Pré-Publicações do Departamento de Matemática
Universidade de Coimbra
Preprint Number 09–20

# SUSTAINED DRUG RELEASED FROM CONTACT LENS

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Abstract: This paper focuses on ophthalmic drug release from a loaded copolymer: the drug is dispersed in the polymeric matrix and entrapped in particles. The copolymer is based in 2-hydroxyethyl methacrylate co-methacrylic acid and silicone is used to prepare the loaded particles. A mathematical model to simulate the drug release is proposed and a qualitative analysis is performed. Experimental results are compared with simulation results. Contact lens made from the presented copolymer are expected to deliver drug at therapeutical levels for a few days.

Keywords: Ophthalmic drug delivery, Contact lenses, p-(HEMA/MAA), Reaction-diffusion equation, Qualitative behaviour, Numerical simulation, Experimental results.

## 1. Introduction

Topical administration of eye drops into the anterior fornix of the conjunctiva is by far the most common route of ocular drug delivery. The conjunctival sac has a volume of approximately $15 - 30\mu l$, the natural tear film volume is $7 - 8\mu l$ and the tear turn over at approximately 16% per minute during a normal blink rate of $15 - 20$ blinks per minute. When a drop is instilled into the eye it is diluted by the lacrimal secretion and 95% is cleared by the tear fluid, highly dependent on environmental conditions particularly temperature and humidity. Drug can also be absorbed in significant concentrations into the circulation by the subconjunctival, stroma and, mainly, via nasal and nasopharyngeal mucosa. As a consequence topical administration is very inefficient because a substantial volume of administered drug is lost, only about 5% penetrates though the cornea to reach the anterior chamber. Consequently, the limitation of the efficiency of eye drops is its short residence time in the tear film and consequently the rapid variation of drug concentration. Moreover serious side effects can occur (for example undesirable heart effects with beta-blockers, widely used to treat glaucoma) ([5], [10]).

Received June 23, 2009.
This work was partially supported by the project PTDC/MAT/74548/2006.

To avoid drug loss, side effects and also to improve the efficiency of drug delivery, many researchers have proposed the use of therapeutical contact lenses as a vehicle to deliver ophthalmic drugs. The main advantage of this method is the possibility of controlling the drug delivery by means of the use of polymeric matrices designed to achieve pre-defined performances.Several techniques have been proposed in the literature ([4],[6], [9]). Without being exhaustive we can mention the use of

(i) soaked simple contact lenses;

(ii) compound contact lenses with a hollow cavity;

(iii) entrapment of proteins, cells and drugs by polymerization of hydrogel monomers in the presence of species to be entrapped or by direct dissolution.

As far as soaking a lens in a drug is concerned even if the method is more efficient than the use of eye drops some disadvantages still occur. We mention the limitation of the drug loading imposed by the solubility of the drug in the matrix and a short delivery period of time. In fact the delay in the delivery is only caused by the diffusion in the polymeric gel matrix and this barrier seems not to be enough to increase the residence time in the precorneal area. In the case of the simultaneous polymerization techniques previously mentioned the main disadvantage is related to the possibility that drug molecules loose their characteristics during the process.

To overcome these disadvantages some authors proposed recently to encapsulate drugs in particles which are entrapped in polymeric matrices [2], [3].This technique not only avoid the lose of therapeutical properties of drug molecules during polymerization but also creates an additional barrier to drug delivery. The drug transport within the contact lens have in this case two causes of resistance: the diffusion through the particles and the diffusion through the polymeric matrix. As a consequence the drug release attains in this case several days. The delivery rates can be tailored to a specific treatment by controlling some of the variables of the problem as the particle and drug loading as well as the diffusion coefficient of the matrix and the mass transfer coefficient across the particle surface.

In a recent paper Gulsen and Chauhan ([3]) focussed on drug filled particles entrapped in a p-HEMA gel. The authors present therein a complete study of chemical and physical properties of the hydrogel matrix loaded with four types of particles. Two of these were opaque - due to the desastibilization or aggregation of particles- and consequently can not be used to design ophthalmic contact lenses. Two other hydrogels exhibited better transparency

properties: to obtain 79% transparency, value close to the 87% transmittance value of the pure p-HEMA gels, a silica shell was deposited on the microemulsion drops. However some drawbacks are still present in these loaded particles hydrogels:

(i) If the particles are not stabilized with the silica shell, there is a initial burst release which is an increasing function of the initial drug load. A small initial burst release is obtained only for small loads that can be inefficient for therapeutical needs;

(ii) When the particles are stabilized with a silica shell there is a delay period that can attain three or four days during which there is practically no drug delivery.

To circumvent the above drawbacks in this paper is proposed to use silicone to encapsulate an ophthalmic drug - flurbiprofen. The drug delivery from a copolymer film prepared using 2-hydroxyethyl methacrylate co-methacrylic acid (p-(HEMA/MAA)) is studied. The loading of a p-(HEMA/MAA) copolymer is made dispersing drug in the polymeric matrix dissolving the drug directly in the mixture of monomers and dispersing silicone particles encapsulating the ophthalmic drug in the polymeric matrix.

The experimental work is completed by a mathematical model with a closed form solution which predicts, for every time t, the total amount of drug released by the contact lens. The model is represented by a system of partial differential equations, coupled with appropriate initial and boundary conditions, which describe the mechanisms of diffusion and transference in the polymeric matrix loaded with particles. The system was solved by using Laplace transforms. The closed form solution can be used not only to predict the total amount of delivered drug but also as a tool to design new polymeric matrices that exhibit a certain pre-defined mass release profile.

In Section 2 the experimental work is presented. In Section 3 the mathematical model is established and the closed form solution is obtained. An analysis of this solution leads to several qualitative conclusions concerning the release profile of the therapeutical lenses based in the p-(HEMA/MAA) copolymer. In Section 4 the mathematical predictions are compared with the experimental profiles. Finally in section 5 some conclusions are presented.

# 2. Experimental work

## 2.1. Materials and methods.

**2.1.1.** *Materials.* In order to synthesize the copolymer the monomers 2-hydroxyethyl methacrylate [Aldrich (HEMA, 97%, CAS $[868-77-9]$)], and methacrylic acid, [Fluka (MAA, $\geq$ 98%, CAS $[79-41-4]$)] were used. Ethylene glycol dimethacrylate was acquired from Aldrich (EGDMA, 98%, CAS $[97-90-5]$), and azobisisobutyronitrile from Fluka (AIBN, $\geq$ 98%, CAS $[78-67-1]$). The monomers were purified with an alumina column.

The microemulsion was prepared by using triethoxy(octyl)silane (TEOS, $\geq$ 97.5%, CAS $[2943-75-1]$ ), decane (99%, CAS $[124-18-5]$), hydrochloric acid (HCl, 37%, CAS $[7647-01-0]$) from Aldrich, and Brij 35 from Acros Organics (CAS $[9002-92-0]$).

The ophthalmic drug employed was flurbiprofen, (97%, Sigma, CAS $[5104-49-4]$) and the drug release media was phosphate buffered saline solution (PBS, pH= 7.4, Sigma).

**2.1.2.** *Synthesis methods.*

- *Preparation of the silicone particles:*
  In order to prepare the particles, the following procedure was used ([3]). $1g$ of Brij 35 was dissolved in $10g$ of water. This solution was heated to $60^0C$ and stirred at $700rpm$. A second solution was prepared by dissolving $0.10ml$ of TEOS and $2mg$ of flurbiprofen in $0.15ml$ of decane. Afterwards, this solution was added to the previous mixture, maintaining the temperature and stirring, until the mixture became clear. Then, $10ml$ of 1N HCl solution was added, and the mixture was kept at $60^0C$, for 6 hours, with continuous stirring.
- *Preparation of the copolymer 2-hydroxyethyl methacrylate co-methacrylic acid:*
  In order to prepare the copolymer, $9.5g$ of HEMA, $0.5g$ of MAA, $0.04g$ of EGDMA (cross-linker) and $30mg$ of AIBN (initiator) were mixed thoroughly, in a beaker. Into the previous solution were added $3ml$ of distilled water. This final solution was degassed by bubbling it with nitrogen. The copolymers with drug in the polymeric matrix were synthesized by dissolving flurbiprofen ($1mg$) directly into the mixture of monomers.

