Proceedings of the 13th International Conference
on Computational and Mathematical Methods
in Science and Engineering, CMMSE 2013
24–27 June, 2013.

Drug Delivery from an ocular implant into the vitreous chamber of the eye

E. Azhdari[1], J.A. Ferreira[1], P. de Oliveira[1] and P.M. da Silva[2]

[1] *Department of Mathematics, University of Coimbra - Portugal*

[2] *Department of Physics and Mathematics, Coimbra Institute of Engineering - Portugal*

emails: ebrahim@mat.uc.pt, ferreira@mat.uc.pt, poliveir@mat.uc.pt, pascals@isec.pt

Abstract

A mathematical model which simulates drug delivery from an ocular implant into the vitreous chamber of the eye is proposed. The model consists of coupled systems of partial differential equations linked by interface conditions. The chemical structure, the viscoelastic properties and the diffusion phenomena are taken into account to simulate the evolution of released drug. Numerical simulations that illustrate the interplay between these phenomena are included.

Key words: diffusion-reaction equation, drug delivery, biodegradable implant, drug delivery.

1 Introduction

The vitreous humor is the clear gel that fills the space between the lens and the retina of the eyeball of humans and other vertebrates (Figure 1). It is often referred to as the vitreous body or simply "the vitreous". It is bounded by the lens, the hyaloid membrane, and the retina. It is stuck to the retina, but with aging, the vitreous can separate from it. The vitreous humor makes up 80% of the eye to hold its fairly spherical shape.
There are a number of severe diseases that can affect the vitreous or the retina, which must be treated over long periods of time and where drugs must be maintained in their therapeutic windows. Among these diseases we mention:

 ISBN: 978-84-616-2723-3

- Age-related macular degeneration which is a medical condition that usually affects older adults and results in a loss of vision in the center of the visual field because of damage to the retina.
- Glaucoma that is an eye disease in which the optic nerve is damaged and that is normally associated with increased fluid pressure in the anterior chamber of the eye.
- Diabetic retinopathy which is a retinopathy caused by complications of diabetes, that change the blood vessels of the retina.

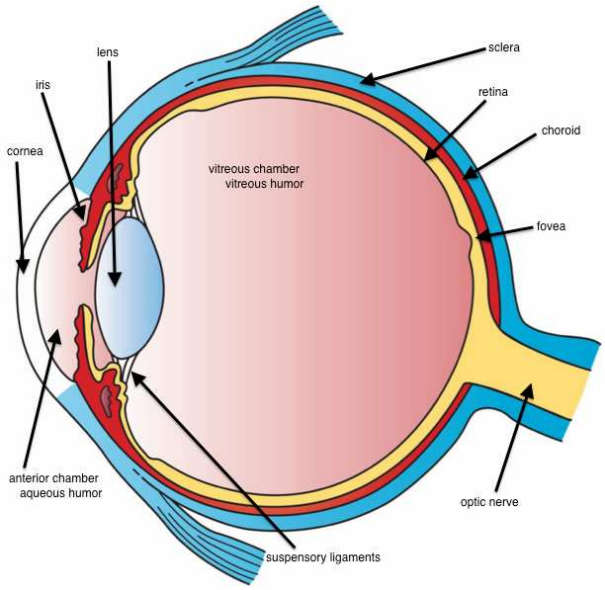

Figure 1: Anatomy of the human eye (http://en.wikipedia.org/wiki/).

Delivering drugs to the vitreous chamber of the eye is a challenge due to the presence of various physiological and anatomical barriers. Classical ocular drug delivery systems for posterior segment diseases fall under one of the following categories:

- Systemic delivery: systemic administration of drugs to the blood stream directly, in the form of injections, or by absorption into the blood stream, in the form of pills.
- Topical delivery: topical delivery in the form of ophthalmic drops is the most common method used to treat ocular diseases.

None of the two first drug delivery systems is effective. In fact systemic delivery is not effective because as the eye has a relatively small size the drug concentration carried by the

 ISBN: 978-84-616-2723-3

blood supply is not enough which means that it does not lie in the therapeutic window of the drug; with topical delivery just a small fraction of drug reaches the posterior segment of the eye.

