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Sustained Drug Release from Contact Lenses[1]

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Abstract: This paper focuses on the release of an ophthalmic drug (flurbiprofen) from a loaded copolymer where the drug is simultaneously 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. In vitro 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 behavior, in vitro experiments, simulation 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 is approximately 16% per minute during a normal blink rate of $15-20$ blinks per minute. When a drop is instilled into the eye it has a short residence time of approximately 2 minutes in the tear film. In fact it is diluted

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by the lacrimal secretion and 95% is cleared by the tear fluid, highly dependent on environmental conditions particularly temperature and humidity (Cohen et al. (1996), Deshpande and Shirolkar (1989)). 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 and only about 5% penetrates though the cornea to reach the anterior chamber. This inefficiency is due to the short residence time of the eye drop in the tear film and consequently to the rapid variation of drug concentration. Moreover serious side effects can occur as for example undesirable heart effects with beta-blockers, widely used to treat glaucoma (Forrester et al. (2008), Rang et al. (1999)).

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 as well as their high degree of comfort and biocompatibility. Several techniques have been proposed in the literature. Without being exhaustive we can mention the use of

(i) soaked simple contact lenses (Bourlais et al. (1998), Hehl et al. (1999), McNamara et al. (1999));

(ii) compound contact lenses with a hollow cavity (Nakada and Sugiyama (1998));

(iii) entrapment of proteins, cells and drugs by polymerization of hydrogel monomers in the presence of species to be entrapped or by direct dissolution (Elisseeff et al. (2000), Podual et al. (2000), dos Santos et al. (2009), Scott and Peppas (1999));

(iv) biodegradable contact lenses (Ciolino et al. (2009)).

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 to be not enough to increase the residence time in the precorneal area. As mentioned in Creech et al. (2001) and McNamara et al. (1999), the drug has a residence time of about 30 minutes in the eye increasing the bioavailability up to 50% (Li and Chauhan (2006)). Concerning compound contact lenses with a hollow cavity it is observed in Xinming et al. (2008) that the oxygen and carbon dioxide permeability of the system is lower than the recommended for a safe daily wear. 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 (Gulsen and Chauhan (2004), Gulsen and Chauhan (2005)). 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 (Gulsen and Chauhan (2005)) focused 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 simulate the delay between the initial burst release, controlled by the diffusion in the gel, and the long time release, controlled by diffusion across the particles, the authors propose in Gulsen and Chauhan (2005) a mathematical model based on two sequential procedures. In a first period of time the release of the drug trapped directly in the gel was modeled by a diffusion partial differential equation; in a second period, beginning when there is no more drug in the gel, the release of the drug trapped inside the particles was described by an ordinary differential equation.

To circumvent the above drawbacks we propose in this paper the use of silicone particles 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 by 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. This experimental work is presented in Section 2.

As one of our aims is to design a software package, that can be used to simulate the drug release from a polymeric matrix with prescribed characteristics, the experimental work is completed by a mathematical model to describe the drug release from a loaded polymeric matrix with dispersed filled particles. The model is introduced in Section 3 and is represented by a system of partial differential equations, coupled with appropriate initial and boundary conditions, which describe the simultaneous mechanisms of diffusion and transference in the polymeric matrix loaded with particles. To establish the robustness and accuracy of the mathematical model we deduce in Section 3 a closed formula for the total mass delivery $M(t)$ and we study its qualitative properties. Namely we compare $M(t)$ for the three delivery scenarios studied experimentally : soaked polymeric lens without particles, polymeric lens with loaded particles and soaked polymeric lens with loaded particles. In Section 4 the system of differential equations is coupled with very realistic boundary conditions which account for the transference phenomena in the boundary of the device. Also the diffusion coefficient is considered time dependent. In vitro experimental results are compared with numerical simulation profiles. These comparisons show the effectiveness of our approach and suggest that the software package can be an useful tool in the design of drug delivery devices. 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]) as crosslinker, and azobisisobutyronitrile from Fluka (AIBN, $\geq$ 98%, CAS [78-67-1]) was the employed initiator. The hydroquinone inhibitor was removed from the monomers employing a chromatograph method, using a glass column containing a packet alumina. 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]) were used to prepare the microemulsion. The employed ophthalmic drug was flurbiprofen, (97%, Sigma, CAS [5104-49-4]). Phosphate buffered saline solution (PBS, pH= 7.4, Sigma) was used as the drug

release media.

2.1.2 Synthesis methods

Preparation of the silicone particles:

In order to prepare the particles, the following procedure was used (Gulsen and Chauhan (2005)): $1g$ of Brij 35 was dissolved in $10g$ of water. This solution was heated to $60°C$ and stirred at $700rpm$. A second solution was prepared by dissolving $0.10m\ell$ of TEOS and $2mg$ of flurbiprofen in $0.15m\ell$ of decane. Afterwards, this solution was added to the previous mixture, maintaining the temperature and stirring, until the mixture became clear. Then, $10m\ell$ of 1N HCl solution was added, and the mixture was kept at $60°C$, 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 and $30mg$ of AIBN were mixed thoroughly, in a beaker. After the mixture was completely homogenized $3m\ell$ of distilled water were added. This final solution was degassed by bubbling it with nitrogen. The copolymers with drug incorporated in the polymeric matrix were synthesized by dissolving flurbiprofen ($1mg$) directly into the mixture of monomers. The solution was injected into a mold, constituted by two glass plates coated with teflon. They were separated by a silicone spacer ($1mm$ of thickness). The polymerization reaction was performed at $60°C$ during 24 hours. The obtained copolymer 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 $10m\ell$ of PBS at $37°C$. The samples used in this assay were dried, previously, in a vacuum oven at $25°C$. After 24 hours, the samples were removed from the PBS, carefully wiped with a soft tissue to remove excess liquid from its surface and weighed was found until constant weight. All the experiments were carried out in triplicate, to compute an average value and associated error (standard deviation).

SEM studies:

In order to observe the copolymer cross-section morphology and the silicone particles, scanning electron microscopy (SEM) (Jeol, JSM-5310 model, Japan) was performed, at $15kV$ and with different magnifications. P-(HEMA/MAA) copolymers with and without silicone particles were analyzed, previously, dried and coated with gold in an appropriated support and argon atmosphere.

