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DRUG DELIVERY: FROM A CONTACT LENS TO THE ANTERIOR CHAMBER

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Abstract: Mathematical models to describe drug concentration profiles of topically administered drug in the anterior chamber aqueous humor have been proposed by several authors. The aim of this paper is to present a mathematical model to predict the drug concentration in the anterior chamber when a therapeutical contact lens with the drug is entrapped in nanoparticles is used.

Keywords: Ophthalmic contact lens, nanoparticles, polymeric matrix, cornea, anterior chamber, diffusion.

1. Introduction

Diseases of the anterior segment of the eye are mostly treated by topical ocular administration in the inferior fornix of the conjunctiva. Nevertheless the procedure is extremely inefficient because when a drop (50 to $100\mu\ell$ per drop) is instilled in the eye, the ophthalmic drug has a short residence time in the conjunctival sac, less than 5 minutes, and only $1-5\%$ of the applied drug penetrates the cornea reaching the intraocular tissues. The biovailability tends to be low and depends on the precorneal fluids dynamics, drug binding to tear proteins, conjunctival drug absorption, tears turn over, resistance to corneal penetration, nasolachrymal drainage, metabolic degradation and non-productive absorption. The absorption and the efficacy of the instilled drug can be increased by altering its formulation and/or by changing the local conditions.

In the last years many researchers have proposed the use of therapeutic contact lenses to increase the ocular bioavailability of ophthalmic drugs. The first attempt to increase the residence time of the ophthalmic drug was the use of soaked contact lenses. The lens is hydrated once placed on to the cornea and releases the drug until an equilibrium is reached between drug concentration in the contact lens and in the conjunctival sac; the maximum

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drug loading is limited by the solubility of the drug in the polymeric matrix and the delivery period of time is still very short.

Several approaches have been considered to overcome the limitations of soaked contact lenses: lenses where the ophthalmic drug is linked with the polymeric matrix ([7], [8], [12], [13]) and contact lenses where the drug is encapsulated in nanoparticles dispersed in the matrix ([3], [5], [6], [10]). The nanoparticles are formed by polymerization, during or after which the drug is added, leading to covalent drug binding to the polymer. This binding of the drug depends on its physicochemical properties as well as the nature of the polymer; experimental and mathematical predictions on drug delivery were provided([4]). Recently delivery system based on PLGA nanoparticles incorporating drug have been proposed in [11].

However, from a medical point of view, the central question is to have a prediction of the drug concentration in the anterior chamber of the eye. In this case, mathematical models are the only available tool to make such prediction. The mathematical models describing the behaviour of drug concentration across the cornea when a drop is instilled were proposed in [2], [14] and [15]. Nevertheless, when the drug is delivered from a contact lens the concentration and mass profiles across the cornea are qualitatively different.

The main contribution of this paper is to present a mathematical model to predict drug concentration in the anterior chamber when the drug is delivered from a therapeutical contact lens where the drug is dispersed in the polymeric matrix and encapsulated in nanoparticles. A particular case of our model is drug delivery from soaked lenses. The model presented in this paper takes into account the essential mechanisms occurring in the delivery system. Drug lost due to tear drainage is not considered. This assumption is based on the observation that there is limited mixing between the fluid in the post tear film and the outside tear fluid ([10]). Moreover we do not take into account the drug lost by the conjunctiva. A more detailed model where drug lost by the conjunctiva is considered and the cornea is decomposed in epithelium, stroma and endothelium, can be developed along the same lines.

The paper is organized as follows. In Section 2 we introduce the mathematical model composed by coupled diffusion partial differential equations linked with flux conditions at the boundaries. The drug concentration in the anterior chamber is obtained using Laplace transforms in Section 3. In Section 4 we present several plots obtained from the theoretical solutions and we compare our results with the concentration plots in the anterior chamber in the case of topical drug administration. In Section 5 the we compare numerically the drug concentration in the anterior chamber when a drop and an ophthalmic contact lens are used in drug administration. In Section 6 some conclusions are established.

2. The mathematical model

We consider a compartmental model to represent a contact lens, the cornea and the anterior chamber of the eye(Figure 1). We assume that the drug is dispersed in the contact lens and entrapped in particles as described in [3].