The solution was placed between two plates with teflon that were separated by a silicone spacer ($1mm$ of thickness). The polymerization reaction was performed at $60^0C$, during 24 hours. This film was cut into circular samples with $1cm$ of diameter.

- *Preparation of the copolymer 2-hydroxyethyl methacrylate co-methacrylic acid containing the silicone particles:*

  To prepare the p-(HEMA/MAA) copolymers containing the silicone particles, the procedure was the same described previously, but the water added to the solution was replaced by the microemulsion containing silicone particles.

**2.1.3.** *Copolymers characterization.*

- *Water content:*

  Equilibrium water content assays were performed by placing a sample of p-(HEMA/MAA) copolymer in $10ml$ of PBS at $37^0C$. After 24 hours, the water on the surface was removed, and the sample was weighed until constant weight. These samples were dried, previously, in a vacuum oven at $25^0C$. All the experiments were carried out in triplicate.
- *SEM studies:*

  In order to determine the structure of the copolymer, and to identify the particles, we performed scanning electron microscopy (SEM) (Jeol, JSM-5310 model, Japan), at $15kV$. We analyzed p-(HEMA/MAA) copolymer with and without particles, these samples were dried and coated with gold.

**2.1.4.** *Drug release studies.* The drug release assays for p-(HEMA/MAA) samples were carried out in a conical tube containing $10ml$ of PBS. At predefined times, an aliquot of $1ml$ was taken replacing it by the same volume of PBS. The tube was placed in a thermal bath at $37^0C$, with continuous stirring.

The samples drug concentration was determined by Ultraviolet Spectroscopy (UV-VIS Spectrophotometer, JASCO, V-530 model) at a wavelength of $247.5nm$.

Release assays were performed for the 3 types of samples, and also for the control samples. The control samples were used to correct any release that it is not drug, such as unreacted monomer, by subtracting their value of absorbance.

### 2.2. Results.

**2.2.1.** *Water content.* The equilibrium water content in PBS at $37^0C$ was determined by the ratio of the weight of water in the copolymer to the total weight of the copolymer (hydration equilibrium).

The percentage of water content of the p-(HEMA/MAA) copolymer was $67.8 \pm 2\%$. This percentage was between the values of the water content required for contact lenses.

**2.2.2.** *SEM images.* In Figure 1 we show the cross section of a pure copolymer with a magnification of $5000 \times$ . As it can be observed, the surface presents uniformity/homogeneity.

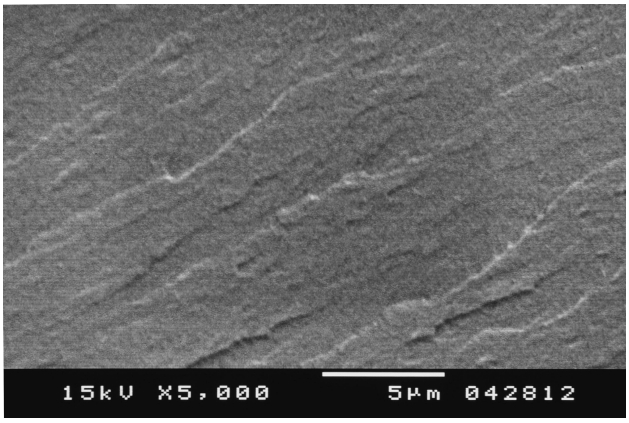



FIGURE 1. SEM image of the cross section of a pure copolymer, at $5000\times$ magnification.

The SEM image of the cross section of the copolymer with microemulsion (Figure 2) disclosed the existence of particles entrapped in the polymeric matrix with multiple sizes, which can reach, approximately, $100nm$ of minimum diameter. During the SEM analysis, we also verified that the particles were not distributed homogeneously in the copolymer.

## 3. Mathematical model

In this section we present a mathematical model to describe the drug release of a contact lens prepared using the p-(HEMA/MAA) copolymer loaded with the therapeutical drug dispersed in the polymeric matrix and in the silicone particles. We consider the schematic illustration of the particle laden therapeutical lens represented in Figure 3. In order to simplify the presentation

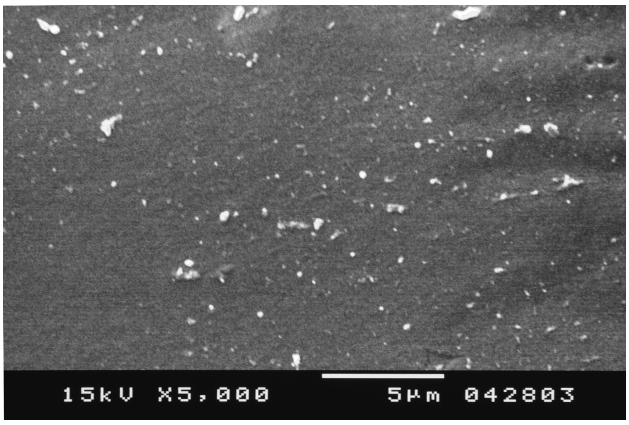



FIGURE 2. SEM image of the cross section of a copolymer with particles, at 5000× magnification.

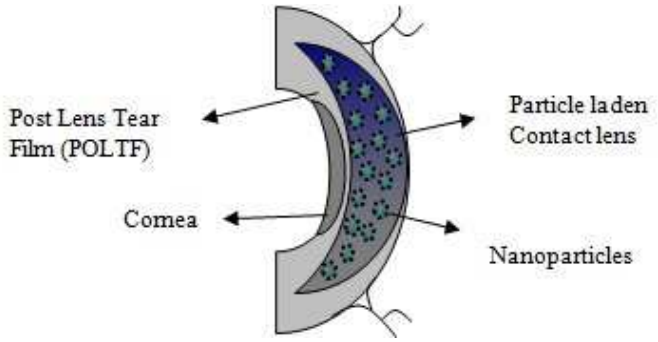



FIGURE 3. Schematic illustration of the ophthalmic lens inserted in the eye.

we assume that the drug leaving the lens is immediately removed. More realistic assumptions will be considered in Section 4. The mathematical model is characterized by a system of partial differential equations coupled with initial and boundary conditions. The expressions of the concentrations in the polymeric matrix and in the silicone particles will be obtained using Laplace transforms. The dependence of the behaviour of such concentrations on the parameters of the model will be analyzed in this section.

The lens has a width of $2\ell$ and is completely immersed in water. During the experiment a mechanism of removal of the released drug was used. The drug entrapped in the complex formed by the hydrogel and particles is described

by

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

where $C^g$ represents the drug concentration in the gel, $C^b$ the drug concentration in the particles, D the diffusion coefficient of the drug in the gel and $\lambda$ stands for the product of the mass transfer coefficient for drug transport across the particle surface and the ratio between the surface and the volume of particles. System (1) is completed with the initial conditions

$$\begin{cases} C^g(x,0) = C^{0g} \\ C^b(x,0) = C^{0b}, \end{cases} \tag{2}$$

where $C^{0g}$ is the initial concentration in the gel and the $C^{0b}$ the initial concentration inside the particles. Along with (1) and (2) the boundary conditions

$$\begin{cases} C^g(-\ell, t) = C^E \\ \dfrac{\partial C^g}{\partial x}(0,t) = 0, \end{cases} \tag{3}$$

are also considered. We note that the first condition in (3) means that the external drug concentration is constant. From an experimental point of view this condition represents the fact that the concentration of drug in water is kept constant by means of a renewal mechanism that takes place at fixed interval of times. From an ophthalmic point of view a boundary condition of type

$$D\frac{\partial C^g}{\partial x}(-\ell, t) = \alpha(C^g(-\ell, t) - C^E),$$

where $\alpha$ stands for a transference coefficient, is a more accurate description of the clearance mechanisms in the precorneal area. The second condition in (3) assumes symmetry in the drug concentration within the lens property. This property is expected to be satisfied in the experiments carried on.