2.1.4 Drug release studies

The drug release assays for p-(HEMA/MAA) copolymer samples were performed in a closed vial containing $10m\ell$ of PBS, at $37°C$, and with continuous stirring ($100rpm$). Samples were, previously, weighed and measured (thickness and diameter). During the drug release experiments, at predefined times, an aliquot of $1m\ell$ was taken replacing it by the same volume of fresh PBS. Drug release assays were carried out until a flurbiprofen mass equilibrium was achieved with the release media. Flurbiprofen concentration was determined using a spectrophotometrical method (UV-VIS Spectrophotometer, JASCO, V-530 model). The amount of flurbiprofen released was quantified by a previous determined standard curve, at $\Lambda = 247.5nm$ in PBS (with the equation Concentration($\mu g/m\ell$)$= 13.150 \times$Absorbance, obtained with linear correlation coefficient $r^2 = 0.9996$).

Release assays were performed for all the prepared polymeric systems, namely:

- System I - Drug incorporated in the polymeric matrix;
- System II - Drug entrapped in the silicone particles that were dispersed in the polymeric matrix;
- System III - Drug incorporated in the polymeric matrix and entrapped in the silicone particles that were dispersed in the polymeric matrix.

Release assays for control samples were also performed. The control samples were used to correct any compound release that was not flurbiprofen, such as unreacted monomer, crosslinker and initiator, by subtracting their value of absorbance. All the release studies were performed in triplicate to take an average and standard deviation.

2.2 Results

2.2.1 Water content

The equilibrium water content in PBS at $37°C$ was determined by the equation

$$\%\text{water content} = \frac{W(t) - W(0)}{W(t)} \times 100, \tag{1}$$

where $W(t)$ and $W(0)$ are the weight of the sample at the time t in PBS and the initial weight (dry polymer), respectively.

The percentage of water content of the p-(HEMA/MAA) copolymer was $67.8 \pm 2\%$. This percentage is between the values of the water content required for contact lenses (Tranoudis and Efron (2004)).

2.2.2 SEM characterization

A cross-section of p-(HEMA/MAA) copolymer without particles and drug incorporated is present in Figure 1 with a magnification of $5000\times$. As it can be observed, it presents an uniform surface without visible pores at this magnification.

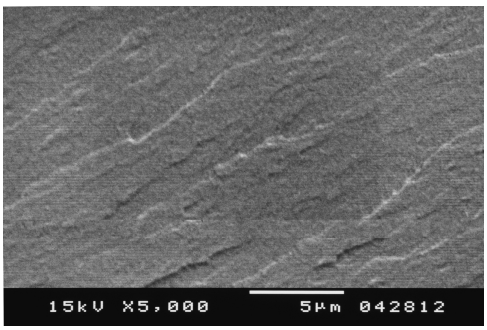


Figure 1: SEM micrographs from the cross section of a copolymer without particles and drug incorporated, at $5000\times$ magnification.

Figure 2 shows a SEM micrograph from the cross-section of the p-(HEMA/MAA) copolymer with silicone particles incorporated. By observing Figure 2 it is possible to disclose the presence of particles entrapped in the polymeric matrix with different sizes. It is also possible to verify a non-homogeneously distribution of the particles in the copolymer matrix.

2.2.3 Drug release profiles

Figure 3 presents the drug release profiles for systems I, II and III. All these profiles were obtained experimentally. In the release experiments cylindrical p-(HEMA/MAA) copolymer samples with $1cm$ of diameter and $1mm$ of thickness were used.

In Figure 3, system I corresponds to the drug release profile from a p-(HEMA/MAA) copolymer with $0.285\mu g/mm^3$ of flurbiprofen dispersed in the polymeric matrix and without silicone particles. It is possible to observe that after 8 hours, 90% of the total amount of drug that was initially introduced was released. The drug

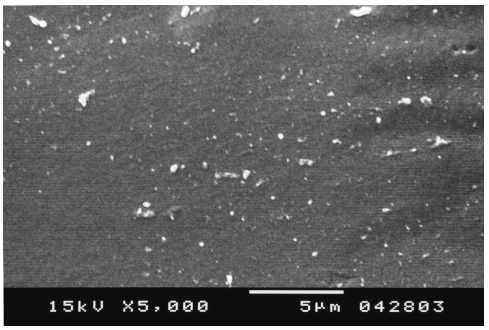


Figure 2: SEM micrographs from the cross section of a copolymer with particles, at 5000× magnification.

release profile for system II (copolymer with entrapped drug in the silicone particles) is also plotted in Figure 3. It can be observed that there is a release delay in the first hour. After this period, the flurbiprofen is released from the copolymer until an equilibrium with the media is achieved. In this system, the concentration of flurbiprofen in the silicone particles is approximately $0.041\mu g/mm^3$ (this value considers that the silicone particles were homogeneously distributed in the polymeric matrix). The delay effect can be justified as there is drug only in the silicone particles dispersed in the polymeric matrix. So a certain time is needed in order that the drug is released from the particles and diffuses through the polymeric matrix until it reaches the boundary of the polymer. However, after 8 hours, 85% of the total amount of flurbiprofen encapsulated in the silicone particles was released.

In order to increase the loaded drug in the polymeric matrix and to have a more sustained release, the drug was not only dispersed in the polymeric matrix but it was also encapsulated in the silicone particles that were entrapped in the polymeric matrix (system III).

The drug release profile obtained for system III is plotted in Figure 3. Only about 40% of the total amount of flurbiprofen was released during the first 8 hours and the equilibrium was not reached. The initial concentrations of flurbiprofen, incorporated during synthesis in the polymeric matrix and silicone particles, are, respectively, $0.285\mu g/mm^3$ and $0.051\mu g/mm^3$. Moreover, the delay effect observed for system II was eliminated, probably due to the fact that the flurbiprofen incorporated in the matrix was released in the first minutes (see system I for comparing).