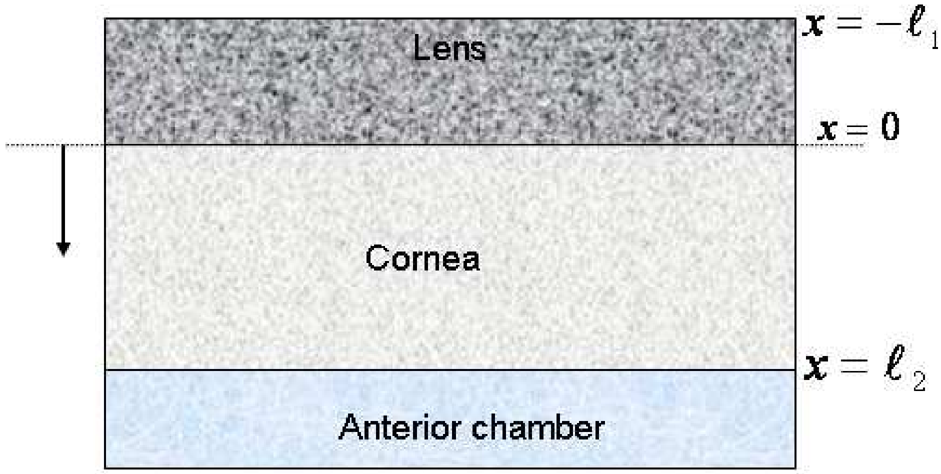

FIGURE 1. Schematic diagram of the drug transport from a therapeutical contact lens.

In this model the cornea is represented by only one compartment because this assumption simplifies the establishment of a closed formula for the drug concentration in the anterior chamber. We note that if the components of the cornea tissue were considered - epithelium, Bowman's layer, stroma, Descemet's membrane and endothelium - the procedure could be generalized in a straightforward way. In Figure 2 we represent schematically a contact lens with nanoparticles.

The main physical mechanisms underlying the drug transport from the therapeutical contact lens to the anterior chamber are the diffusion, metabolism and binding. The drug release from the therapeutical lens can be

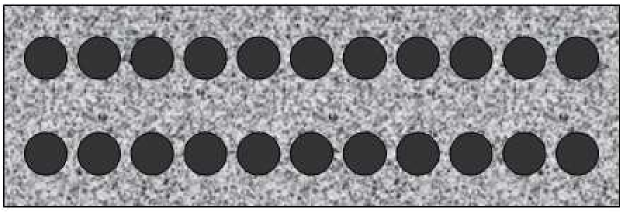

FIGURE 2. Schematic diagram of the lens with nanoparticles filled with drug.

described by the system of partial differential equations

$$\begin{cases} \dfrac{\partial C^g}{\partial t} = D_g \dfrac{\partial^2 C^g}{\partial x^2} - \dfrac{\partial C^b}{\partial t}, x \in (-\ell_1, 0), t > 0, \\ \dfrac{\partial C^b}{\partial t} = \lambda (C^b - C^g), x \in (-\ell_1, 0), t > 0, \end{cases} \tag{1}$$

where C^g represents the drug concentration in the gel, C^b the drug concentration in the nanoparticles, D_g the diffusion coefficient of the drug in the gel and λ is defined by

$$\lambda = -\frac{S}{V} K,$$

where S and V represent respectively the surface and the volume of the nanoparticles and K the mass transfer coefficient for drug transport across the particle surface.

The behavior of the drug concentration in the cornea, C^c, is described by

$$\frac{\partial C^c}{\partial t} = D_c \frac{\partial^2 C^c}{\partial x^2} - K_c C^c, \ x \in (0, \ell_2), t > 0, \tag{2}$$

where D_c stands for the diffusion coefficient in the cornea and K_c represents a coefficient that takes into account the metabolic consumption.

The conservation of drug in the anterior chamber is described by ([14])

$$\frac{dC^a}{dt} = \frac{1}{V_a}\Big(- D_c f_c A_c \frac{\partial C^c}{\partial x}(\ell_2, t) - Cl_a C^a(t)\Big), \tag{3}$$

where A_c is the surface area of the cornea, f_c represents the fraction of A_c occupied by the diffusional route considered and V_a is the distribution volume of solute in the anterior chamber.

