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Mathematical Analysis of Waiting Times for Reaching Therapeutic Effects

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Abstract: In two previous papers the authors presented mathematical models that simulate the mass of drug delivered, in vitro Ferreira, Oliveira, Silva, Carreira, Gil and Murta (2010) and in vivo Ferreira, Oliveira, Silva and Murta (2011), from a therapeutic contact lens. In the present paper the time it takes to reach an equilibrium state is studied. A closed formula based on the concept of effective time is derived and the influence of the parameters of the model is analyzed.

1 Introduction

In two recent papers Ferreira, Oliveira, Silva, Carreira, Gil and Murta (2010) and Ferreira, Oliveira, Silva and Murta (2011) the authors presented a new therapeutic contact lens used to control drug delivery into the cornea. The lens is composed by a polymeric platform loaded with drug where silicone particles - also encapsulating drug - are dispersed. The process aims to release the drug over an extended duration in order to overcome the drawbacks associated with topical administration, as the high rate of clearance by the tear fluid and the absorption into the circulation via nasal and nasopharingeal mucosa. A continuous flux, with no initial burst has been achieved, for a period of 8 days. In this paper we are concerned with theoretical investigations based on mathematical models that describe the physical and chemical mechanisms of release, completing the results presented in the previously referred papers. Namely the time it takes to reach therapeutic effects is studied and its dependence on the parameters of the model is analysed.

Some authors have proposed the use of microparticles delivering drug to the cornea (Gulsen and Chauhan (2004), Gulsen and Chauhan (2005)). In the first paper the particles were stabilized with a silica shell which causes a discontinuity in the deliv-

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ery, occurring between the end of the release of the drug within the polymeric matrix and the beginning of delivery from the drug inside the particles. When no stabilization was made an initial burst release occurs followed by subtherapeutic levels of drug release. Even though the lens presented in Gulsen and Chauhan (2004), Gulsen and Chauhan (2005) and the lens presented in Ferreira, Oliveira, Silva, Carreira, Gil and Murta (2010) and Ferreira, Oliveira, Silva and Murta (2011) are conceptually analogous - polymeric platforms with dispersed particles loaded with drug - they have been prepared with different materials and procedures. The mathematical models describing the behaviors of the lens reflect these differences. In the present paper the release from the platform and the particles are modelled as simultaneous phenomena while in Gulsen and Chauhan (2004), Gulsen and Chauhan (2005) these phenomena are modelled sequentially.

The control of the flux in the drug release from the therapeutic lens is a consequence of the two barriers that the drug must surmount: the polymeric matrix and the dispersed particles. Apart from the use of dispersed particles loaded with drug, a delay can also be induced by "sandwich type" structures (Ciolino, Hoare, Iwata, Behlau, Dohlman, Langer and Kohane (2009)) where a drug-PLGA film is contained between two layers of p-Hema.

Within the field of drug delivery two different but complementary approaches can be found in the literature: laboratory experiments and theoretical studies based on mathematical simulations of the phenomena. We follow this last approach by developing a systematic framework to analyze the influence of the parameters of the model on the time it takes to reach predefined therapeutic effects. The study is based on the concept of effective time, a time constant which measures, in a certain sense, the mean time needed to reach equilibrium (Collins (1980), Simon (2009), Simon, Kim and Kanneganti (2011)). The explicit dependence on the parameters provides information on the waiting period before the therapeutic effects of the drug are achieved.

In Section 2 after shortly recalling the mathematical model presented in Ferreira, Oliveira, Silva, Carreira, Gil and Murta (2010) we establish a closed formula for the effective time of the therapeutical lens. The explicit dependence of this time constant, on the parameters of the model, provides a qualitative and quantitative understanding of its behavior. In Section 3 an approximation formula for total mass released at time t is presented. The formula is based on the concept of effective time. A comparison of this approximation with theoretical values of the released mass show the effectiveness of the approach. Finally we show how to conjugate effective time and released mass equations to tailor the therapeutic lens to a specified treatment.