Figure 4 shows the drug release profile for the total time release (8 days) for system III. As it can be seen only after 8 days a equilibrium with the media is achieved. The

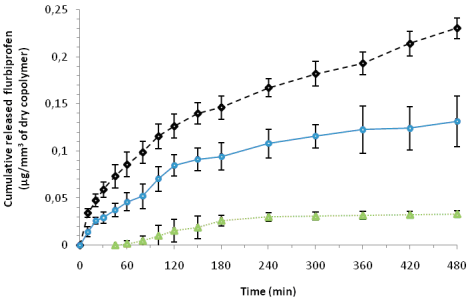


Figure 3: Release profiles of flurbiprofen in PBS at $37°C$, of system I (black lozenges), system II (green triangles) and system III (blue circles). Results are expressed as mean $\pm$ standard deviation ($n = 3$).

particles present in the polymeric matrix can retard the release of the drug. This can be due to the fact that flurbiprofen may have more affinity to the particles than to the release media. Probably, the presence of silicone particles in the copolymer increases the affinity of the copolymer for the flurbiprofen. In this way, it is possible to obtain a more sustained release profile.

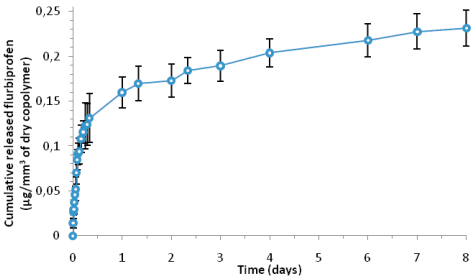


Figure 4: Release profile of flurbiprofen in PBS at 37ºC, of system III (blue circles). Results are expressed as mean $\pm$ standard deviation ($n = 3$).

In order to study the kinetic and the drug release mechanism equation

$$\frac{M(t)}{M_\infty} = kt^n, \tag{2}$$

was used (Brazel and Peppas (1999)), where $M(t)$ and $M(\infty)$ are, respectively, the amount of drug released from the copolymer at time t and in the equilibrium, K is

a constant which is characteristic of the system and n is the diffusional exponent characteristic of the release mechanism.

Linearizing (2) by taking the logarithm in both members and plotting $\ln\left(\frac{M(t)}{M(\infty)}\right)$ as a function of $\ln(t)$, the coefficient n is obtained from the slope of the least squares line. This linearization is considered only until 60% of the total amount of drug is released (Singh and Chauhan (2008)).

For cylindrical systems, if n is equal to 0.45 the process is considered diffusion-controlled, that is Fickian; if $0.5 < n < 0.89$ then the diffusion is considered non-Fickian or anomalous transport; and if $n = 0.89$ the transport mechanism is considered of Type II (García et al. (2004)).

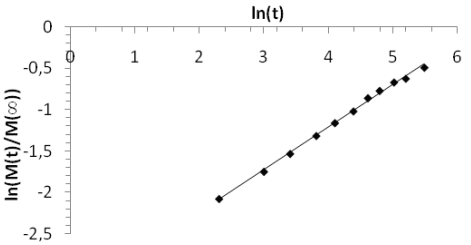


Figure 5: Least squares line to calculate diffusional exponent, n, for the system I.

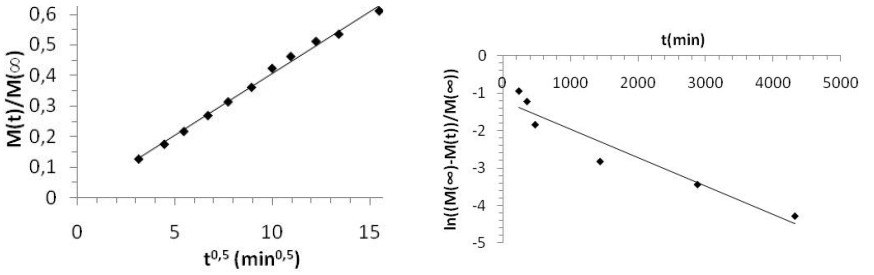
In order to calculate the initial and final diffusion coefficient for all the systems, we considered a Fickian behavior. For example, for system I a value $n = 0.51$ was obtained. From the Fickian diffusion equation for one-dimensional transport (using initial and boundary conditions) and by approximations for the early time ($\frac{M(t)}{M(\infty)} \leq 0.6$), the drug release behavior is described by

$$\frac{M(t)}{M(\infty)} = 4\left(\frac{D_i t}{\pi \ell^2}\right)^{0.5}, \tag{3}$$

where D_i is the initial diffusion coefficient in the polymer and ℓ the thickness of the sample (Brazel and Peppas (1999)). By plotting $\frac{M(t)}{M(\infty)}$ as a function of $t^{0.5}$, and using linear regression, the coefficient k,

$$k = 4\left(\frac{D_i}{\pi \ell^2}\right)^{0.5},$$

is obtained approximately. Finally the drug diffusion coefficient is computed from such approximation. In Figure 6 (a) we plot the least squares line obtained for system I being the diffusion coefficient $2.57 \times 10^{-04} mm^2/min$. For systems II and III the calculation procedure was similar and the results are reported in Table 1.



(a) (b)

Figure 6: Least squares line to calculate: (a) the initial diffusion coefficient; and (b) final diffusion coefficient, for system I.

To compute the drug coefficient, for more than 60% release, we use

$$\frac{M(t)}{M(\infty)} = 1 - \frac{8}{\pi^2} exp\Big(-\frac{\pi^2 D_f t}{\ell^2}\Big)$$

where D_f is the final diffusion coefficient (Brazel and Peppas (1999)), or equivalently

$$\frac{M(\infty) - M(t)}{M(\infty)} = \frac{8}{\pi^2} exp\Big(-\frac{\pi^2 D_f t}{\ell^2}\Big). \tag{4}$$

This coefficient can be calculated using the least squares line for the linearization of (4) obtained taking the logarithm is both members of this equation

$$\ln\Big(\frac{M(\infty) - M(t)}{M(\infty)}\Big) = \ln\frac{8}{\pi^2} - \frac{\pi^2 D_f t}{\ell^2}.$$

The least squares line for the final diffusion coefficient for system I is plotted in Figure 6 (b). The initial and final diffusion coefficients for the three systems are presented in Table 1.

Table 1: Drug diffusion coefficients for systems I,II and III.