To solve(1) we use Laplace transforms in time. Let us represent by $\overline{X}$ the Laplace transform of $X$. From (1), (2) we have

$$\begin{cases} -C^{0g} + p\overline{C^g} = D\dfrac{d^2\overline{C^g}}{dx^2} + C^{0b} - p\overline{C^b} \\ -C^{0b} + p\overline{C^b} = \lambda(\overline{C^g} - \overline{C^b}). \end{cases} \tag{4}$$

Computing $C^b$ from the second equation in (4) and replacing in the first one we obtain

$$D\frac{d^2\overline{C^g}}{dx^2} - \frac{p(p+2\lambda)}{p+\lambda}\overline{C^g} = -C^{0g} - C^{0b}\frac{\lambda}{p+\lambda}, \tag{5}$$

which has the general solution

$$\overline{C^g} = F_1 e^{k_1 x} + F_2 e^{k_2 x} + \frac{(p+\lambda)C^{0g} + \lambda C^{0b}}{p(p+2\lambda)}, \tag{6}$$

where $F_1, F_2$ are constants to be computed and $k_1, k_2$ are defined by

$$k_1, k_2 = \pm\sqrt{\frac{p(p+2\lambda)}{D(p+\lambda)}}. \tag{7}$$

**Remark 1.** *We note that from the second equation in (1) we have*

$$C^b = \lambda\int_0^t e^{-\lambda(t-\tau)}C^g(x,\tau)d\tau + e^{-\lambda t}C^{0b} \tag{8}$$

*and replacing in the first equation in (1) we obtain*

$$\frac{\partial C^g}{\partial t} = D\frac{\partial^2 C^g}{\partial x^2} - \lambda(C^g - \lambda\int_0^t e^{-\lambda(t-\tau)}C^g(x,\tau)d\tau) + \lambda e^{-\lambda t}C^{0b}. \tag{9}$$

*Using Laplace transform in this last equation and considering that the integral therein represents a convolution product we then have*

$$-C^{0g} + p\overline{C^g} = D\frac{\partial^2\overline{C^g}}{\partial x^2} - \lambda(\overline{C^g} - \frac{\lambda}{p+\lambda}\overline{C^g}) + \frac{\lambda}{p+\lambda}C^{0b} \tag{10}$$

*which leads to equation (5).*

As

$$\overline{C^g}(-\ell, t) = \frac{C^E}{p} \tag{11}$$

and

$$\frac{\partial\overline{C^g}}{\partial x}(0,t) = 0, \tag{12}$$

we can compute constants $F_1, F_2$ obtaining

$$\overline{C^g} = (\frac{C^E}{p} - \frac{(p+\lambda)C^{0g} + \lambda C^{0b}}{p(p+2\lambda)})\frac{\cosh(k_1 x)}{\cosh(k_1\ell)} + \frac{(p+\lambda)C^{0g} + \lambda C^{0b}}{p(p+2\lambda)}, \tag{13}$$

that is

$$\overline{C^g} = \frac{C^E(p+2\lambda) - C^{0g}(p+\lambda) - \lambda C^{0b}}{p(p+2\lambda)} \frac{\cosh(k_1 x)}{\cosh(k_1 \ell)} + \frac{(p+\lambda)C^{0g} + \lambda C^{0b}}{p(p+2\lambda)}. \quad (14)$$

To invert (14) we note that the first term in the right hand side is of form

$$\frac{f(x,p)}{g(p)},$$

where $f$ and $g$ can be seen as polynomials with an infinite number of factors more exactly

$$f(x,p) = (C^E(p+2\lambda) - C^{0g}(p+\lambda) - \lambda C^{0b})(1+\frac{4k_1^2x^2}{\pi^2})(1+\frac{4k_1^2x^2}{3^2\pi^2})(1+\frac{4k_1^2x^2}{5^2\pi^2})\ldots \quad (15)$$

and

$$g(p) = p(p+2\lambda)(1+\frac{4k_1^2\ell^2}{\pi^2})(1+\frac{4k_1^2\ell^2}{3^2\pi^2})(1+\frac{4k_1^2\ell^2}{5^2\pi^2})\ldots. \quad (16)$$

Following Crank [1], we then have

$$C^g = \sum_{n=0}^{\infty} \frac{f(x,a_n)}{g\prime(a_n)} e^{a_n t} + e^{-2\lambda t}(\frac{C^{0g} - C^{0b}}{2}) + (\frac{C^{0b} + C^{0g}}{2}), \quad (17)$$

where $a_n$, $n = 0, 1, \ldots$, represent the roots of $g(p) = 0$ which may be real or complex.

As

$$g(p) = p(p+2\lambda)\cosh(k_1\ell) \quad (18)$$

the roots are $p = 0, p = -2\lambda$ and also the roots of equation

$$\cosh(\sqrt{\frac{p(p+2\lambda)}{D(p+\lambda)}}\ell) = 0, \quad (19)$$

that is

$$\sqrt{\frac{p(p+2\lambda)}{D(p+\lambda)}} = \pm\frac{(2n+1)\pi i}{2\ell}, n = 0, 1, \ldots \quad (20)$$

which lead to

$$p = \frac{-8\lambda\ell^2 - D(2n+1)^2\pi^2 \pm \sqrt{(8\lambda\ell^2)^2 + D^2(2n+1)^4\pi^4}}{8\ell^2}, n = 0, 1, \ldots. \quad (21)$$

Let us compute $g^{'}(p)$. As

$$g^{'}(p) = (p+2\lambda)\cosh(k_1\ell) + p\cosh(k_1\ell) + p(p+2\lambda)senh(k_1\ell)(\frac{dk_1}{dp})\ell \quad (22)$$

we have

$$\begin{cases} g'(0) = 2\lambda \\ g'(-2\lambda) = -2\lambda \\ g^{'}(a_n) = a_n(a_n+2\lambda)(\pm i)(-1)^n(\frac{dk_1}{dp})\mid_{a_n}\ell \end{cases} \quad (23)$$

where $a_n$ are defined in (21). From (17) we then have

$$\begin{aligned} C^g(x,t) &= \sum_{n=0}^{\infty}(-1)^n D\cos(\frac{(2n+1)\pi x}{2\ell})\frac{b(a_n)(2n+1)\pi(a_n+\lambda)^2}{a_n(a_n+2\lambda)\ell^2(a_n^2+2\lambda^2+2a_n\lambda)}e^{a_nt} \\ &\quad +C^E \end{aligned} \quad (24)$$

where

$$b(a_n) = C^E(a_n+2\lambda) - C^{0g}(a_n+\lambda) - \lambda C^{0b}.$$

Considering that

$$\frac{a_n(a_n+2\lambda)}{D(a_n+\lambda)} = -\frac{(2n+1)^2\pi^2}{4\ell^2} \quad (25)$$

we can give $C^g$ the following form

$$C^g = C^E + \sum_{n=0}^{\infty}(-1)^{n+1}4\cos(\frac{(2n+1)\pi x}{2\ell})\frac{b(a_n)(a_n+\lambda)e^{a_nt}}{(2n+1)\pi(a_n^2+2\lambda^2+2a_n\lambda)}. \quad (26)$$