Due to physiological barriers within the eye, which prevent drug in the systemic circulation from entering the vitreous. Those classical drug delivery systems are being replaced by direct intravitreal injection or intravitreal implants of drug. As vitreal injections imply several treatments and can cause side effects as the increase of intraocular pressure and damage of crystalline lens intravitreal implants have been developed these last years. In this paper we will study intravitreal delivery of drug through implants. This delivery system is nowadays the most used method to treat the vitreous chamber of the eye. Intravitreal implants include nonbiodegradable and biodegradable polymers. Controlled release of a therapeutic agent from a biodegradable polymeric system presents an alternative to traditional treatment strategies that can overcome some of the problems associated with pulsed delivery [7].
Many drugs have a narrow concentration window of effectiveness and may be toxic at higher concentration [7], so the ability to predict local drug concentrations is necessary for proper loading of the delivery system. Mathematical models play a central role in drug release because not only they explain the kinetics of the delivery by describing the interplay of the different phenomena as they quantify the effect of physical parameters in the delivery trend. Several authors have studied mathematical models to describe transport and elimination

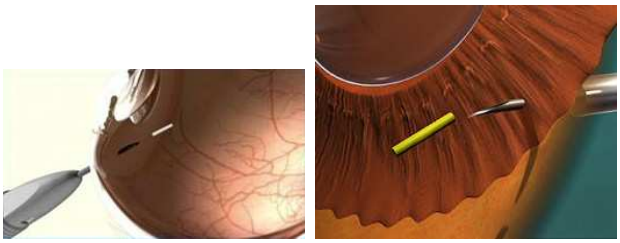

Figure 2: Ocular implant (http://www.tanner-eyes.co.uk/patient_ozurdex.html and http://marcelohosoume.blogspot.pt/2010/10/iluvien-and-future-of-ophthalmic-drug.html).

of drugs in the vitreous [3, 4, 5, 7]. However at the best of our knowledge the delivery of drug from a biodegradable implant has not been yet addressed. There are several type of implants already approved for ophthalmic applications. The model presented in this paper is a general transport model in a biodegradable viscoelastic material. However in the numerical simulations physical data from a FDA [1] approved intravitreal implant, Ozurdex, have been used (Figure 2) .

[1]FDA- Food and Drug Administration.

 ISBN: 978-84-616-2723-3

In Section 2 the geometry of the vitreous chamber of the eye and of the intravitreal implant are described. In Section 3 the mathematical model is presented. Numerical simulations that illustrate the kinetics of the drug release are exhibited in Section 4. Finally in Section 5 some conclusions are addressed.

2 Geometry

The geometrical model of the human eye adopted in the present study is shown in Figure 3 and is based on the physiological dimensions ([5]).

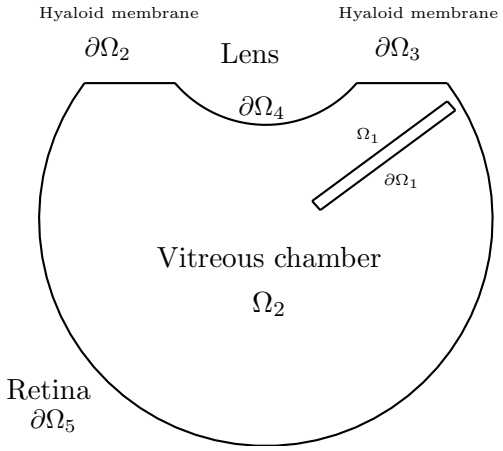

Figure 3: Geometry of the vitreous chamber of the human eye (Ω_2), hyaloid membrane ($\partial\Omega_2$, $\partial\Omega_3$), lens ($\partial\Omega_4$), retina ($\partial\Omega_5$), ocular implant (Ω_1) and its boundary ($\partial\Omega_1$).

The vitreous chamber is mainly composed of vitreous humor and comprises about two-third of the eye. The lens is located behind the iris and is modeled here as an ellipsoid. The hyaloid membrane and the lens separate the anterior chamber and the posterior chamber of the eye from the vitreous chamber. The retina forms the boundary for the vitreous on the posterior surface and is modeled here as a spherical surface with a radius of 9.1 mm. The intravitreal implant is placed into the vitreous, as shown in Figure 3, and it is geometrically represented by a cylinder with radius 0.023 mm and height 0.6 mm.

 ISBN: 978-84-616-2723-3

3 Mathematical model

The implant with dispersed drug is placed into the vitreous, near the retina (Figure 3). The drug is released in a controlled manner through the vitreous which is a porous media, and its target is the retina, affected by an inflammatory process.

The diffusion-reaction equation that describes the drug dynamics in the polymer is represented by

$$\begin{cases} \dfrac{\partial C_1}{\partial t} = \nabla(D_1(M)\nabla C_1) + D_v\Delta\sigma - k_1 C_1 \ \texttt{in}\ \Omega_1 \times (0,T] \\ \dfrac{\partial \sigma}{\partial t} + \dfrac{E}{\mu}\sigma = EC_1 \ \texttt{in}\ \Omega_1 \times (0,T] \\ \dfrac{\partial M}{\partial t} + \beta_1 M = \beta_2 C_1 \ \texttt{in}\ \Omega_1 \times (0,T] \end{cases}, \tag{1}$$