System	$D_i(mm^2/min)$	r^2	$D_t(mm^2/min)$	r^2
I	2.57×10^{-4}	0.995	6.46×10^{-5}	0.930
II	1.92×10^{-3}	0.986	1.89×10^{-4}	0.946
III	2.00×10^{-4}	0.960	2.22×10^{-5}	0.930

3 Mathematical model

In this section we present a mathematical model to describe the drug release from a contact lens prepared using a p-(HEMA/MAA) copolymer loaded with a therapeutical drug dispersed in the polymeric matrix and in the silicone particles. In order to simplify the presentation we assume that the drug leaving the lens is immediately removed. More realistic assumptions will be considered in Section 4. The mathematical model is represented 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 behavior of such concentrations on the parameters of the model will be analyzed in this section.

The lens has a width of 2ℓ and is completely immersed in water. During the experiment a mechanism of removal of the released drug was used. The drug release is described by

$$\begin{cases} \dfrac{\partial C^g}{\partial t} = D\dfrac{\partial^2 C^g}{\partial x^2} - \dfrac{\partial C^b}{\partial t},\ x\in(-\ell,\ell),\ t>0 \\ \dfrac{\partial C^b}{\partial t} = \lambda(C^g - C^b),\ x\in(-\ell,\ell),\ t>0, \end{cases} \tag{5}$$

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 λ 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. The reaction-diffusion equation for C^g is established combining Fick's law for the mass flux j

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

and the mass conservation law

$$\frac{\partial C^g}{\partial t} + \frac{\partial j}{\partial x} = -\lambda(C^g - C^b), \tag{6}$$

where the term $-\lambda(C^g - C^b)$ is induced by the drug transfer from the silicone particles to the polymeric matrix.

System (5) is completed with the initial conditions

$$\begin{cases} C^g(x,0) = C^{0g} \\ C^b(x,0) = C^{0b}, \end{cases} \tag{7}$$

where C^{0g} is the initial concentration in the gel and the C^{0b} the initial concentration inside the particles. Along with (5) and (7) we assume the symmetry condition

$$\begin{cases} \dfrac{\partial C^g}{\partial x}(0,t) = 0, \\ \dfrac{\partial C^b}{\partial x}(0,t) = 0, \end{cases} \tag{8}$$

which represents the symmetric distribution of both concentrations within the lens. This property is expected to be satisfied in the experiments carried on.

System (5), (7) and (8) is complemented with the boundary conditions

$$\begin{cases} C^g(-\ell,t) = C^E \\ C^g(\ell,t) = C^E. \end{cases} \tag{9}$$

Conditions (9) mean that the drug is immediately removed and the external drug concentration is constant. In fact in the experiments 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 experimental point of view boundary conditions of type

$$\begin{cases} D\dfrac{\partial C^g}{\partial x}(-\ell,t) = \alpha_1(C^g(-\ell,t) - C^E) \\ -D\dfrac{\partial C^g}{\partial x}(\ell,t) = \alpha_2(C^g(\ell,t) - C^E), t > 0, \end{cases} \tag{10}$$

where $\alpha_i, i = 1,2$, stand for the transference coefficients, are a more accurate description, meaning that the drug flux at the boundary lens is proportional to the difference between the drug concentration in the water and the drug concentration at the lens surface. This condition will be used in the numerical simulations presented in Section 4. In the analytical solution of (5) developed in this section conditions (9) are used to simplify the computations.

To solve(5) we use Laplace transforms in time. Applying the Laplace transforms in (5), (7) and integrating by parts we obtain

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

where $\overline{C^g}(x,p) = \int_0^\infty e^{-pt} C^g(x,t)\,dt$ and $C^b(x,p) = \int_0^\infty e^{-pt} C^b(x,t)\,dt$.

Computing $\overline{C^b}$ from the second equation in (11) and replacing in the first one we obtain

$$D\frac{\partial^2 \overline{C^g}}{\partial x^2} - \frac{p(p+2\lambda)}{p+\lambda}\overline{C^g} = -C^{0g} - C^{0b}\frac{\lambda}{p+\lambda}, \tag{12}$$

which has the general solution

$$\overline{C^g}(x,p) = F_1 e^{k_1 x} + F_2 e^{k_2 x} + \frac{(p+\lambda)C^{0g} + \lambda C^{0b}}{p(p+2\lambda)}, \tag{13}$$

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

$$k_1, k_2 = \pm\sqrt{\frac{p(p+2\lambda)}{D(p+\lambda)}}. \tag{14}$$

Applying Laplace transform in (9) we obtain

$$\overline{C^g}(-\ell, p) = \frac{C^E}{p} \tag{15}$$

and

$$\frac{\partial \overline{C^g}}{\partial x}(0,p) = 0. \tag{16}$$

Taking into account conditions (15), (16) in (13) we compute the constants F_1, F_2 obtaining

$$\overline{C^g}(x,p) = \frac{C^E(p+2\lambda) - C^{0g}(p+\lambda) - \lambda C^{0b}}{p(p+2\lambda)}\frac{\cosh(k_1 x)}{\cosh(k_1 \ell)} + \frac{(p+\lambda)C^{0g} + \lambda C^{0b}}{p(p+2\lambda)}. \tag{17}$$

To compute $C^g(x,t)$ 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

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

(18)

and

$$g(p) = p(p+2\lambda)(1+\frac{4k_1^2\ell^2}{\pi^2})(1+\frac{4k_1^2\ell^2}{3^2\pi^2})(1+\frac{4k_1^2\ell^2}{5^2\pi^2})\ldots, \tag{19}$$

being these expressions obtained using $\cosh(y) = \prod_{j=0}^{\infty}\left(1+\frac{4y^2}{(2j+1)^2\pi^2}\right)$ (see Crank (1975)).