Equations (1), (2) and (3) are coupled with the initial conditions

$$C^g(x, 0) = C^{0g}, \ C^b(x, 0) = C^{0b}, \ x \in [-\ell_1, 0], \tag{4}$$

$$C^c(x,0) = 0,\ x \in [0,\ell_1], \tag{5}$$

$$C^a(0) = 0, \tag{6}$$

and the boundary conditions

$$\frac{\partial C^g}{\partial x}(-\ell_1,t) = 0, t > 0, \tag{7}$$

$$D_g f_g A_g \frac{\partial C^g}{\partial x}(0,t) = D_c f_c A_c \frac{\partial C^c}{\partial x}(0,t), t > 0, \tag{8}$$

$$C^g(0,t) = K_{g,c} C^c(0,t), t > 0, \tag{9}$$

$$-D_c f_c A_c \frac{\partial C^c}{\partial x}(\ell_2,t) = K_{c,a}\Big(C^c(\ell_2,t) - C^a(t)\Big), t > 0. \tag{10}$$

In (8) f_g represents the fraction of the lens surface A_g that is occupied by the diffusional route. The constants $K_{g,c}$ (9) and $K_{c,a}$ (10) represent respectively the quotient of the distribution coefficient in the lens and the cornea ($K_{g,c}$) and in the cornea and the anterior chamber ($K_{c,a}$).

3. Drug concentration in the anterior chamber

Equations (1)-(3) coupled with initial conditions (4)-(6) and boundary conditions (7)-(10) are solved using Laplace transforms.

Let us represent by $\overline{X}$ the Laplace transform of X. From (1), (4) we have

$$\begin{cases} -C^{0g} + p\overline{C^g} = D\dfrac{\partial^2 \overline{C^g}}{\partial x^2} + C^{0b} - p\overline{C^b} \\ \\ -C^{0b} + p\overline{C^b} = \lambda(\overline{C^g} - \overline{C^b}). \end{cases} \tag{11}$$

Computing C^b from the second equation in (11) and replacing in the first one we obtain

$$D\frac{\partial^2 \overline{C^g}}{\partial x^2} - \frac{p(p+2\lambda)}{p+\lambda}\overline{C^g} = -C^{0g} - C^{0b}\frac{\lambda}{p+\lambda},$$

which has the general solution

$$\overline{C^g}(x,p) = F_1 e^{\alpha_1 x} + F_2 e^{-\alpha_1 x} + \frac{(p+\lambda)C^{0g} + \lambda C^{0b}}{p(p+2\lambda)}, \tag{12}$$

where F_1, F_2 are constants to be computed and α_1 is defined by

$$\alpha_1 = \sqrt{\frac{p(p+2\lambda)}{D_g(p+\lambda)}}. \tag{13}$$

From (2) and (5) we obtain for $\overline{C^c}(x,p)$ the following expression

$$\overline{C^c}(x,p) = B_1 e^{\alpha_2 x} + B_2 e^{-\alpha_2 x}, \tag{14}$$

where B_1, B_2 are constants to be computed and α_2 is defined by

$$\alpha_2 = \sqrt{\frac{p+K_c}{D_c}}. \tag{15}$$

From (3) and (6) we get

$$(p + \frac{Cl_a}{V_a})\overline{C^a}(p) = -\frac{D_c f_c A_c}{V_a}\frac{\partial \overline{C^c}}{\partial x}(\ell_2, p). \tag{16}$$

As from (10) we have

$$-D_c f_c A_c \frac{\partial \overline{C^c}}{\partial x}(\ell_2, p) = K_{c,a}\Big(\overline{C^c}(\ell_2, p) - \overline{C^a}(p)\Big), \tag{17}$$

we conclude from (16)

$$\overline{C^a}(p) = \frac{K_{c,a}}{V_a p + Cl_a + K_{c,a}}\Big(B_1 e^{\alpha_2 \ell_2} + B_2 e^{-\alpha_2 \ell_2}\Big). \tag{18}$$

We establish in what follows a linear system for the coefficients F_1, F_2, B_1, B_2 : As from (7) we have

$$\frac{\partial \overline{C^g}}{\partial x}(-\ell_1, p) = 0$$

we obtain from (12)

$$F_1 e^{-\alpha_1 \ell_1} - F_2 e^{\alpha_1 \ell_1} = 0. \tag{19}$$

Analogously, as from (9) we have

$$\overline{C^g}(0,p) = K_{g,c}\overline{C^c}(0,p),$$

we obtain from (12) and (14)

$$F_1 + F_2 - K_{g,c}(B_1 + B_2) = -\frac{(p+\lambda)C^{0g} + \lambda C^{0b}}{p(p+2\lambda)}. \tag{20}$$