2 Effective time for a therapeutic lens

2.1 Mathematical model of the drug delivery

In Ferreira, Oliveira, Silva, Carreira, Gil and Murta (2010) a therapeutical lens prepared with a p-HEMA/MAA copolymer platform, loaded with drug, where silicone particles encapsulating drug are dispersed, was presented. In vitro, drug release is described by the system

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

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 λ stands for a transfer coefficient. The system is coupled with initial conditions

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

where C^{0g} and C^{0b} are known initial concentrations in the gel and in the particles, respectively. Assuming symmetry and immediate removal of the drug, the system is completed with conditions

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

where C_{ext} represents the external drug concentration.
Let the total delivered mass at time t, $M(t)$, be defined by

$$M(t) = -2D\int_0^t \frac{\partial C^g}{\partial x}(\ell,\tau)d\tau. \tag{4}$$

Using Laplace transforms we obtain

$$\overline{M}(p) = -\frac{2D}{p}\frac{A(p)}{p(p+2\lambda)}k_1\tanh(k_1\ell), \tag{5}$$

where $\overline{M}(p)$ is the Laplace transform of $M(t)$, with $\overline{M}(p) = \int_0^\infty e^{-pt} M(t)dt$. In (5), $A(p) = C_{ext}(p+2\lambda) - C^{0g}(p+\lambda) - \lambda C^{0b}$ and $k_1 = \sqrt{\frac{p(p+2\lambda)}{D(p+\lambda)}}$. We then have

$$M(t) = -\frac{4D}{\ell} \sum_{n=0}^{\infty} \frac{A(a_n)}{a_n(a_n^2 + 2\lambda^2 + 2a_n\lambda)}(a_n+\lambda)(e^{a_n t} - 1) \tag{6}$$

where, for every natural number n, a_n satisfies

$$\frac{a_n(a_n+2\lambda)}{D(a_n+\lambda)} = -\frac{(2n+1)^2\pi^2}{4\ell^2}. \tag{7}$$

Different scenarios of drug delivery from this lens can be considered:

(1) The gel and the particles are both loaded with drug;

(2) The polymeric matrix is loaded with drug and contains no particles ($\lambda = 0, C^{0b} = 0$);

(3) Only the particles are loaded with drug ($\lambda \neq 0, C^{0g} = 0$);

(4) The matrix is loaded with drug and the particles are initially void ($\lambda \neq 0, C^{0b} = 0$).

Let $M_i(t)$, $i = 1,2,3,4$, represents the total mass released at instant t, in the previous scenarios. It can be established analitically that

$$M_2(t) \geq M_4(t) \geq M_1(t) \geq M_3(t), \tag{8}$$

when the initial drug concentration is the same in the four experiments (Figure 1). We observe that, in the case of Scenario 3, this is a theoretical hypothesis because, due to small particles size and its large surface area, the same drug loading of Scenarios 1 2 and 4 is not achieved.

The therapeutic lens corresponds to Scenario 1. Scenario 2 represents a simple platform loaded with drug. Scenario 3 and 4 are academic but they are useful to understand the delay effect when only the particles are loaded and when they are void. Observing Figure 1 we conclude that the largest delay occurs in Scenario 3 when the drug is encapsulated in the particles. In fact in this case the drug must surmount two barriers - the matrix and the particles - to be released.

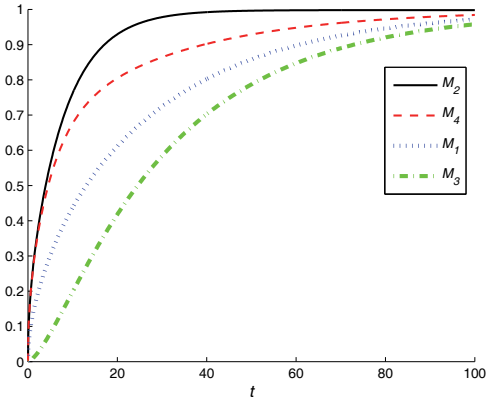


Figure 1: Comparison of Mass: $M_i(t)$, $i = 1,2,3,4$.

2.2 Effective time

To improve the design of the lens it is important to know the waiting time that is the period of time elapsed before the mass attains a certain therapeutic level and how to adjust the parameters to produce a pre-defined delivery profile. In this subsection we present the concept of effective time (Collins (1980)).

Let M^s represents the stationary mass that is $M^s = \lim_{t \longrightarrow \infty} M(t)$. The effective time t_{eff} is defined as the mean time to achieve the equilibrium,

$$t_{eff} = \frac{\int_0^\infty t(M^s - M(t))dt}{\int_0^\infty (M^s - M(t))dt}, \tag{9}$$

which can be seen as the first moment of the probability density function

$$d(t) = \frac{M^s - M(t)}{\int_0^\infty (M^s - M(t))dt}. \tag{10}$$

To compute t_{eff} only $\overline{M}(p)$, the Laplace transform of $M(t)$, must be known. In fact it can be proved (Collins (1980)) that if $\overline{M}(p)$ can be expanded in powers of p,

$$\overline{M}(p) = \frac{1}{p}(B_1 + B_2 p + B_3 p^2 + ...), \tag{11}$$

then

$$t_{eff} = -\frac{B_3}{B_2},$$

provided that $B_2 \neq 0$.