The total mass released during $t$ units of time, $M(t)$, is defined by

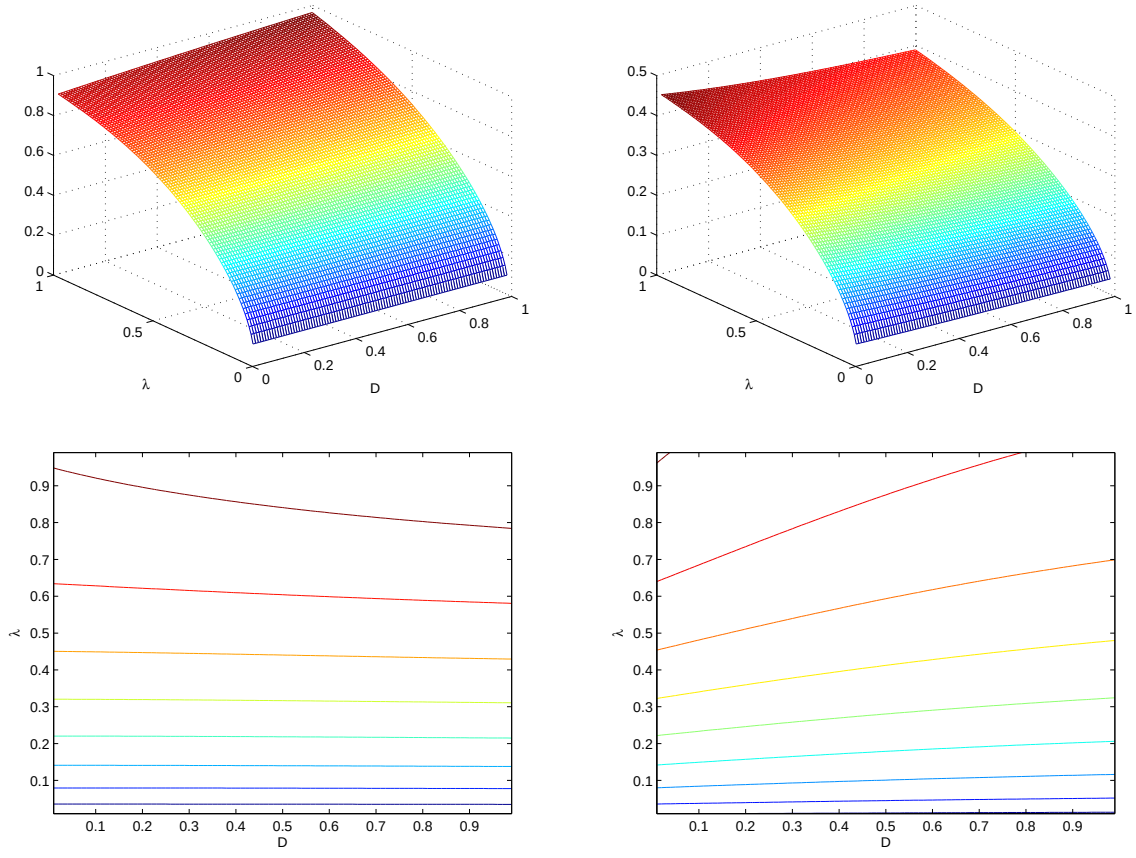
$$M(t) = -2D\int_0^t \frac{\partial C^g}{\partial x}(\ell,\tau)d\tau. \quad (27)$$

Computing $\dfrac{\partial C^g}{\partial x}(\ell,\tau)$ from (26) and replacing in (27) we have

$$M(t) = -\frac{4D}{\ell}\sum_{n=0}^{\infty}\frac{C^E(a_n+2\lambda) - C^{0g}(a_n+\lambda) - \lambda C^{0b}}{a_n(a_n^2+2\lambda^2+2a_n\lambda)}(a_n+\lambda)(e^{a_nt}-1). \quad (28)$$

The behaviour of $M(t)$ as function of the parameters $C^E, C^{0g}, C^{0b}$, $D$ and $\lambda$, characterizing the polymeric matrix and the drug, is considered in what follows.

In Figure 4 are exhibited 3D plots of the mass $M(t)$, for $t = 1, C^{0g} = 0.5, C^{0b} = 0.25$ and $C^E = 0, 0.25$. The corresponding level curves are also plotted in this figure. As expected, an increase of the exterior concentration implies a decreasing of the released mass.

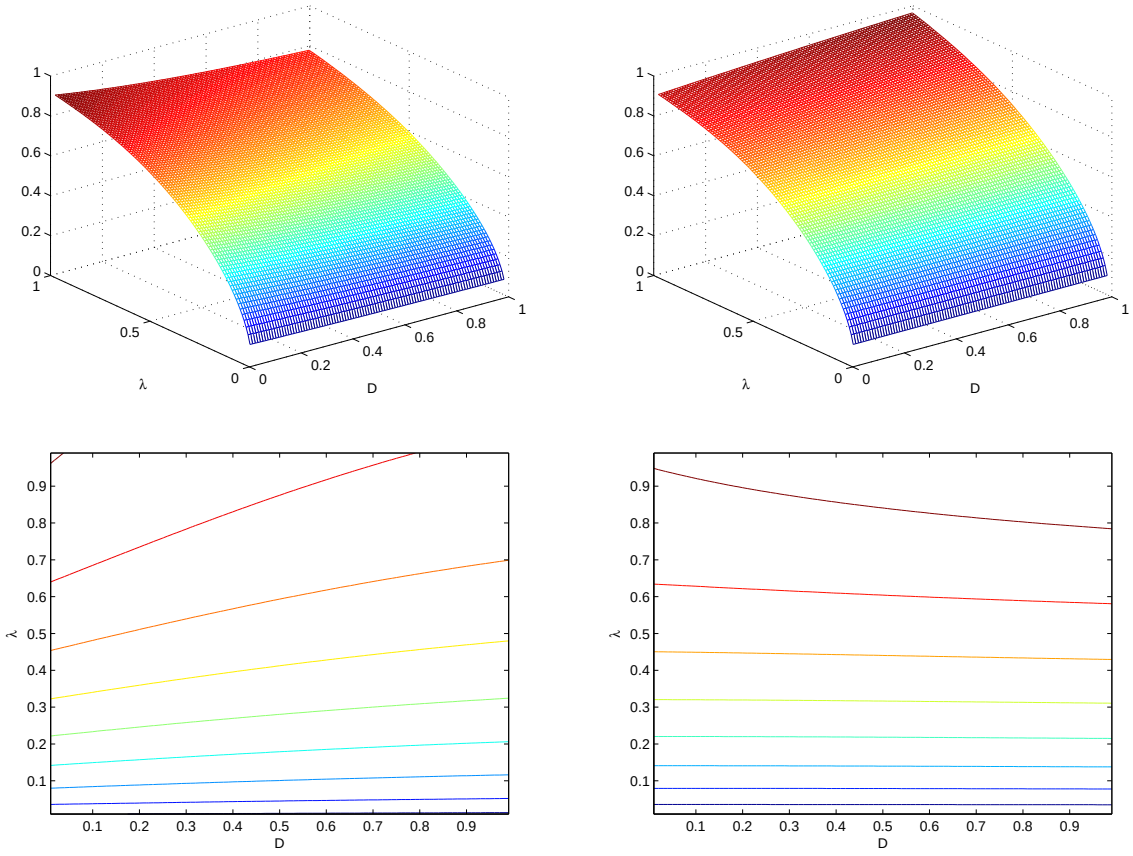



(a) (b)

FIGURE 4. The behaviour of M(t) as a function of $\lambda$ and $D$ for $C^E = 0$ ((a)) and $C^E = 0.25$ ((b)).

In Figure 5 we consider the behaviour of $M(t)$, for $t = 1, C^E = 0, C^{0g} = 0.5$, as function of $D$ and $\lambda$, for increasing values of $C^{0b}$. As expected such increasing leads to an increasing of the released mass.

Assuming now that $C^E, \lambda$ and $D$ are fixed we present in Figure 6 the plots and the level curves of M(t), for $t = 1, C^E = 0, \lambda = 0.01$, as function of $C^{0g}$ and $C^{0b}$ when $D$ increases. As $D$ increases the mass $M(1)$ also increases.




(a) (b)