Condition (8) implies that

$$D_g f_g A_g \frac{\partial \overline{C^g}}{\partial x}(0,p) = D_c f_c A_c \frac{\partial \overline{C^c}}{\partial x}(0,p)$$

which combined with (12) and (14) allow us to obtain

$$D_g f_g A_g \alpha_1 \Big(F_1 - F_2\Big) - D_c f_c A_c \alpha_2 \big(B_1 - B_2\big) = 0. \tag{21}$$

Finally from (14), (17) and (18) we establish

$$-R_1 e^{\alpha_2 \ell_2} B_1 + R_2 e^{-\alpha_2 \ell_2} B_2 = 0, \tag{22}$$

where

$$R_1 = D_c f_c A_c \alpha_2 + K_{c,a} \frac{V_a p + Cl_a}{V_a p + Cl_a + K_{c,a}}$$

and

$$R_2 = D_c f_c A_c \alpha_2 - K_{c,a} \frac{V_a p + Cl_a}{V_a p + Cl_a + K_{c,a}}.$$

Solving linear system (19)-(22) and replacing in (18) the parameters B_1 and B_2 we obtain

$$\overline{C^a}(p) = \frac{1}{g(p)} \Big(K_{c,a} \sqrt{D_g D_c} A_g A_c f_g f_c \sqrt{(p + k_c)} \Big((p+\lambda) C^{0g} + \lambda C^{0b} \Big) \Big), \tag{23}$$

where

$$g(p) = p(p + 2\lambda) K_{g,c} \sqrt{D_g} A_g f_g S_1(p)$$

$$+ \sqrt{p(p+\lambda)(p+2\lambda)(p+K_c)} \sqrt{D_c} A_c f_c \coth(\alpha_1 \ell_1) S_2(p)$$

and

$$S_1(p) = A_c f_c \sqrt{D_c} \sqrt{p + K_c} \cosh(\alpha_2 \ell_2)(V_a p + CL_a + K_{c,a})$$

$$+ K_{c,a} \sinh(\alpha_2 \ell_2)(V_a p + Cl_a),$$

$$S_2(p) = A_c f_c \sqrt{D_c} \sqrt{p + K_c} \sinh(\alpha_2 \ell_2)(V_a p + Cl_a + K_{c,a})$$

$$+ K_{c,a} \cosh(\alpha_2 \ell_2)(V_a p + Cl_a)$$

and α_1, α_2 are defined respectively by (13) and (15).

To prove the existence of $C^a(t)$ it is sufficient to point out that

$$\lim_{p \to +\infty} \overline{C^a}(p) = 0$$

and

$$\lim_{p \to +\infty} p\overline{C^a}(p) = 0$$

hold.

4. Simulation of the drug concentration in the anterior chamber

Following [1] we compute from (23) an approximation for $C^a(t)$ defined by

$$C^a(t) \simeq \frac{1}{T} e^{\gamma t} \Big(\frac{1}{2} \overline{C^a}(\gamma) + \sum_{n=1}^{\infty} Re\Big(\overline{C^a}(\gamma + \frac{in\pi}{T}) e^{\frac{in\pi t}{T}} \Big) \Big), \qquad (24)$$

for $t \in (0, 2T)$, where $\gamma = \alpha - \dfrac{ln(E_r)}{2T}$ and with α representing a constant larger than

$$\max\{Re(P) : P \, \text{is a pole of} \, \overline{C^a}(s)\}$$

and E_r is a tolerance error.

In the simulations presented we consider a therapeutical lens loaded with nanoparticles studied in [3] characterized by the parameters presented in Table 1.

Symbol	Definition (unities)	Numerical value
C^{0g}	initial drug concentration in the hydrogel (g/cm^3)	0.28×10^{-3}
C^{0b}	initial drug concentration in the nanoparticles (g/cm^3)	0.05102×10^{-3}
ℓ_1	lens thickness (mm)	0.8
D_g	diffusion coefficient of the drug in the hydrogel (cm^2/min)	2×10^{-6}
λ	transfer coefficient	2×10^{-4}

Table 1: Parameters characterizing the therapeutical lens loaded with nanoparticles ([3]).

The parameters characterizing the anatomical and physiological human eye were considered in [2], [14] and they are presented in Table 2.

