $C_{c,h}$, $C_{e,h}$ and $C_{a,h}$ grid functions with entries $C_{l,h}(x_i, t)$, $C_{b,h}(x_i, t)$, $C_{e,h}(x_i, t)$, $C_{c,h}(x_i, t)$, $C_{e,h}(x_i, t)$ and $C_{a,h}(x_i, t)$. The semi-discretezed model is given by the following ordinary differential equations:

$$\begin{aligned}\frac{dC_{l,h}(x_i,t)}{dt} =& D_l D_2 C_{l,h}(x_i,t) + \delta_1(C_{b,h}(x_i,t) - C_{l,h}(x_i,t)) \\ &+ \delta_2(C_{e,h}(x_i,t) - C_{l,h}(x_i,t)), \quad i = 0, \ldots, I-1, \quad t > 0,\end{aligned} \tag{4.1}$$

$$\frac{dC_{b,h}(x_i,t)}{dt} = -\delta_1(C_{b,h}(x_i,t) - C_{l,h}(x_i,t)), \quad i = 1, \ldots, I-1,\ t > 0, \tag{4.2}$$

$$\frac{dC_{e,h}(x_i,t)}{dt} = -\delta_2(C_{e,h}(x_i,t) - C_{l,h}(x_i,t)), \quad i = 1, \ldots, I-1,\ t > 0, \tag{4.3}$$

$$\frac{dC_{c,h}(x_i,t)}{dt} = D_c D_2 C_{c,h}(x_i,t), \quad i = I+1, \ldots, N-1,\ t > 0, \tag{4.4}$$

$$\frac{dC_{a,h}(t)}{dt} = \frac{1}{V_a}(-S D_c D_{-x} C_{c,h}(x_N,t)) - \gamma C_{a,h}(t),\ t > 0. \tag{4.5}$$

Being this equations coupled with the following initial conditions

$$\begin{cases} C_{l,h}(x_i,0) = C_l^0, & i = 1,\dots,I-1 \\ C_{b,h}(x_i,0) = C_b^0, & i = 1,\dots,I-1 \\ C_{e,h}(x_i,0) = C_e^0, & i = 1,\dots,I-1 \\ C_{c,h}(x_i,0) = 0, & i = I+1,\dots,N-1 \\ C_{a,h}(0) = 0. \end{cases} \tag{4.6}$$

To conclude the definition of the coupled semi-discrete approximation we need to introduce the semi-discrete boundary and transition conditions. For the boundary condition in $x = 0$ we need to consider an auxiliary mesh point $C_{l,h}(x_{-1},t)$, that, from the boundary condition (4.7), it is given by

$$C_{l,h}(x_{-1},t) = C_{l,h}(x_1,t), \tag{4.7}$$

The transition conditions (4.8), (4.9) and (4.10) are replaced by

$$-D_l D_{-x} C_{l,h}(x_I,t) = -D_c D_x C_{c,h}(x_I,t),\ t>0, \tag{4.8}$$

$$C_{l,h}(x_I,t) = C_{c,h}(x_I,t),\ t>0, \tag{4.9}$$

$$-D_c D_{-x} C_{c,h}(x_N,t) = \alpha(C_{c,h}(x_N,t) - C_{a,h}(t)),\ t>0. \tag{4.10}$$

The semi-discrete model $C_{k,h}$, $k \in \{l,b,e,c,a\}$ is defined by (4.1)-(4.10).

Now we need to integrate in time the introduced semi-discrete problem. To do that, we introduce a time grid $\{t^n, n = 0,\dots,M\}$ with $t^0 = 0$, $t^n = T$ and $t^{n+1} - t^n = \Delta t$.

In time integration we use an implicit-explicit approach: the diffusion terms are discretized implicitly and the reaction term in equation (4.1) is discretized explicitly; the differential equations (4.2), (4.3), (4.4) are integrated using the implicit-Euler method.