where Ω_1 stands for the implant (a cylindrical device with dispersed drug), C_1 is the drug concentration in the polymer, σ is the stress exerted by the polymer and M represents the polymer molecular weight. The diffusion coefficient of the drug in the polymer, D_1, is a function of the molecular weight, the parameter D_v stands for a stress-driven diffusion coefficient and k_1 is the degradation rate of the drug. The second equation in (1) results from the Maxwell fluid model ([1])

$$\frac{\partial \sigma}{\partial t} + \frac{E}{\mu}\sigma = E\frac{\partial \varepsilon}{\partial t}, \tag{2}$$

that relates the stress with the strain ε where E represents the young modulus of the polymer and μ its viscosity. To eliminate the from the system we considered that the strain satisfies

$$\varepsilon = k\int_0^t C_1(x,s)ds. \tag{3}$$

From (2) and (3) the second equation in (1) is obtained where we represented k by E.

The third equation in (1) represents the degradation of the polymer and β_1, β_2 are physical constant which are material dependent. It is expected that as the polymer erodes, the diffusion of the drug concentration becomes larger, so we define

$$D_1(M) = \lambda e^{\frac{M_0}{M_0+M}}, \tag{4}$$

where M_0 is the initial molecular weight.

Let us now consider the drug dynamics in the vitreous, where the diffusion of drug occurs from the polymer towards the vitreous and the retina. In general, mass transport in the

 ISBN: 978-84-616-2723-3

vitreous is not described by diffusion only, but convection is equally important. Convection is due to the steady permeation of the aqueous humor through the vitreous, and diffusion is driven by the concentration gradient. To simulate the dynamics of drug in the vitreous we take into account a diffusion reaction equation, where the velocity of aqueous permeation ([3]) is given by Darcy's law in Ω_2, as follows:

$$\frac{\partial C_2}{\partial t} + \mathbf{v}.\nabla C_2 - D_2 \Delta C_2 = 0 \,\texttt{in}\, \Omega_2 \times (0,T], \tag{5}$$

and

$$\begin{cases} \mathbf{v} = -\dfrac{K}{\mu_1}\nabla p \,\texttt{in}\, \Omega_2 \times (0,T] \\ \nabla.\mathbf{v} = 0 \,\texttt{in}\, \Omega_2 \times (0,T] \end{cases}. \tag{6}$$

In system (5) C_2 represents the concentration of the drug in the vitreous, D_2 is the diffusion coefficient of the drug in the vitreous and $\mathbf{v}$ the velocity of aqueous permeation given by (6). In this last system K is the permeability of the vitreous and μ_1 is the viscosity of the vitreous. The term $\dfrac{K}{\mu_1}$ is referred to as the hydraulic conductivity.

Equations (1-6) are completed with initial conditions represented by

$$\begin{cases} C_1 = c_0, \,\texttt{in}\, \Omega_1, \, t = 0 \\ \sigma = \sigma_0, \,\texttt{in}\, \Omega_1, \, t = 0 \\ M = M_0, \,\texttt{in}\, \Omega_1, \, t = 0 \\ C_2 = 0, \,\texttt{in}\, \Omega_2, \, t = 0 \\ \mathbf{v} = 0, \,\texttt{in}\, \Omega_2, \, t = 0 \\ p = 2000, \,\texttt{in}\, \Omega_2, \, t = 0 \end{cases}. \tag{7}$$

Boundary conditions of different type will be used in the model:

- Boundary conditions for the pressure:

$$p = 2000, \,\texttt{in}\, \partial\Omega_2, \cup \partial\Omega_3 \, t > 0,$$

$$p = 1200, \,\texttt{in}\, \partial\Omega_5, \, t > 0.$$

We note that $\partial\Omega_2, \cup \partial\Omega_3$ represent the hyaloid membrane $\partial\Omega_5,$ the retina.

- Interface boundary conditions for the flux of drug concentration:

$$D\nabla C_1.\eta = A(C_1 - C_2), \,\texttt{in}\, \partial\Omega_1, \, t > 0.$$

- Wall conditions for the velocity: $\mathbf{v} = 0$, in the boundary $\partial\Omega_4$, of vitreous chamber Ω_2, and in the boundary of the implant $\partial\Omega_1$ (Figure 3).

 ISBN: 978-84-616-2723-3

4 Numerical simulations

In this section we will present some simulations to illustrate the behaviour of drug concentration in the implant and in the vitreous. In the case the values of the constants were not available, we used values that make physical sense but that do not correspond to the intravitreous implant. For this reason this study has essentially qualitative character.

The numerical simulations have been obtained with $C_0 = 1.7887 \times 10^{-6}, mol/mm^3$, $M_0 = 0.5 \times 10^{-6}, mol/mm^3$ and $\sigma_0 = 0.5 \times 10^{-6}, mol/mm^3$.