As the Laplace transform of $e^{-2\lambda t}(\frac{C^{0g}-C^{0b}}{2})+(\frac{C^{0b}+C^{0g}}{2})$ is given by $\frac{(p+\lambda)C^{0g}+\lambda C^{0b}}{p(p+2\lambda)}$, following Crank (1975), we then have

$$C^g(x,t) = \sum_{n=0}^{\infty}\frac{f(x,a_n)}{g\prime(a_n)}e^{a_n t} + e^{-2\lambda t}(\frac{C^{0g}-C^{0b}}{2})+(\frac{C^{0b}+C^{0g}}{2}), \tag{20}$$

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

As

$$g(p) = p(p+2\lambda)\cosh(k_1\ell), \tag{21}$$

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

$$\cosh(\sqrt{\frac{p(p+2\lambda)}{D(p+\lambda)}}\ell) = 0, \tag{22}$$

that is

$$\sqrt{\frac{p(p+2\lambda)}{D(p+\lambda)}} = \pm\frac{(2n+1)\pi i}{2\ell}, n = 0,1,\ldots \tag{23}$$

which lead to

$$p = \frac{-8\lambda\ell^2 - D(2n+1)^2\pi^2 \pm \sqrt{(8\lambda\ell^2)^2 + D^2(2n+1)^4\pi^4}}{8\ell^2}, n = 0,1,\ldots. \tag{24}$$

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

$$g^{'}(p) = (p+2\lambda)\cosh(k_1\ell) + p\cosh(k_1\ell) + p(p+2\lambda)senh(k_1\ell)(\frac{dk_1}{dp})\ell \tag{25}$$

we have

$$\begin{cases} g'(0) = 2\lambda \\ g'(-2\lambda) = -2\lambda \\ g^{'}(a_n) = a_n(a_n+2\lambda)(\pm i)(-1)^n(\dfrac{dk_1}{dp})\,|_{a_n}\,\ell \end{cases} \tag{26}$$

where a_n are defined in (24). From (20) we then have

$$C^g(x,t) = C^E + \sum_{n=0}^{\infty}(-1)^n D\cos(\frac{(2n+1)\pi x}{2\ell})\frac{b(a_n)(2n+1)\pi(a_n+\lambda)^2}{a_n(a_n+2\lambda)\ell^2(a_n^2+2\lambda^2+2a_n\lambda)}e^{a_n t} \tag{27}$$

where

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

Considering that

$$\frac{a_n(a_n+2\lambda)}{D(a_n+\lambda)} = -\frac{(2n+1)^2\pi^2}{4\ell^2} \tag{28}$$

we can give C^g the following form

$$C^g(x,t) = C^E + \sum_{n=0}^{\infty}(-1)^{n+1}4\cos(\frac{(2n+1)\pi x}{2\ell})\frac{b(a_n)(a_n+\lambda)e^{a_n t}}{(2n+1)\pi(a_n^2+2\lambda^2+2a_n\lambda)}. \tag{29}$$

If we consider in (29) $\lambda = 0$ and $C^{0b} = 0$, we obtain the expression of the concentration corresponding to a pure diffusion problem (Crank (1975)).

The total mass released during t units of time, $M(t)$, can be computed using the flux at each time t at the boundary $x = \ell$

$$M(t) = -2D\int_0^t \frac{\partial C^g}{\partial x}(\ell,\tau)d\tau. \tag{30}$$

Computing $\dfrac{\partial C^g}{\partial x}(\ell,\tau)$ from (29) and replacing in (30) we finally have

$$M(t) = -\frac{4D}{\ell}\sum_{n=0}^{\infty}\frac{C^E(a_n+2\lambda) - C^{0g}(a_n+\lambda) - \lambda C^{0b}}{a_n(a_n^2+2\lambda^2+2a_n\lambda)}(a_n+\lambda)(e^{a_n t}-1). \tag{31}$$

In what follows using (31) we study from an analytical point of view the behavior of systems I,II and III referred in Section 2. This allow us to assess the robustness of our model and to have some insight on the interpretation of delivery profiles obtained in the in vitro experiments.

- System I: *The polymeric matrix is loaded with drug - the lens has no particles*. Considering that, in this case, $\lambda = 0$ and $C^{0b} = 0$, we obtain, from (31),

$$M_1(t) = \frac{4D}{\ell}(C^{0g} - C^E) \sum_{n=0}^{\infty} \frac{e^{a_n t} - 1}{a_n}. \tag{32}$$

  Moreover, from (32) we have $M_1'(t) > 0$ and $M_1''(t) < 0$ for $C^{0g} > C^E$.

- System II: *The drug in entrapped in the particles and there is no drug in the polymeric matrix at* $t = 0$. In this case we have $C^{0g} = 0$, $\lambda \neq 0$, and to simplify we take $C^E = 0$. From (31) we deduce

$$M_2(t) = \frac{4DC^{0b}}{\ell} \sum_{n=0}^{\infty} \frac{\lambda(a_n + \lambda)}{[(a_n + \lambda)^2 + \lambda^2]} \frac{e^{a_n t} - 1}{a_n}. \tag{33}$$

  As

$$M_2''(t) = \frac{4DC^{0b}}{\ell} \sum_{n=0}^{\infty} \frac{\lambda a_n (a_n + \lambda)}{(a_n + \lambda)^2 + \lambda^2} e^{a_n t},$$

  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 (28).

  We compare now $M_2(t)$ with $M_1(t)$ when $C^E = 0$. We take C^{0g}, in system I, equal to C^{0b} of system II. As

$$\lambda(a_n + \lambda) \leq \lambda^2 + (a_n + \lambda)^2,$$

  we deduce that

$$\frac{\lambda(a_n + \lambda)}{\lambda^2 + (a_n + \lambda)^2} \leq 1.$$

  Then, from (32) and (33), $M_2(t) \leq M_1(t)$ as established experimentally in Section 2. We conclude that the use of filled particles induces a delay effect on the drug release.

- System III: *The drug is entrapped in the particles dispersed in the loaded polymeric matrix*. In order to simplify we consider the case $C^{0g} = C^{0b}$. From (31) we have

$$M_3(t) = \frac{4D}{\ell}(C^{0g} - C^E) \sum_{n=0}^{\infty} \frac{(a_n + 2\lambda)(a_n + \lambda)}{a_n[(a_n + \lambda)^2 + \lambda^2]} (e^{a_n t} - 1). \tag{34}$$

Replacing (28) in (34) we can give $M_3(t)$ the following form

$$M_3(t) = -\frac{D^2}{\ell^3}(C^{0g} - C^E)\sum_{n=0}^{\infty}\frac{(2n+1)^2\pi^2(a_n+\lambda)^2}{a_n^2[(a_n+\lambda)^2+\lambda^2]}(e^{a_n t}-1). \tag{35}$$

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 (35) that for $C^{0g} > C^E$, $M_3'(t) > 0$ and $M_3''(t) < 0$. It can be also established that $M_3'(0^+) = +\infty$.