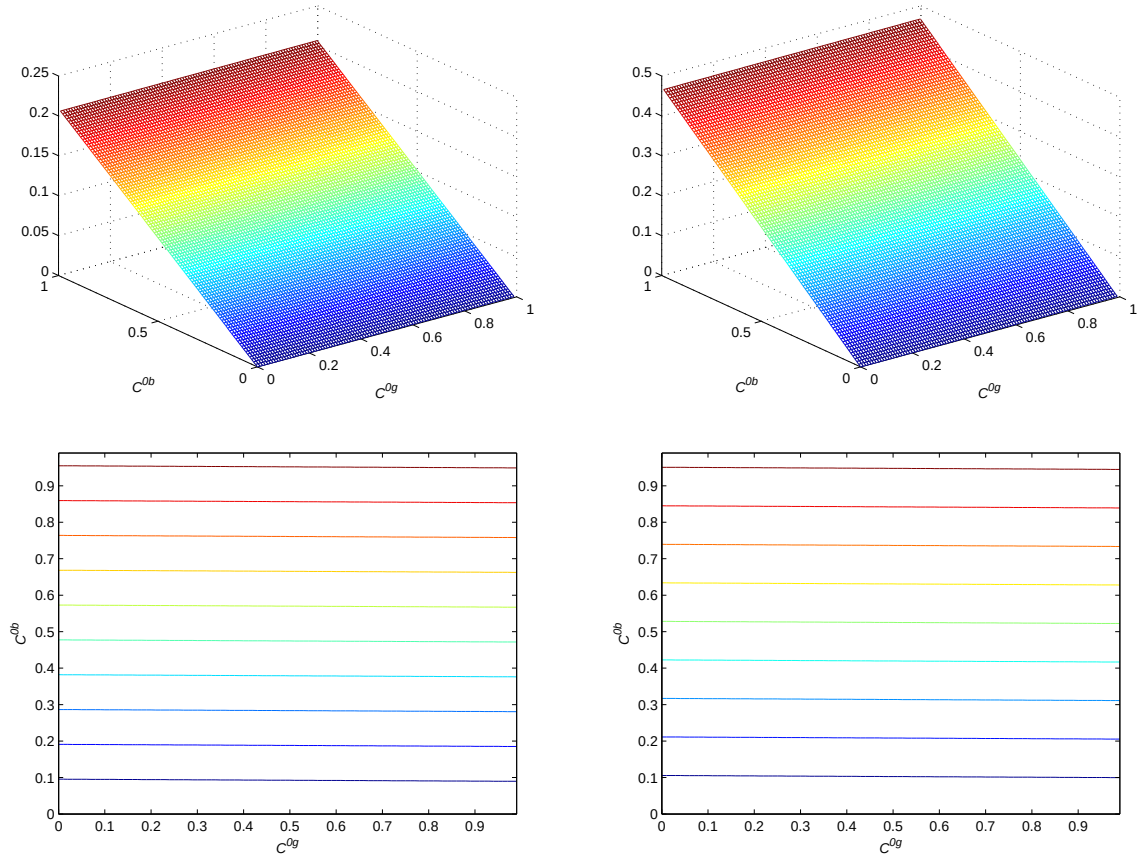
FIGURE 5. The behaviour of M(t) as function of $\lambda$ and $D$ for $C^{0b} = 0$ ((a)) and $C^{0b} = 0.25$ ((b)).

Let us now study the qualitative behaviour of $M(t)$ given by (28) in some particular cases:

($i$) *The initial drug concentrations in the gel and in the particles are the same*

In this case $C^{0g} = C^{0b}$ and we have from (28)

$$M(t) = \frac{4D}{\ell}(C^{0g} - C^E) \sum_{n=0}^{\infty} \frac{(a_n + 2\lambda)(a_n + \lambda)}{a_n[(a_n + \lambda)^2 + \lambda^2]}(e^{a_n t} - 1). \tag{29}$$




(a) (b)

FIGURE 6. The mass M(t) as a function of $C^{0b}, C^{0g}$ for $D = 0.01$ ((a)) and $D = 0.05$ ((b)).

Replacing (25) in (29) we can give M(t) the following form

$$M(t) = -\frac{D^2}{\ell^3}(C^{0g} - C^E)\sum_{n=0}^{\infty}\frac{(2n+1)^2\pi^2(a_n+\lambda)^2}{a_n^2[(a_n+\lambda)^2+\lambda^2]}(e^{a_n t}-1). \qquad (30)$$

As $a_n \leq 0$ we conclude from this last equation that, for each t, the total released mass is an increasing function of $C^{0g} - C^E$. We deduce from (30) that for $C^{0g} > C^E$, $M'(t) > 0$ and $M''(t) < 0$. It can be also established that $M'(0^+) = +\infty$. This behaviour can be observed in Figure 7, we plot $M(t)$ as function of $C^{0g} - C^E$ for $D = \lambda = 0.05$ for $C^{0g} = C^{0b} = 0.5$.

(*ii*) *The lens has no particles*

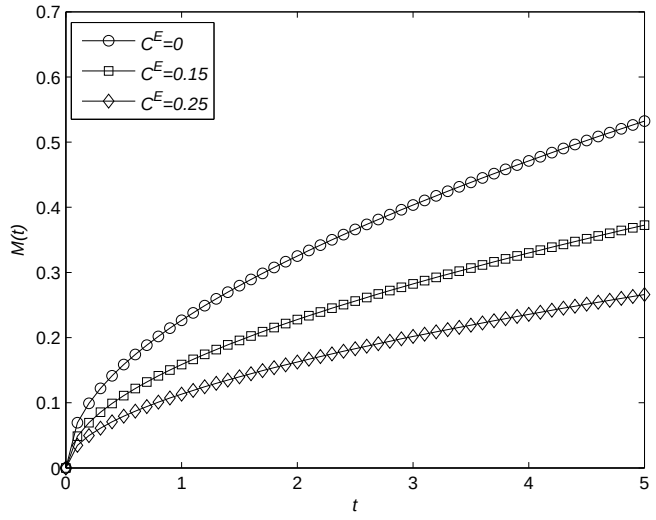



FIGURE 7. The mass $M(t)$ for $C^{0g} = 0.5, C^E = 0, 0.15, 0.25$.

Considering that in this case $\lambda = 0$ and $C^{0b} = 0$ we obtain from (28)

$$M(t) = \frac{4D}{\ell}(C^{0g} - C^E)\sum_{n=0}^{\infty}\frac{e^{a_n t} - 1}{a_n}. \tag{31}$$

Equation (31) represents the total mass released from a polymeric matrix in a diffusion process under boundary and initial conditions

$$\begin{cases} C^g(x,0) = C^{0g} \\ C^g(-\ell,t) = C^E \\ \dfrac{\partial C^g}{\partial x}(0,t) = 0. \end{cases} \tag{32}$$

From (31) we have $M'(t) > 0$ and $M''(t) < 0$ for $C^{0g} > C^E$. This behaviour is observed in Figure 8 where we plot the mass $M(t)$ for $D = 0.05, C^E = 0$ when $C^{0g} = 0.5, 0.75$.

(*iii*) *There is no drug in the polymeric matrix at t=0 and* $C^E = 0$

In this case we have $C^{0g} = 0$. From (28) we deduce

$$M(t) = \frac{4DC^{0b}}{\ell}\sum_{n=0}^{\infty}\frac{\lambda(a_n + \lambda)}{[(a_n + \lambda)^2 + \lambda^2]}\frac{e^{a_n t} - 1}{a_n}. \tag{33}$$

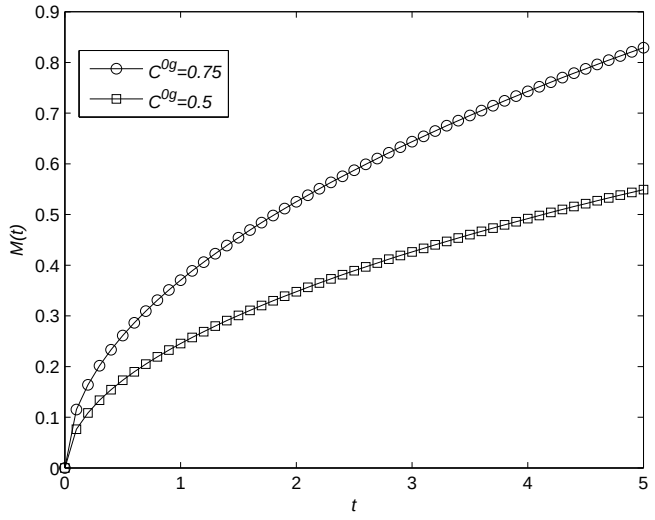



FIGURE 8. The mass $M(t)$ for $D = 0.05, C^E = 0, C^{0g} = 0.5, 0.75$.

In this case as

$$M''(t) = \frac{4DC^{0b}}{\ell} \sum_{n=0}^{\infty} \frac{\lambda a_n (a_n + \lambda)}{(a_n + \lambda)^2 + \lambda^2} e^{a_n t},$$

we cannot conclude the sign of the curvature. In fact $a_n \leq 0, n = 0, 1, \ldots,$ but $a_n + \lambda$ can be positive or negative, as we take the plus sign or the minus sign in the second order equation (25). Observing Figure 11 b we note that the plot of $M(t)$ is $S-$shaped with the sign of $M''(t)$ inverting for some $\bar{t} \in [5, 10]$.