Let $C_{k,i}^m$, $k \in \{a,l,b,e,c\}$ represent the numerical approximations for $C_k(x_i,t^m)$, $k \in \{a,l,b,e,c\}$, that are defined in what follows:

1. For $i = 0,\dots,I-1$, $j = 1,\dots,M$ we consider

$$\frac{C_{l,i}^{j+1} - C_{l,i}^j}{\Delta t} = D_l \frac{C_{l,i-1}^{j+1} - 2C_{l,i}^{j+1} + C_{l,i+1}^{j+1}}{h^2} + \delta_1(C_{b,i}^j - C_{l,i}^j) + \delta_2(C_{e,i}^j - C_{l,i}^j);$$

2. For $i = 1\dots,I-1$, $j = 1,\dots,M$

$$\frac{C_{b,i}^{j+1} - C_{b,i}^j}{\Delta t} = -\delta_1(C_{b,i}^{j+1} - C_{l,i}^{j+1}),$$

$$\frac{C_{e,i}^{j+1} - C_{e,i}^j}{\Delta t} = -\delta_2(C_{e,i}^{j+1} - C_{l,i}^{j+1});$$

3. For $i = I+1,\dots,N_1$, $j = 1,\dots,M$

$$\frac{C_{c,i}^{j+1} - C_{c,i}^j}{\Delta t} = D_l \frac{C_{c,i-1}^{j+1} - 2C_{c,i}^{j+1} + C_{c,i+1}^{j+1}}{h^2};$$

4. For $C_{a,h}^j$, $j = 1, \ldots, M$ we have

$$\frac{C_a^{j+1} - C_a^j}{\Delta t} = \frac{1}{V_a}\left(-SD_c \frac{C_{c,N}^{j+1} - C_{c,N-1}^{j+1}}{h}\right) - \gamma C_a^{j+1};$$

5. We consider the initial conditions (4.6);

6. As boundary and transition conditions, for all $t = j\Delta t$, $j = 1 \ldots, M$ is given by (4.7), (4.8), (4.9) and (4.10).

Remark. The theoretical support for the previous numerical method will not be developed in this work. We observe that the method is consistent, provided that the solution C_k, $k \in \{l, b, e, c, a\}$ is smooth enough, in the sense that when $\Delta t \to 0$, $h \to 0$, the correspondent truncation error goes to zero. Moreover, the diffusion errors are implicit discretized, we expect that the method is at least conditionally stable.

4.3 Numerical Results

In this section we present some numerical results that intend to illustrate the behaviour of the constructed model. We present the time evolution of the drug concentration that reaches the anterior chamber for different parameter values. As we do not consider real parameter values, we fix the parameter of interest in a fixed interval.

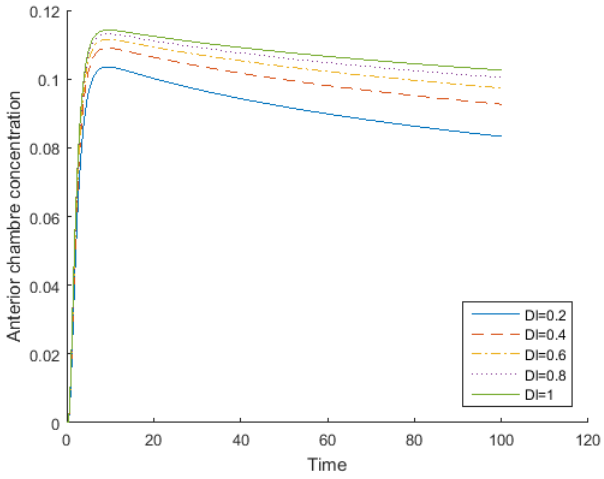

Figure 9: Influence of the coefficient: $D_l \in [0.2, 1]$.

In Figure 9 we plot the evolution of the concentration C_a for different values of the coefficient D_l. This numerical experiment can be used to illustrate the drug evolution when different drugs or different polymeric matrices are used.

We observe that if we increase the drug diffusion coefficient then we increase the drug available in the anterior chamber.

The same behaviour is observed in Figure 10 if we increase the drug diffusion coefficient in the cornea.