In the case $D \neq 0$, $\lambda \neq 0$, we give (5) the form (11), with

$$B_1 = -2a\frac{\ell}{\lambda}, B_2 = \frac{\ell}{\lambda}(\frac{a}{\lambda} + \frac{4a}{3D}\ell^2 - 2\varpi),$$

$$B_3 = \frac{\ell}{\lambda}(-\frac{4a}{3\lambda D}\ell^2 - \frac{16a}{15D^2}\ell^4 + \frac{2}{\varpi}\lambda + \frac{4\varpi}{3D}\ell^2 - \frac{a}{\lambda^2} + \frac{\varpi}{\lambda}),$$

where

$$a = 2\lambda C_{ext} - \lambda(C^{0g} + C^{0b}), \varpi = \frac{C^{0b} - C^{0g}}{2}.$$

After some tedious but straightforward computations we obtain (Silva (2010))

$$t_{eff} = \frac{1}{\lambda D}\frac{2\varpi D^2\lambda - aD^2 - \frac{4}{3}a\lambda D\ell^2 - \frac{16}{15}a\lambda^2\ell^4 + \frac{4}{3}\varpi D\lambda^2\ell^2}{2\varpi D\lambda - aD - \frac{4}{3}a\lambda\ell^2}. \tag{12}$$

In the case of Scenario 2 ($\lambda = 0, C^{0b} = 0$), effective time can not be obtained from (12). A direct calculus from (11) leads to

$$t_{eff} = \frac{2\ell}{5D}. \tag{13}$$

In Figure 2 a plot of t_{eff} given by (12), as a function of D and λ, is exhibited with $C^{0g} = 0.5, C^{0b} = 0.25, C_{ext} = 0, \ell = 1$. As expected effective time is a decreasing function of D, for constant λ, and a decreasing function of λ, for constant D. In fact when D increases the drug diffuses faster; when λ increases the drug encapsulated in the particles easier surmounts the barrier represented by their boundary. In Figure 3 we present plots of the surface in Figure 2. We note that the influence of D is more significant than the influence of λ.

In engineering literature (Simon (2009)) it is generally accepted that the onset of equilibria is defined by the response time t_r, where $t_r = 4t_{eff}$. We postpone for Section 3 an explanation of this assumption. If we compute $4t_{eff}$ for the previous scenarios, for $D = 0.05, \ell = 1, \lambda = 0.05, C^{0g} = 0.5, C^{0b} = 0.5, C_{ext} = 0$, we obtain the values presented in Table I.

	Scenario 1	Scenario 2	Scenario 3	Scenario4
$4t_{eff}$	116.5716	32	121.6	104

Table I - Response times.

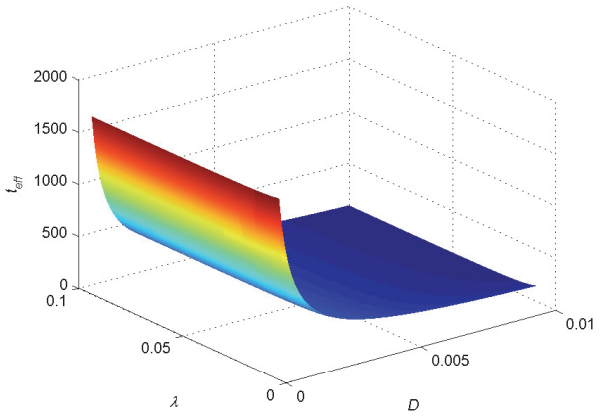


Figure 2: Behavior of t_{eff} as a function of the parameters D and λ.

We note that $t_r^2 < t_r^4 < t_r^1 < t_r^3$, where the superscript refers to the scenarios. This result agrees with the inequalities established in (8) for the delivered masses.

We note that the use of particles induces a significant delay in the drug release. In fact the smallest response time t_r^2 corresponds to Scenario 2, where there are no particles. Response times exhibited in Table I, and the values resulting from other experiences that have been carried on, suggest that $4t_r^2 \approx t_r^1$, even if we have no theoretical support for this observation. This aspect stresses the importance of the use of particles in controlled drug delivery. In the present state of development of particles technology, there are still severe restrictions to their loading and consequently the hypothesis underlying Scenario 3 is purely academic. It is precisely in this scenario that the largest delay is observed. It is also worthwhile mentioning that in Scenario 4, where particles are initially void, significant delay in the release is observed. This is explained by the fact that initially the drug in the polymeric matrix penetrates the particles.