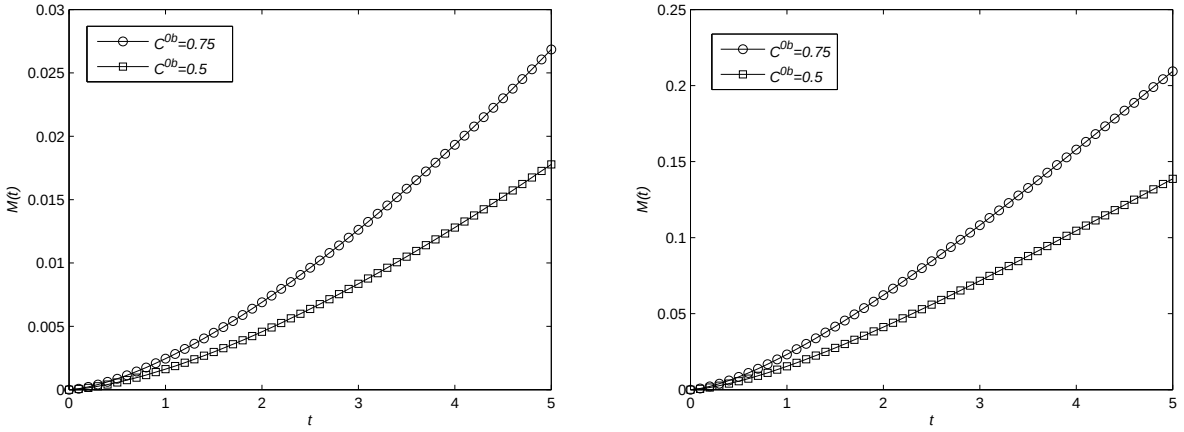
In Figure 9 we plot the mass $M(t)$ for $D = 0.05, C^E = C^{0g} = 0$ and for $\lambda = 0.01, 0.1$. The released mass $M(t)$ is an increasing function of $\lambda$.

(*iv*) *The lens has particles but they are not filled with drug at t=0 and* $C^E = 0$.

We note that in this case $C^{0b} = 0$ but $\lambda \neq 0$. From (28) we then have

$$M(t) = \frac{4DC^{0g}}{\ell} \sum_{n=0}^{\infty} \frac{(a_n + \lambda)^2}{(a_n + \lambda)^2 + \lambda^2} \frac{e^{a_n t} - 1}{a_n}. \tag{34}$$

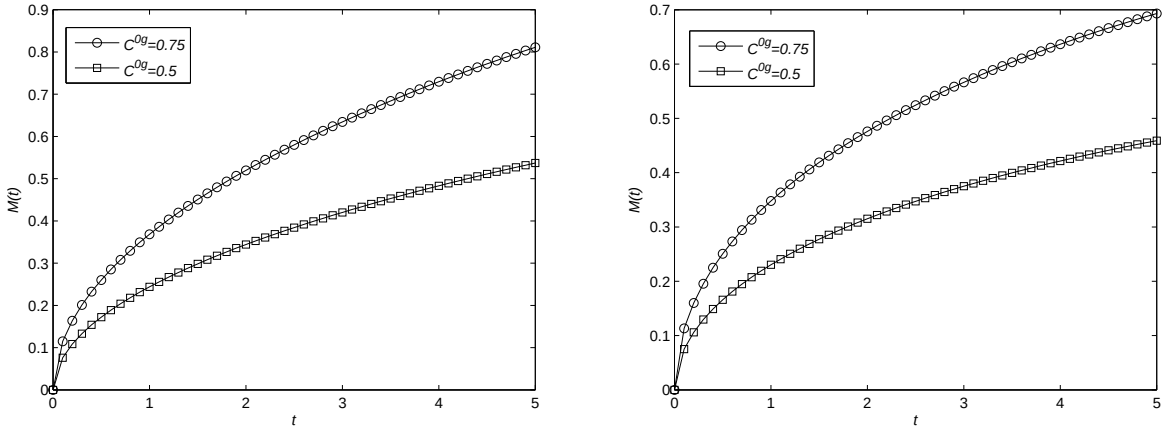
We easily conclude from (34) that $M'(t) > 0$ and $M''(t) < 0$.




(a) (b)

FIGURE 9. The mass $M(t)$ for $\lambda = 0.01$ ((a)) and $\lambda = 0.1$ ((b)).

In Figure 10 we plot the mass $M(t)$ for $C^{0b} = C^E = 0, D = 0.05$ when $\lambda$ increases. As $\lambda$ increases a decreasing of the released mass is observed.




(a) (b)

FIGURE 10. The mass $M(t)$ as function of $C^{0g}$ for $\lambda = 0$ $\lambda = 0.01$ ((a)) and $\lambda = 0.05$ ((b)).

Let us now compare $(i)$ with $(ii)$ and $(iii)$ with $(iv)$ :

- *Comparison of the values of M(t) given by (i) and (ii)*

We assume that $C^{0g} - C^E \geqslant 0$. As $a_n < 0$ we have

$$\frac{(a_n + 2\lambda)(a_n + \lambda)}{(a_n + \lambda)^2 + \lambda^2} \frac{e^{a_n t} - 1}{a_n} \leq \frac{e^{a_n t} - 1}{a_n}. \tag{35}$$

In fact (35) is equivalent to

$$(a_n + 2\lambda)(a_n + \lambda) \leq (a_n + \lambda)^2 + \lambda^2 \tag{36}$$

and finally to

$$a_n \lambda \leq 0.$$

which is always satisfied. From (30), (31) and (35) we conclude that for each $t$ the total released mass is delayed in the case of a lens with particles. This behaviour can be observed in Figures 7 and 8. In fact, in Figure 7 the first curve ($C^E = 0, C^{0g} = 0.5$) presents a delay effect when compared with the second curve of Figure 8 ($C^E = 0, C^{0g} = 0.5$).

- *Comparison of M(t) given by (iii) and (iv)*

  In case (*iii*) there is no drug in the polymeric matrix at $t = 0$, this means that all the drug is inside the particles. In case (*iv*) there is no drug inside the particles at $t = 0$, and all drug is inside the polymeric matrix. In order to compare the masses in the two cases we suppose that in (*iii*) the initial drug concentration $C^{0b}$ in the particles is equal to the initial drug concentration $C^{0g}$ in (*iv*).

  All the terms of the series in (34)are positive. The terms of the series (33) that correspond to taking a sign plus in (21) are positive because $a_n + \lambda \geq 0$; *the terms corresponding to taking a sign minus in (21) are negative because in this case* $a_n + \lambda \leq 0$.

  Let us consider the terms for which $a_n + \lambda \geq 0$. As $a_n \leq 0$ we have

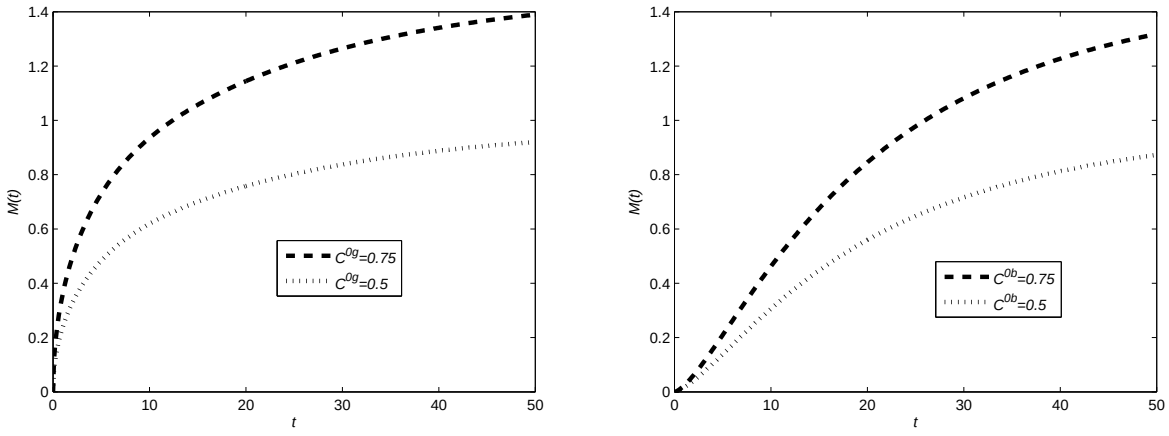
$$\lambda(a_n + \lambda) \geq (a_n + \lambda)^2. \tag{37}$$

  For the terms for which $a_n + \lambda \leq 0$ then

$$\lambda(a_n + \lambda) \leq (a_n + \lambda)^2. \tag{38}$$

  From (37) and (38) it is clear that in a general case we can not compare (33) and (34). However if $\lambda$ is very small $(a_n + \lambda) \leq 0$ *and consequently (38) holds. This means that the mass given by (34) is larger than the mass given by (33).* The plots of the mass $M(t)$ in Figures 9 and 10 exhibit this behaviour.