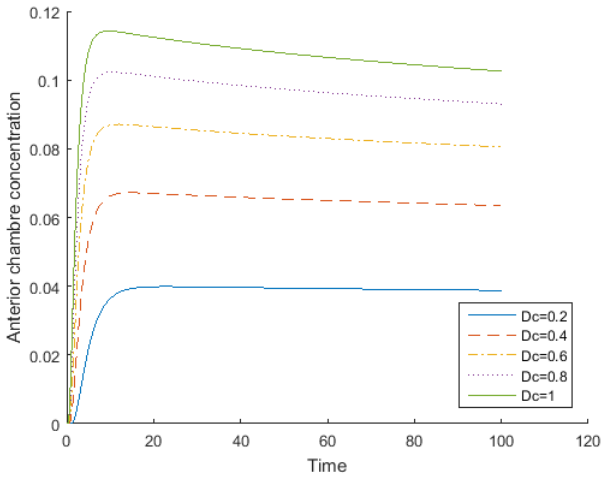

Figure 10: Influence of the coefficient: $D_c \in [0.2, 1]$.

The results in Figure 10 can be used to illustrate the effect of the same drug in different patients, because D_c is different for each cornea.

A larger values of D_c corresponds with a easier drug diffusion in the cornea, thus the drug goes faster from the lens to the anterior chamber. Also, we can conclude that D_c have a greater effect in results than D_l and that the lens used in each patient must be adapted to each case.

Figure 11 intend to illustrate the role of γ coefficient. We recall that γ represents a clearance rate due to the drug absorption or degradation.

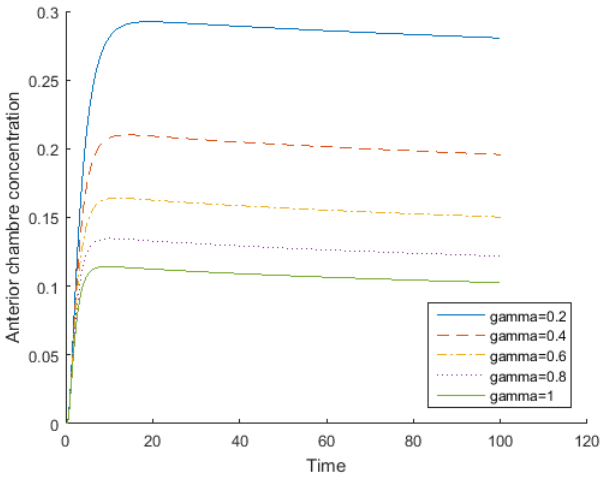

Figure 11: Influence of the coefficient: $\gamma \in [0, 0.4]$

Different drugs have different degradation rates. Different patients have different absorption rate. Then Figure 11 can be used to illustrate the drug evolution for different drugs in the same patient or different patients for the same drug.

For the results presented in Figure 11 we conclude that when γ increases, the drug available in the anterior chamber decreases.

In Figure 12 we can see the influence of the α coefficient. Different patients have different corneas and consequently different permeability coefficients α. Different drugs have different permeability coefficients α. Different drug have different permeabilities for the same patient. In Figure 12 we plot the time evolution of the drug concentration in the anterior chamber.

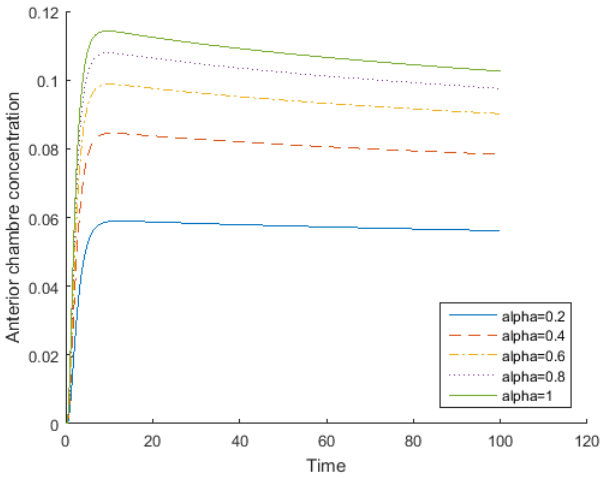

Figure 12: Influence of the coefficient: $\alpha \in [0.2, 1]$

In a fixed patient, if the drug permeability coefficient increases, the drug concentration in the anterior chamber increases too. For a fixed drug, if the permeability of the contact zone of the cornea with the anterior chamber increases, then the drug concentration in this region increases.