Symbol	Definition (unities)	Numerical value
$K_{c,a}$	quotient of the distribution coefficient in the cornea	10
K_c	metabolic consumption drug coefficient in the cornea	1.0713×10^{-5}
ℓ_2	cornea thickness (mm)	0.5
V_a	distribution volume of solute in the anterior chamber (μl)	$150 - 3000$
Cl_a	clearence in the anterior chamber ($\mu l/min$)	$1 - 30$
D_c	diffusion coefficient in the cornea (cm^2/s)	5.74×10^{-6}
A_c	surface area of the cornea	0.9
f_c	fraction of the cornea surface occupied by the diffusional route	1

Table 2: Parameters characterizing the anatomical and physiological human eye ([2], [14]).

The values of D_c and K_c presented in Table 2 are an average of the corresponding values in the epithelium, stroma and endothelium for a lipophilic drug. In the simulations we considered $A_g = 1$(surface area of the lens) $K_{g,c} = 1$(quotient of the distribution coefficient in the lens and the cornea) and $f_g = 0.75$ (fraction of the lens surface occupied by the diffusional route).

In what concerns the numerical approximation for the Laplace inverse $C^a(t)$ we took $E_r = 10^{-6}, \alpha = 0.001, T = 10^4$.

In Figure 3 we plot the drug concentration in the anterior chamber for different values of the distribution volume of solute. An increase of such volume implies a decrease of the maximum drug concentration. However for large times the drug concentration appears as an increasing function of V_a. A possible explanation for this fact is given by equation (10). In fact the lower is C^a, the higher is the flux from the cornea, which can justify the large time behaviour of the model.

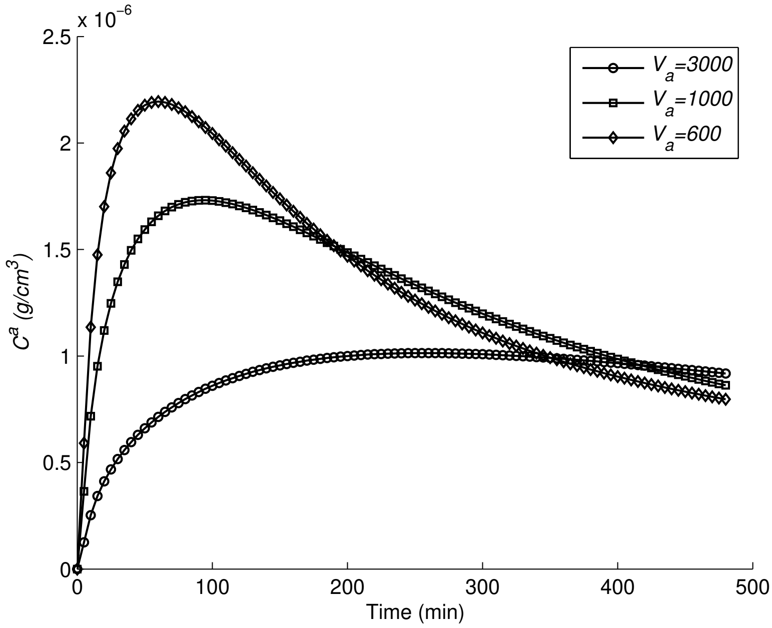

FIGURE 3. Dug concentration in the anterior chamber, C^a, for different values of the distribution volume of solute.

The dependence of C^a on the diffusion coefficient of the drug in the contact lens is illustrated in Figure 4. As the drug diffusion in the lens increases, an increasing of the drug concentration in the anterior chamber is observed.

An increasing of the drug clearance in the anterior chamber produces a decreasing of the drug concentration in this compartment. This behavior is illustrated in Figure 5

The influence of the fraction of the lens surface occupied by the diffusional route on the behavior of the drug concentration in the anterior chamber is illustrated in Figure 6. As this factor increases an increasing of the dug concentration in the anterior chamber is observed.