We compare now $M_3(t)$ with $M_1(t)$. We consider for system I the initial concentration $2C^{0g}$ where C^{0g} is the initial concentration in the polymeric matrix of system III. We assume that $C^{0g} - C^E \geqslant 0$. As $a_n < 0$ we have

$$\frac{(a_n+2\lambda)(a_n+\lambda)}{(a_n+\lambda)^2+\lambda^2}\frac{e^{a_n t}-1}{a_n} \leq 2\frac{e^{a_n t}-1}{a_n}. \tag{36}$$

In fact (36) is equivalent to

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

To prove (37) we remark that this inequality is satisfied provided

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

holds. As (38) is equivalent to

$$a_n\lambda \leq 0,$$

which is always satisfied, from (35), (32) and (36) we conclude that, for each t, the total released mass is delayed when filled particles are used on the loaded polymeric matrix, that is, $M_3(t) \leq M_1(t)$. This result was obtained experimentally in Section 2.

In order to compare $M_3(t)$ with $M_2(t)$ we take in system II the initial concentration in the silicone particles given by $2C^{0g}$ where C^{0g} is the initial concentration in the polymeric matrix in system III. As

$$2\lambda(a_n+\lambda) - (a_n+2\lambda)(a_n+\lambda) = -a_n(a_n+\lambda),$$

we have

$$M_2(t) - M_3(t) = -\sum_{n=0}^{\infty}\frac{a_n(a_n+\lambda)}{(a_n+\lambda)^2+\lambda^2}\frac{e^{a_n t}-1}{a_n}. \tag{39}$$

For each n, two different a_n are given by (24). In this case we can not establish analytically the sign of $M_2(t) - M_3(t)$. However several runs of the sum in the right hand side of (39) showed that

$$\sum_{\pm} \frac{a_n(a_n+\lambda)}{(a_n+\lambda)^2+\lambda^2} \frac{e^{a_n t}-1}{a_n} \geq 0, \tag{40}$$

and this fact suggest that $M_2(t) \leq M_3(t)$. This result illustrates the delay effect of particles to entrap the drug into the polymeric matrix.

We analyse now what is the effect of void particles in the polymeric matrix loaded with drug. We note that this situation is qualitatively analogous to having $C^{0b} \ll C^{0g}$. In fact during the in vitro experiments it was observed that in this case there was an initial delay in the delivery du to the fact that drug entered in the particles. We prove analytically in what follows this remark. We called such case system IV.

- System IV: *The lens has particles but they are not filled with drug at* $t = 0$. We assume that $C^E = 0$. We note that in this case $C^{0b} = 0$ but $\lambda \neq 0$. From (31) we then have

$$M_4(t) = \frac{4DC^{0g}}{\ell} \sum_{n=0}^{\infty} \frac{(a_n+\lambda)^2}{(a_n+\lambda)^2+\lambda^2} \frac{e^{a_n t}-1}{a_n}. \tag{41}$$

We easily conclude from (41) that $M_4'(t) > 0$ and $M_4''(t) < 0$.

We compare now $M_4(t)$ with $M_i(t), i = 1,2,3$. We consider $C^E = 0$. To compare $M_4(t)$ with $M_3(t)$ we consider in the polymeric matrix of system IV the initial concentration $2C^{0g}$ where C^{0g} is the initial concentration in the polymeric matrix of system III. As

$$M_4(t) - M_3(t) = \sum_{n=0}^{\infty} \frac{a_n(a_n+\lambda)}{(a_n+\lambda)^2+\lambda^2} \frac{e^{a_n t}-1}{a_n},$$

from (40) we conclude that $M_4(t) \geq M_1(t)$.

Let us take now, in both systems I and IV, the the same concentration in the polymeric matrices. From the expressions of $M_4(t)$ and $M_1(t)$ it is clear that $M_4(t) \leq M_1(t)$. To compare $M_4(t)$ with $M_2(t)$ we consider C^{0b} in system II equal to C^{0g} of system IV. For $M_4(t) - M_2(t)$ holds the representation obtained before for $M_4(t) - M_3(t)$. This fact leads to the inequality $M_4(t) \geq M_2(t)$.

In figure 7 we plot the masses $M_i, i = 1,2,3,4$ with $C^E = 0$, $D = 0.05, \lambda = 0.05$. We took $C^{0b} = 0.5$ for $M_2(t)$ and $C^{0g} = 0.5$ for $M_1(t)$ and $M_4(t)$. For $M_3(t)$ we considered $C^{0g} = C^{0b} = 0.25$. The delay effect of particles is well illustrated by this figure and is in complete agreement with experimental results (Figure 3). In fact, as shown before, the mass released from a loaded polymeric matrix, for each time t, is greater than the mass released from a polymeric matrix where filled or empty particles were used. The delay effect is greater if only filled particles are considered.

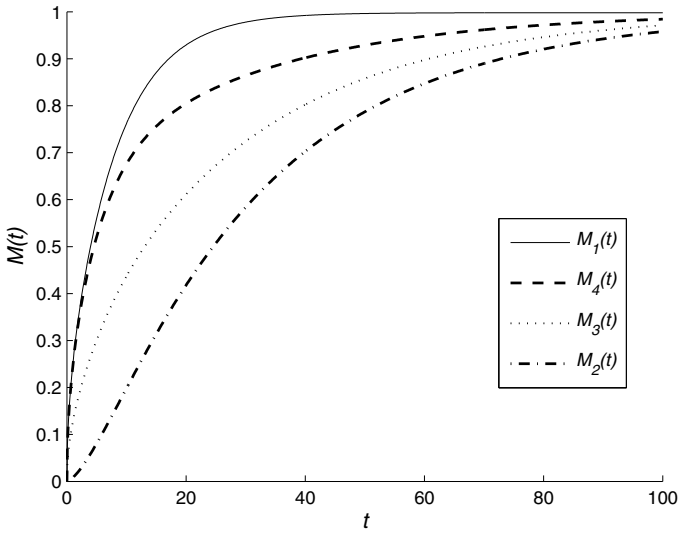


Figure 7: Delay effect on the drug release of the particles for systems I,II, III and IV.