In Figure 11 we plot the mass $M(t)$ obtained with $D = 0.05, \lambda = 0.1, C^E = 0$, and for $C^{0g} = 0.5, 0.75, C^{0b} = 0$ (Figure 11(a)) and $C^{0b} = 0.5, 0.75, C^{0g} = 0$ (Figure 11(b)). A delayed effect is observed when the drug is encapsulated in the particles.




(a) (b)

FIGURE 11. The mass $M(t)$ for $t \in [0, 50]$: (a) $C^{0g} = 0.5, 0.75, C^{0b} = 0$; (b) $C^{0b} = 0.5, 0.75, C^{0g} = 0$.

## 4. Experimental results versus numerical simulation

In the previous section we consider the drug release model (1) with homogeneous Dirichlet boundary conditions (3) which means that the drug attaining the boundary is immediately removed. Exact solution were computed and the qualitative behaviour of such model was studied and illustrated. Our aim in what follows is to simulate numerically the behaviour of model (1) under more realistic assumptions and to compare the simulation with experimental results.

As long as the drug is being released, some quantity still remains in the neighborhood of the lens. This fact means that in a more realistic model the homogeneous Dirichlet boundary conditions should be replaced by the Robin boundary conditions

$$\begin{cases} D\dfrac{\partial C^g}{\partial x}(-\ell, t) = \alpha_1(C^g(-\ell, t) - C^E) \\ -D\dfrac{\partial C^g}{\partial x}(\ell, t) = \alpha_2(C^g(\ell, t) - C^E),\ t > 0. \end{cases} \tag{39}$$

As a fraction of the released drug is absorbed by the eye, the exterior concentration should be assumed time dependent and depending on the concentration at the boundary. We consider $C^E = \gamma C^{0g}(-\ell, t)$.

An expression for the solution of the initial boundary value problem (1), (2), (39) can be obtained using the procedure followed in the previous section. As the computation of the solution $C^g$ in this case is a tedious task we present in what follows the numerical simulation of the mass $M(t)$ obtained using a standard finite difference discretization. In all figures we consider that time is represented in the $x$-axis and that the amount of drug released by the lens per unit volume of lens in the $y$-axis.

We begin by verifying that the model coupled with the new boundary conditions still presents a delayed behaviour. In Figure 12 we plot the simulation results obtained for the contact lenses with and without particles. In the numerical simulation for the mass drug released from a contact lens without particles $M_{dif}(t)$ we considered

$$\begin{aligned} &C^{0b} = 0, \lambda = 0, C^{0g} = 0.285, D = 0.2565 \times 10^{-3}, \\ &\alpha_1 = \alpha_2 = 0.05, \gamma = 0.5. \end{aligned} \tag{40}$$

In the numerical simulation of the released mass $M_{nano}(t)$ for the contact lens with particles we used

$$\begin{aligned} &C^{0b} = 0.05102, \lambda = 0.02, C^{0g} = 0.285, \\ &\alpha_1 = \alpha_2 = 0.01, \gamma = 0.5. \end{aligned} \tag{41}$$

and a time dependent Heaviside diffusion coefficient is considered to describe the adaptation of the polymeric matrix to the drug delivery phenomena

$$D(t) = \begin{cases} 0.1996 \times 10^{-3},\ t \in [0, 420] \\ \\ 0.9 \times 10^{-5},\ t \in (420, 11520]. \end{cases} \tag{42}$$

We point out that the initial concentration of the drug dispersed in the polymeric matrix and in the particles as well the diffusion coefficients characterizing the contact lenses were determined by the experimental work. The delay effect of the use of particles to retard the drug delivery it is well illustrated in this figure. In fact we observe that $M_{dif}(t)$ attains the stationary state at the first day while $M_{nano}(t)$ still increasing at eighth day: some drug remains inside of the polymeric matrix or/and in particles.

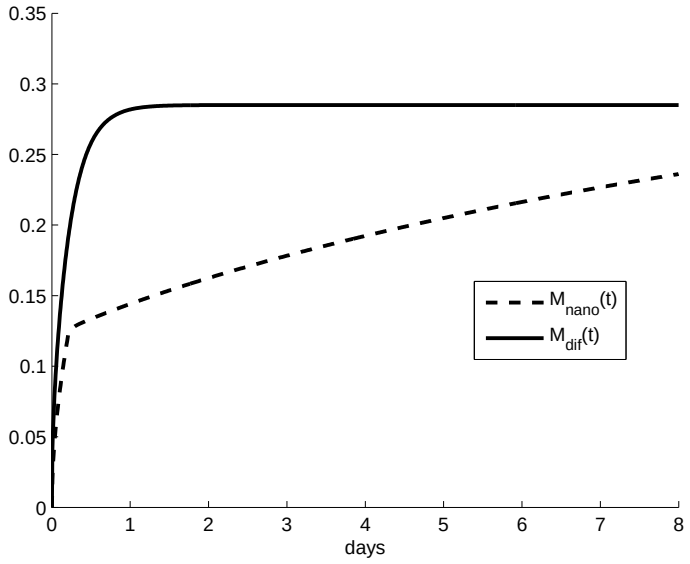



FIGURE 12. Numerical masses delivery: $M_{dif}(t)$, $M_{nano}(t)$ obtained with (40) and (41), (42) respectively.

In what follows we compare the experimental data with the simulation results. In Figure 13 we present the plot of the mass $M(t)$ released from the lens when the drug is entrapped in the polymeric matrix. The numerical and the experimental results, respectively $M_n(t)$ and $M_e(t)$, were obtained with (40). Several experimental and numerical simulations have been carried on showing an agreement as can be seen in the example of Figure 13.

The experimental and numerical results for the contact lens for the case of drug only entrapped in particles are plotted in Figure 14. In this case the transfer time of the drug from the particles to the polymeric matrix and the diffusion time have a central role on the initial behaviour. We take

$$\begin{aligned} &C^{0b} = 0.04075, C^{0g} = 0, \\ &\alpha_1 = \alpha_2 = 0.05, \lambda = 0.02, \gamma = 0.5, \end{aligned} \tag{43}$$

and

$$D(t) = \begin{cases} 0.19244 \times 10^{-2},\ t \in [0, 250] \\ \\ 0.189 \times 10^{-3},\ t \in (250, 540]. \end{cases} \tag{44}$$

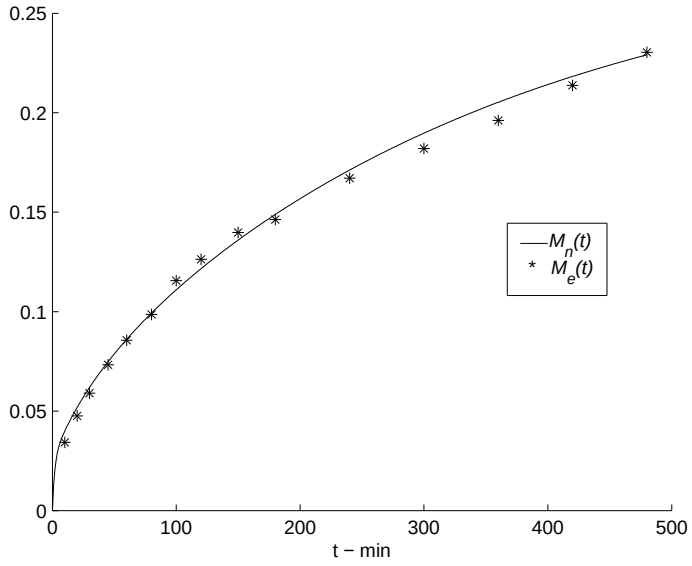



FIGURE 13. Numerical and experimental mass delivery from a lens with dispersed drug during the first 8 hours obtained with (40).

The numerical predictions are very accurate as can be observed from the fact that both experimental and numerical results present the same behaviour.