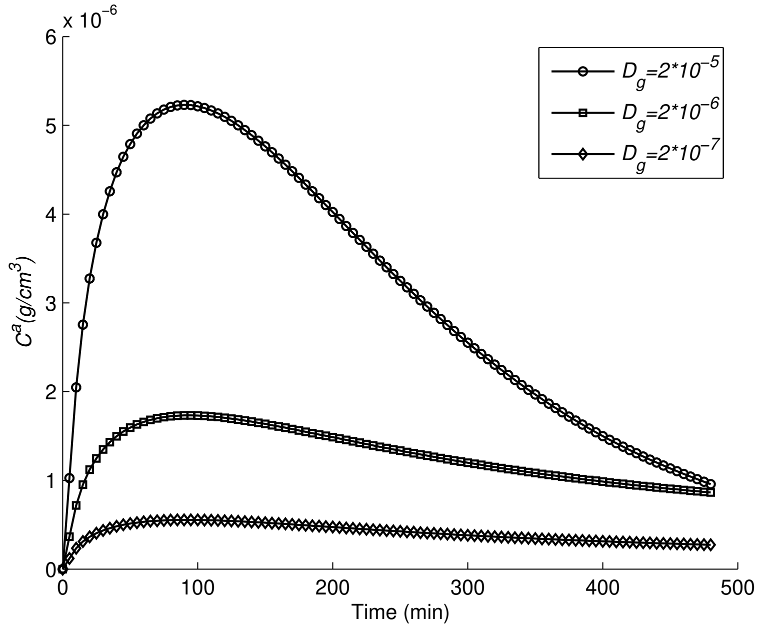

FIGURE 4. Drug concentration in the anterior chamber C^a for different values of the diffusion coefficient in the lens.

5. Topical administration versus ophthalmic lens

In what follows we compare numerically the drug concentration in the anterior chamber when a drop and a ophthalmic lens are used in drug administration. As previously mentioned we did not considered the cornea divided in epithelium, stroma and endothelium. The same assumption is considered in the mathematical model for topical administrations introduced in [14] and considered later in [2]. Using the previous assumption the evolution of a drug in the anterior chamber is defined by

$$\frac{dC_f}{dt} = \frac{D_c f_c A_c \frac{\partial C^c}{\partial x}(0,t) - SC_f}{V_H + V_i e^{-K_d t}}, \tag{25}$$

where C_f denotes the drug concentration in the tear film and S represents the (fixed) lacrimal secretion rate. In (25) k_d denotes the drainage constant, V_L and V_i represent the normal lacrimal volume and the initial tear volume after an instillation of drug. The previous equation is coupled with the differential equations (2), (3), initial conditions (5), (6),

$$C_f(0) = C_f^0, \tag{26}$$

and with the boundary condition (10). The coupling between the drug evolution in the tear film and in the cornea is defined by

$$-D_c f_c A_c \frac{\partial C^c}{\partial x}(0,t) = K_{c,a}\Big(C_f(t) - C^c(0,t)). \tag{27}$$

In Figure 7 we plot the time evolution of drug concentration in the anterior chamber when a drop (C^a_{drop}) and a lens (C^a_{lens}) are used in drug administration. In the computation of

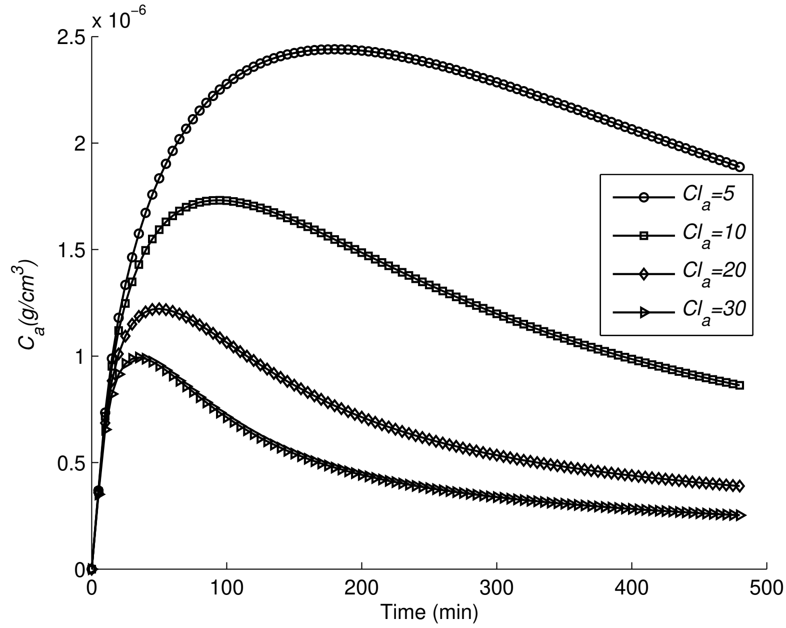

FIGURE 5. Drug concentration in the anterior chamber C^a for different values of the clearance in the anterior chamber.