In Figure 13 we plot the drug concentration in anterior chamber when the unbinding rate δ_1 changes. These results can be used to illustrate the drug time evolution when a drug is fixed and we change the polymeric matrix or the lens is fixed and we change the drugs.

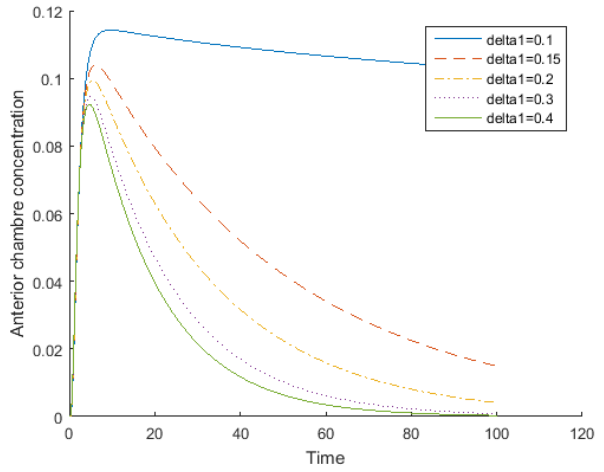

Figure 13: Influence of the coefficient: $\delta_1 \in [0.1, 0.4]$

If the unbinding coefficient increases then we decrease the drug available in the anterior chamber. Moreover we decrease the residence time of the drug.

Finally, in Figure 14 we plot the evolution of the drug concentration in the anterior chamber when the release rate for the encapsulated particles increases.

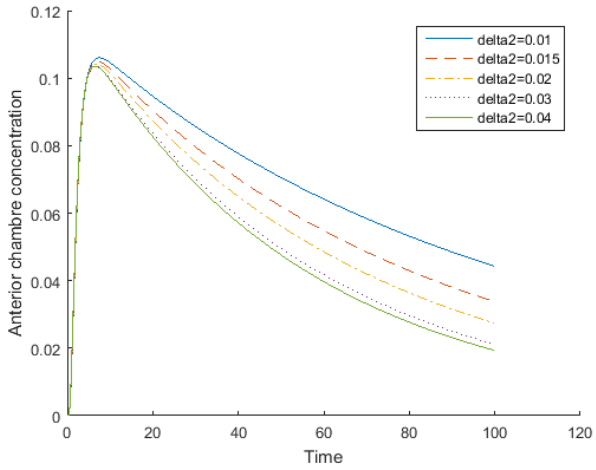

Figure 14: Influence of the coefficient: $\delta_2 \in [0.01, 0.04]$

When δ_2 increases, the drug concentration in the anterior chamber decreases. Moreover, the residence period of the drug in the anterior chamber also decreases. We can analyse Figure 14 likewise we analyse Figure 13 but for encapsulated drug.

5 Conclusions

The diseases of the anterior segment of the eye are traditionally treated using topical drug administration. Since this type of treatment is very inefficient, several approaches were proposed to increase the treatment efficacy.

The use of therapeutic lens to treat glaucoma arises as an efficient and safe alternative to the traditional methodology. This work aims to model the drug release from different types of lenses: lenses with drug dispersed, lenses with drug in two different states - dispersed and bound to the polymeric structure and dispersed, bound and encapsulated drug. We remark that the use of particles loaded with drug that are dispersed in the polymeric matrix aims to increase the drug loading as well as to increase the time period of drug availability in the anterior chamber.

From the results presented in this work we conclude that if we decrease the unbinding coefficient then we increase the residence period of time for the drug in the anterior chamber. The same behaviour is observed if we decrease the transference rate from encapsulating particles.

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