From the qualitative analysis previously performed, we concluded that $M_4(t) \geq M_3(t)$. In Figure 8 we illustrate the delay effect of λ on drug release. We observe that the delay effect increases when λ decreases when filled particles are used (system II). However, when empty particles are used we observe that the delay effect decreases when λ decreases (system IV).

4 Experimental results versus numerical simulation

In the previous section we considered the drug release model (5) with constant diffusion and homogeneous Dirichlet boundary conditions (9) which means that the

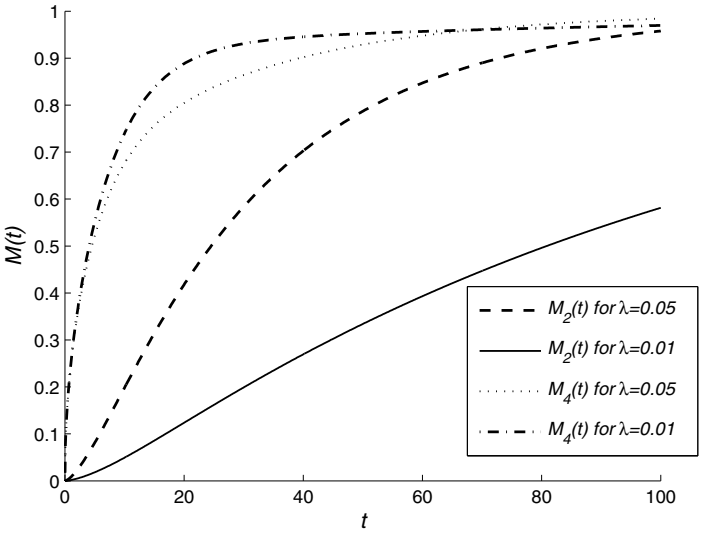


Figure 8: Delay effect on drug release of the transference properties of the particles.

drug attaining the boundary is immediately removed. The exact solution was computed and the qualitative behavior of such model was studied and illustrated. Our aim in what follows is to simulate numerically the behavior of model (5) under time dependent diffusion and 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 (10). 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 $C^E = \gamma C^{0g}(-\ell, t)$.

The analytical solution of the initial boundary value problem (5), (7), (10) can be obtained using the procedure followed in the previous section, but the computation of the solution C^g in this case is a tedious task. As a consequence we present in what follows the numerical approximation for the mass $M(t)$ at $t = t_n$, M^n, obtained using an implicit Euler method to integrate in time and a second order centered finite difference operator to discretize the partial derivative in (5). In all figures we consider that time is represented in the horizontal axis and that the amount of drug released by the lens per unit volume of lens in the vertical axis. Moreover the con-

centrations and the parameter values are presented without units (see Appendix).

We begin by verifying that the model coupled with the new boundary conditions presents a delayed behavior. In Figure 9 we plot the simulation results obtained for the contact lenses with and without particles. In the numerical simulation for the mass released from a contact lens without particles, system I, M_1^n we used

$$C^{0b} = 0, \lambda = 0, C^{0g} = 0.285, D = 0.2565 \times 10^{-3},$$
$$\alpha_1 = \alpha_2 = 0.05, \gamma = 0.5. \tag{42}$$

In the numerical simulation of the released mass for the contact lens with particles, M_3^n, we used

$$C^{0b} = 0.05102, \lambda = 0.02, C^{0g} = 0.285,$$
$$\alpha_1 = \alpha_2 = 0.01, \gamma = 0.5, \tag{43}$$

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

$$D(t) = \begin{cases} 0.1996 \times 10^{-3}, t \in [0, 420] \\ 0.9 \times 10^{-5}, t \in (420, 11520]. \end{cases} \tag{44}$$

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 is well illustrated in Figure 9. In fact we observe that released mass from the lens when the drug is only entrapped in the polymeric matrix, M_1^n, attains the steady state at the first day while M_3^n is still increasing at eighth day: some drug remains inside of the polymeric matrix or/and in particles.

In what follows we compare the experimental data with the simulation results. In Figure 10 we present the plot of the mass released from the lens when the drug is entrapped in the polymeric matrix (system I). The numerical and the experimental results, respectively M_1^n and $M_{1,e}^n$, were obtained with (42). Several experimental and numerical simulations have been carried on showing a very good agreement, as can be seen in the example of Figure 10.

The experimental and numerical results for the contact lens with drug only entrapped in particles (system II) are plotted in Figure 11. The following values have

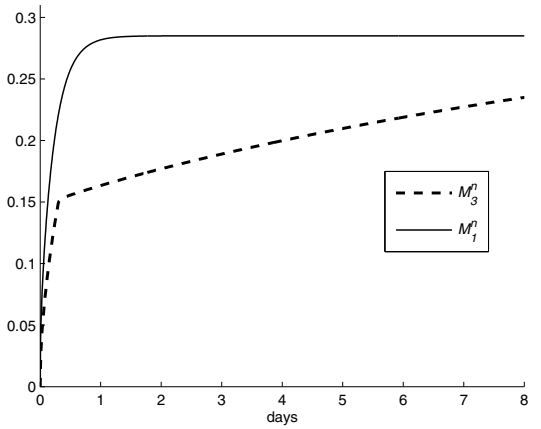


Figure 9: Numerical masses delivery from system I, M_1^n, and from system III, M_3^n, obtained with (42) and (43), (44) respectively.

been considered:

$$\begin{aligned} &C^{0b} = 0.04075,\ C^{0g} = 0, \\ &\alpha_1 = \alpha_2 = 0.05,\ \lambda = 0.02,\ \gamma = 0.5, \end{aligned} \tag{45}$$

and

$$D(t) = \begin{cases} 0.19244 \times 10^{-2}, t \in [0,250] \\ 0.189 \times 10^{-3}, t \in (250,540]. \end{cases} \tag{46}$$

We note that in this case, as the drug is only entrapped in the particles, there is an initial period of time where no drug delivery occurs.