The experimental and numerical released masses when the drug is entrapped in the polymeric gel and in particles are plotted in Figure 15. We consider

$$\begin{aligned} &C^{0b} = 0.05102, C^{0g} = 0.28 \\ &\alpha_1 = \alpha_2 = 0.01, \lambda = 0.02, \gamma = 0.5 \end{aligned} \tag{45}$$

and

$$D(t) = \begin{cases} 0.1996 \times 10^{-3},\ t \in [0, 300] \\ \\ 0.11 \times 10^{-4},\ t \in (300, 480]. \end{cases} \tag{46}$$

The same qualitative behaviour of numerical and experimental results is observed. From Figures 13 and 15 we conclude that the presence of particles induces a delay effect on the delivery mass during 8 hours. The long term behaviour of the lens when the drug is entrapped in the particles and in the polymeric matrix is illustrated in Figure 16. In this case we consider the

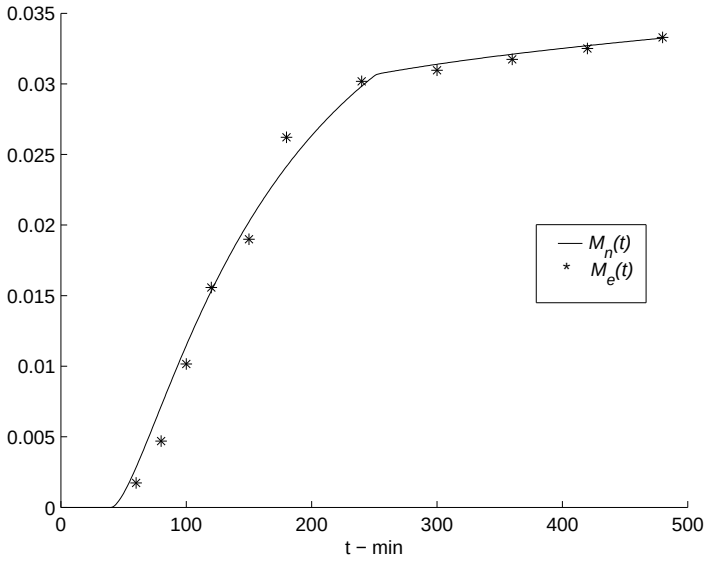



FIGURE 14. Numerical and experimental mass delivery from a lens with entrapped particles loaded with the drug during the first 9 hours obtained with (43) and (44).

coefficient diffusion defined by (42). The experimental data was well fitted by the simulation results predicted by model (1), (2), (39).

## 5. Conclusions

In this paper a drug delivery system based on p-(HEMA/MAAA) copolymer is proposed. The loading of copolymer contact lens was made by dispersing the drug in the the polymeric matrix by entrappement while the monomers are polymerizing. Silicone particles encapsulating the ophthalmic drug were dispersed in the polymeric matrix. This "two barriers" delivery system was studied from experimental and mathematical point of views.

When a simplified boundary conditions are assumed in the system of partial differential equations a close form for the total released mass was obtained. A qualitative analysis was then performed leading to a better understanding of the dependence of the mass on the problem parameters as the diffusion coefficient, the product of the mass transfer coefficient across the particles surface and the ration between the surface and volume particles, the initial concentrations in the polymeric matrix and in the silicone particles and the drug transfer coefficients. In the case of more realistic boundary conditions,

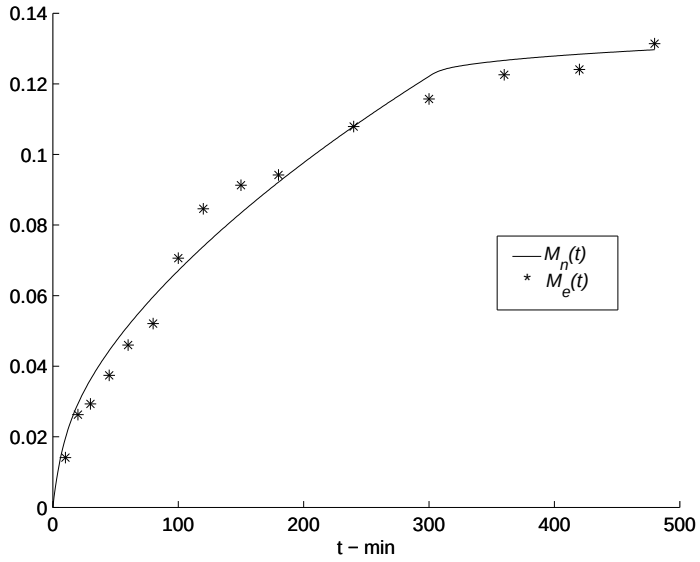



FIGURE 15. Numerical and experimental mass delivery from a lens with dispersed drug and entrapped particles loaded with drug during the first 8 hours obtained with (45) and (46).

the model was solved numerically and the simulation showed a very good agreement with experimental data.

The results obtained confirm that replacing a polymeric matrix with dispersed drug by a polymeric matrix with dispersed drug and with entrapped particles loaded with drug leads to:

- a greater total loaded drug mass,
- a significant delay in the drug delivery,
- a continuous drug release,

when p-HEMA/MAA copolymer is used. This last characteristic means that the released drug mass is strictly increasing. As mention before, this behaviour was not observed in [3] where a p-HEMA gel was used to entrap the silica particles loaded with drug. The results obtained confirm that the system studied in this paper can be a potential ophthalmic drug delivery vehicle. Future work includes a wider experimental studies and in-vivo experiments.

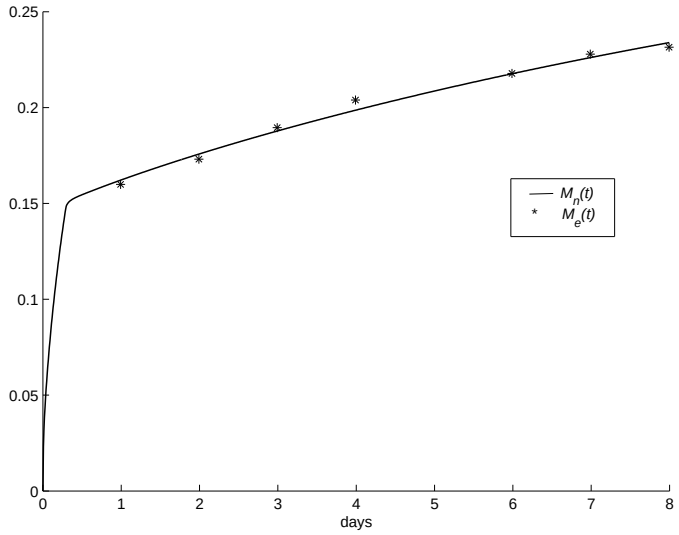



FIGURE 16. Numerical and experimental mass delivery from a contact lens with dispersed drug and entrapped particles loaded with drug during the first 8 days obtained with (45) and (42).

# 6. Appendix

| Symbol | Definition (units) |
|---|---|
| $x$ | Spatial variable $(mm)$ |
| $t$ | time variable $(min)$ |
| $\frac{\partial}{\partial x}$ | Partial derivative with respect to $x$ |
| $\frac{\partial^2}{\partial x^2}$ | Second order partial derivative with respect to $x$ |
| $\frac{\partial}{\partial t}$ | Partial derivative with respect to $x$ |
| $C^g$ | Drug concentration in the polymeric matrix $(\mu g/mm^3)$ |
| $C^b$ | Drug concentration in the silicone particles $(\mu g/mm^3)$ |
| $C^E$ | Exterior drug concentration $(\mu g/mm^3)$ |
| $C^{0g}$ | Initial drug concentration in the polymeric matrix $(\mu g/mm^3)$ |
| $C^{0b}$ | Initial drug concentration in the silicone particles $(\mu g/mm^3)$ |
| $D$ | Diffusion coefficient in the polymeric matrix $(mm^2/min)$ |
| $\lambda$ | Product of the mass transfer coefficient across the particles surface and the ration between the surface and volume particles $(1/min)$ |
| $2\ell$ | Thickness of the contact lens $(mm)$ |
| $\alpha_1$ | Drug transference coefficient at the right side of the contact lens $(mm/min)$ |
| $\alpha_2$ | Drug transference coefficient at the right side of the contact lens $(mm/min)$ |
| $M(t)$ | Total mass released during $t$ units of time. |

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