3 Qualitative behavior and mass estimations

In Section 2 we showed that the concept of effective time provides an accurate prediction of the onset of equilibrium. In this section we illustrate how to use such concept to obtain closed formulas that give a priori estimations of released masses. We will be concerned with $M_1(t)$ the mass of the drug delivered by the therapeutic lens presented in this paper.

We begin by explaining why the response time is defined by $4t_{eff}$.

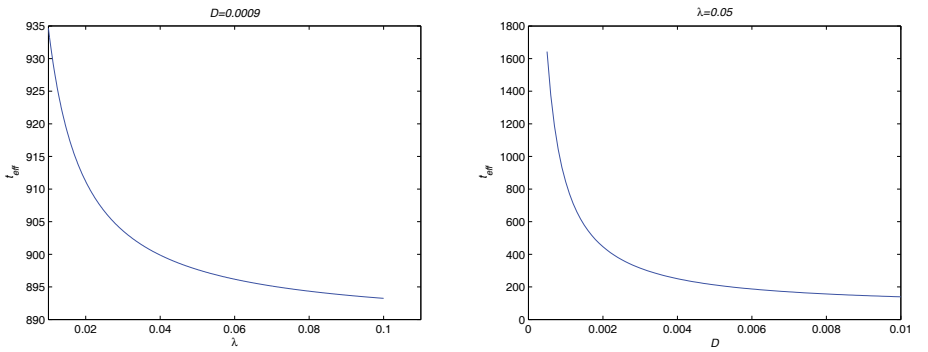


Figure 3: Behavior of t_{eff} as a function of λ (left) and D (right).

Let us suppose that drug release was modeled by an ordinary differential equation. It seems then natural to make the ansatz that the density $d(t)$ can be approximated by an exponential like function of form $d^*(t) = ae^{-bt}$. As $\int_0^\infty d^*(t)dt = 1$ and $\int_0^\infty td^*(t)dt = t_{eff}$, then

$$d^*(t) = \frac{1}{t_{eff}} e^{-t/t_{eff}}. \tag{14}$$

This function represents the density of a first order system with time constant t_{eff}. It is expected that the predictions obtained from d^* are not accurate at short times because of "the lag time that occurs in a system which is partly driven by diffusion" (Simon, Kim and Kanneganti (2011)). In Figure 4 we plot the density $d(t)$ and its approximation $d^*(t)$, (14), with t_{eff} given by (12), where $D = 0.05$, $\ell = 1$, $\lambda = 0.05$, $C^{0g} = 0.5$, $C^{0b} = 0.5$, $C_{ext} = 0$.

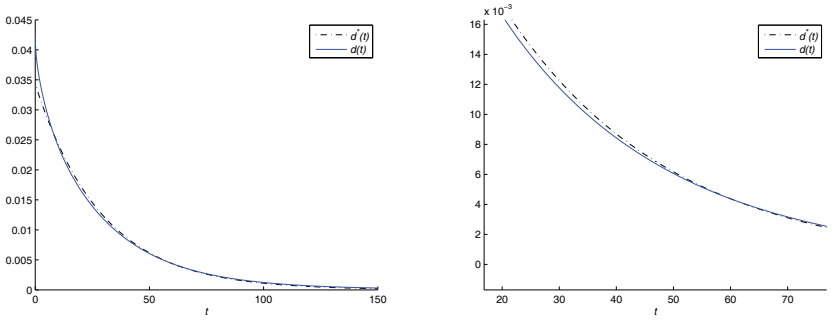
Interpreting t as a statistical variable, with exponential density distribution $d^*(t)$, the probability that $t \leq kt_{eff}$, $P(t \leq kt_{eff})$, is defined, for every $k \in \mathbb{R}$, by

$$P(t \leq kt_{eff}) = 1 - e^{-k}. \tag{15}$$

As this probability can be viewed as $\frac{M_e(t)}{M^s}$, we have

$$M_e(t) = (1 - e^{-\frac{t}{t_{eff}}})M^s, \tag{16}$$

where $M_e(t)$ represents an estimation for $M(t)$.



a) b)

Figure 4: a) Density function $d(t)$ and $d^*(t)$, b) zoom of a) for $t \in [20,75]$.