The experimental and numerical released masses when the drug is entrapped in the polymeric gel and in particles (system III) are plotted in Figure 12. The following values have been considered:

$$\begin{aligned} &C^{0b} = 0.05102, C^{0g} = 0.28 \\ &\alpha_1 = \alpha_2 = 0.01, \lambda = 0.02, \gamma = 0.5 \end{aligned} \tag{47}$$

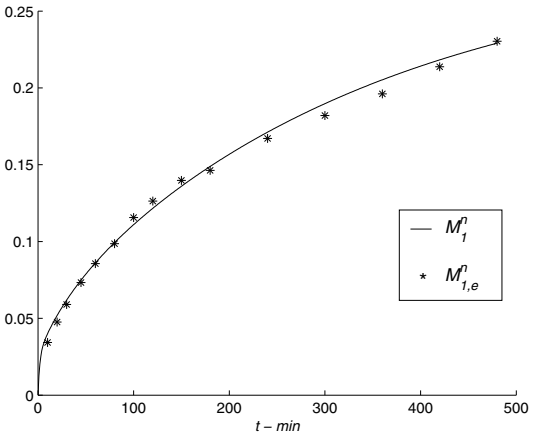


Figure 10: Numerical and experimental mass delivery from a lens with dispersed drug during the first 8 hours obtained with (42) (system I).

and

$$D(t) = \begin{cases} 0.1996 \times 10^{-3}, t \in [0,300] \\ \\ 0.11 \times 10^{-4}, t \in (300,480]. \end{cases} \tag{48}$$

The same qualitative behavior is observed in numerical and in vitro results. From Figures 10 and 12 we conclude that the presence of particles induces a delay effect on the delivery mass during 8 hours. The long term behavior of the lens when the drug is entrapped in the particles and in the polymeric matrix is illustrated in Figure 13. In this case we consider the coefficient diffusion defined by (44). The experimental data was well fitted by the simulation results predicted by model (5), (7), (10).

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.

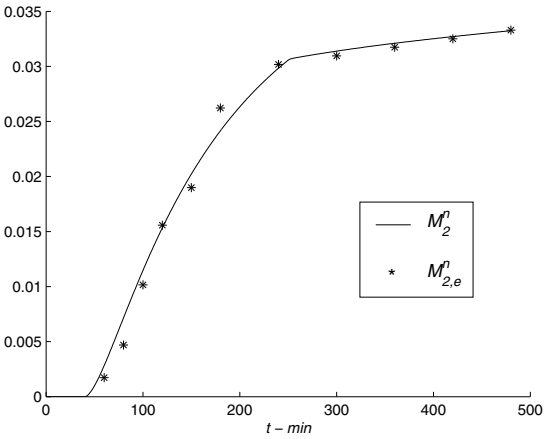


Figure 11: Numerical and experimental mass delivery from a lens with entrapped particles loaded with the drug (system II) during the first 8 hours obtained with (45) and (46).

When simplified boundary conditions (perfect sink conditions) are assumed in the system of partial differential equations a closed 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 ratio between the surface and volume particles, the initial concentrations in the polymeric matrix and in the silicone particles and the drug transfer coefficients. It was also possible to compare analytically, for each t, the total mass released by systems I, II and III and consequently the delay caused by diffusion in gel and the presence of particles. In the case of more realistic boundary conditions and time dependent diffusion coefficient, 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,

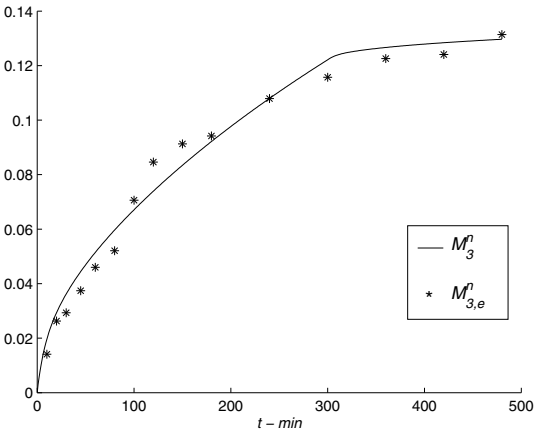


Figure 12: Numerical and experimental mass delivery from a lens with dispersed drug and entrapped particles loaded with drug (system III) during the first 8 hours obtained with (47) and (48).

when p-HEMA/MAA copolymer is used. This last characteristic means that the released drug mass is strictly increasing. As mentioned before, this behavior was not observed in Gulsen and Chauhan (2005) where a p-HEMA gel was used to entrap the silica particles loaded with drug. The results obtained suggest that the system studied in this paper can be a potential ophthalmic drug delivery vehicle. Future work includes a wider range of experimental studies and in-vivo experiments. The accuracy of numerical simulation results, when compared with in vitro results, make us believe that the software package implemented is a useful tool to be used in the design of therapeutical contact lenses.

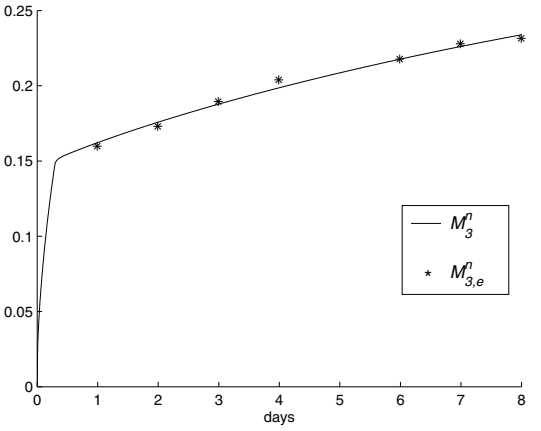


Figure 13: Numerical and experimental mass delivery from a contact lens with dispersed drug and entrapped particles loaded with drug (system III) during the first 8 days obtained with (47) and (44).

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)
λ	Product of the mass transfer coefficient across the particles surface and the ration between the surface and volume particles ($1/min$)
2ℓ	Thickness of the contact lens (mm)
α_1	Drug transference coefficient at the right side of the contact lens (mm/min)
α_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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