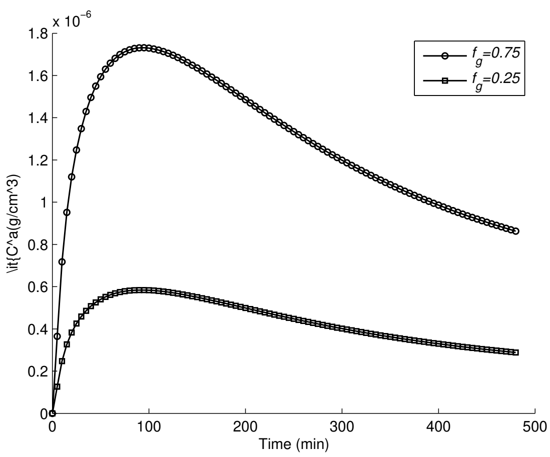

FIGURE 6. Drug concentration in the anterior chamber C^a for different values of the of the lens surface occupied by the diffusional route.

$C^a_{drop}(t)$ the following parameters

$$k_d = 1.45(min^{-1}),\ C_f^0 = 0.5 \times 10^{-3} g/cm^3,\ V_L = 7\mu L, V_i = 10\mu l,\ S = 1.2\mu l/min$$

are used.

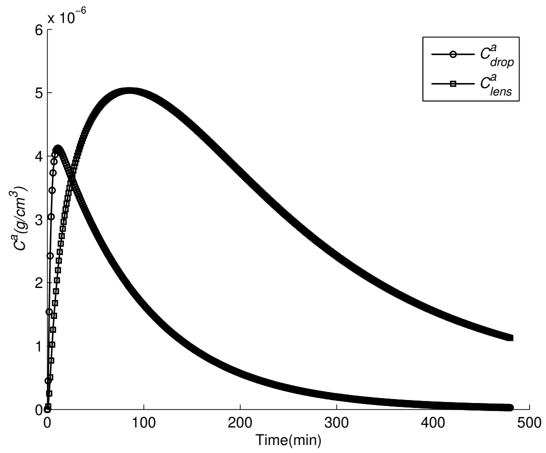

Figure 7. Evolution of the drug concentration in the anterior chamber when a drop (C^a_{drop}) and a lenses (C^a_{lens}) are used in the eye drug administration.

From Figure 7 we conclude that the use of contact lens leads to a higher concentration of the drug in the anterior chamber during a larger period of time than topical administrations. We observe that after the first hour of the application of the eye drop the maximum concentration is reached in the anterior chamber. After this time the drug concentration decreases rapidly approaching zero after five hours. This behavior is not observed when we use the polymeric lens. In fact in this case after five hours the drug concentration is larger than half of the maximum of the drug concentration reached by eye drops. Moreover, after eight hours the drug concentration in the anterior chamber is nearly one quarter of the maximum attained when a drop is used.

6. Conclusions

Several authors proposed the use of ophthalmic contact lenses to replace the traditional topically administration ([5], [6], [10]). The evolution in time of the drug concentration in the anterior chamber is crucial for the treatment of the majority of diseases of the anterior segment of the eye. Mathematical models are the only tools available to predict such evolution.

In this paper a mathematical model to predict the behaviour of drug mass and concentration in the anterior chamber is proposed. Drug is delivery from dispersed and encapsulated nanoparticles on a therapeutical contact lens. The theoretical expression for the drug concentration in the anterior chamber was obtained which can be used to study the qualitative properties of the model.

The evolution in time of the drug concentration in the anterior chamber C^a and its dependence on several parameters of the model were simulated. Such evolution was also numerically compared with the drug concentration in the anterior chamber when a eye drop is used. For the contact lens, highest values of C^a were observed during a larger time period.

We remark that topical delivery eye drops leads to a short residence time of the drug because most part of the applied drug is lost due to tear drainage.

If a lens is used as an ophthalmic drug delivery system then the released drug remains entrapped in the interface tear film between the contact lens and the cornea ([10]). This fact leads to an increase of the drug residence time. Moreover the total amount of drug contained in the ophthalmic lens with nanoparticles is greater than the corresponding value for an eye drop.

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