Using the Final Value theorem, $M^s = \lim_{p \longrightarrow 0} p\overline{M}(p)$, we obtain

$$M^s = -2\ell(2C_{ext} - C^{0g} - C^{0b}), \tag{17}$$

and finally from (16) and (17) we obtain the following estimation

$$M_e(t) = -2\ell(1 - e^{-\frac{t}{t_{eff}}})(2C_{ext} - C^{0g} - C^{0b}). \tag{18}$$

We observe that this estimation avoids the numerical solution of (1) or the computation of the inversion of Laplace transforms. It can be used with (12) as a simple tool to estimate the mass released until a certain time.

In Table II the estimated masses for several times t, computed using (16), are presented.

t	$M_e(t)$
t_{eff}	$63.21\%M^s$
$2t_{eff}$	$86.47\%M^s$
$3t_{eff}$	$95.02\%M^s$
$4t_{eff}$	$98.17\%M^s$

Table II - Estimated delivery masses.

In Table III are presented the estimated delivered masses $M_e(t)$, (18), and $M_1(t)$, (6), computed with $D = 0.05$, $\ell = 1$, $\lambda = 0.05$, $C^{0g} = 0.5$, $C^{0b} = 0.5$, $C_{ext} = 0$.

Effective Time	Estimated Mass $M_e(t)$	Mass $M_1(t)$	Relative Error
$t_{ef} = 29.15$	$63.21\%M^s = 1.2642$	1.4306919	1.320×10^{-1}
$2t_{ef} = 58.29$	$86.47\%M^s = 1.7294$	1.7825530	3.073×10^{-2}
$3t_{ef} = 87.43$	$95.02\%M^s = 1.9004$	1.9145475	7.445×10^{-3}
$4t_{ef} = 116.57$	$98.17\%M^s = 1.9634$	1.9645691	5.954×10^{-4}

Table III- Estimated mass and mass computed from (11)
($D = 0.05$, $\ell = 1$, $\lambda = 0.05$, $C^{0g} = 0.5$, $C^{0b} = 0.5$, $C_{ext} = 0$).

The plots of the released mass $M_1(t)$ and the corresponding estimated mass $M_e(t)$ for the parameters in Table III, are represented in Figure 5. The values of $M_1(t)$ have been computed from (6) with 100 terms.

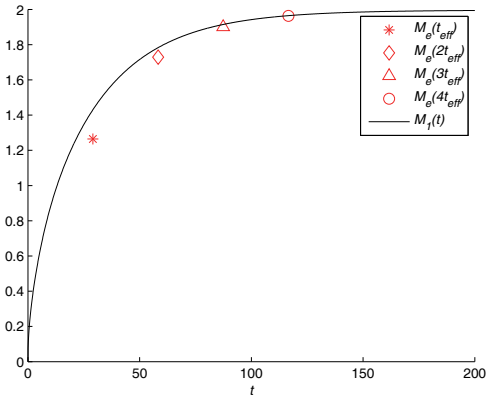


Figure 5: Mass tracking of $M_1(t)$, for parameters in Table III.

As expected when t increases a better approximation $M_e(t)$ of $M_1(t)$ is obtained. Once fixed a certain therapeutic mass and a certain waiting time to reach this mass, the lens can be tailored in order to fullfil these requirements. Let us consider, for example, that D and C^{0g} are free parameters. If we define that at $t_{eff} = 1000$, the released mass should be $M_e(4t_{eff}) = 1$, then

$$C^{0g} = 0.484329, D = 8.415 \times 10^{-3},$$

where $C^{0b} = 0.025$, $C_{ext} = 0$, $\ell = 1$, $\lambda = 0.01$. If the same therapeutic mass is to be delivered within a shorter period of time, $t_{eff} = 100$, then as expected the diffusion coefficient increases, obtaining in this case $D = 1.774 \times 10^{-2}$.

4 Conclusion

A therapeutic lens used to deliver drug to the anterior segment of the eye for an extended period of time was studied by the authors in two previous papers Ferreira, Oliveira, Silva, Carreira, Gil and Murta (2010) and Ferreira, Oliveira, Silva and Murta (2011). To fully understand the kinetics of the delivery, and namely the waiting times before predefined therapeutic levels are reached, a methodology based on effective time is proposed. Closed expressions for the waiting times and the corresponding total delivered masses are established. These expressions incorporate properties such as the drug diffusion coefficient, the transfer coefficient from the particles, the initial concentration of drug in the gel and in the particles. Consequently, a tool that evaluates the effects of a host of conditions on the waiting times and delivered masses is provided by such closed formulas. They give indications on the characteristics of the materials and on the initial concentrations. The contents of the paper represents an approach to the tailoring of a therapeutic lens to a specified treatment.

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