The diffusion coefficient of the drug in the implant is defined considering $\lambda = 1 \times 10^{-11}$ in (4) and its diffusion coefficient in the vitreous is defined by $D_2 = 1 \times 10^{-8}$. We recall that the diffusion in the polymer will increase as the molecular weight decreases. The following values for the parameters:

$$k_1 = 1 \times 10^{-10},\ \beta_1 = 5 \times 10^{-4},\ \beta_2 = 1 \times 10^{-9},\ \mu = 2 \times 10^{-4},\ E = 1 \times 10^{-7},$$

and

$$A_c = 5 \times 10^{-5},\ D_v = 1 \times 10^{-11},\ \mu_1 = 0.7,\ \rho = 970,\ K = 0.7 \times 8.4 \times 10^{-8},$$

have been considered.

In Figure 4 the drug concentration at time $t = 5\,min$ and $t = 1\,h$ are presented. It can be observed that as time evolves the drug is released and less drug concentration is inside the implant.

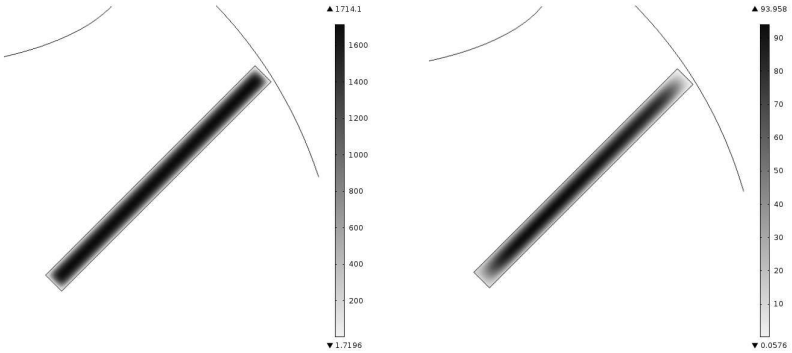

Figure 4: Drug concentration in the implant at $5\,min$ (left) and $1\,h$ (right).

The pressure in the vitreous chamber is showed in Figure 5. The evolution of the pressure from the top ($p = 2000\,Pa$) until the boundary of the vitreous chamber that is in contact with the retina ($p = 1200\,Pa$), can be observed. In Figure 6 the drug concentration in the vitreous chamber is plotted for $t = 5\,min$ and $t = 1\,h$.

 ISBN: 978-84-616-2723-3

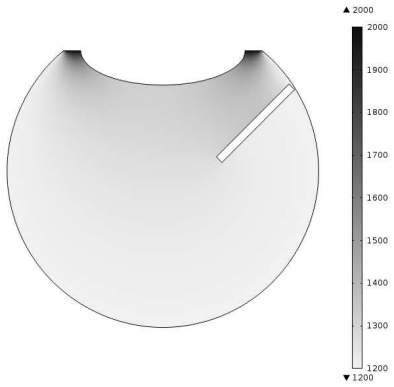

Figure 5: Steady pressure in the vitreous chamber.

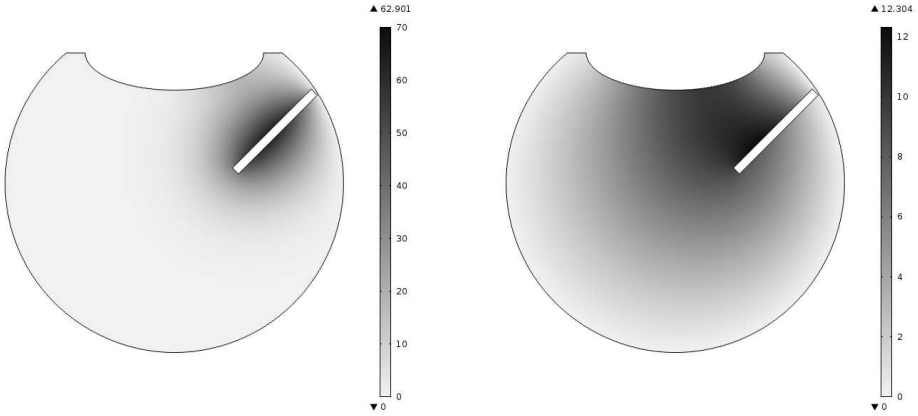

Figure 6: Drug concentration in the vitreous chamber at $5\,min$ (left) and $1\,h$ (right).

 ISBN: 978-84-616-2723-3

During the first instants of the delivery process, no drug is observed in the vitreous, except near the ocular implant, and as time increases more drug concentration is available to diffuse. For a better understanding of the qualitative behaviour of the drug concentration in the vitreous chamber, we present in Figure 7, the plot of drug concentration *vs* time at a point located inside the vitreous chamber and close to the lens. It can be observed that the drug concentration increases until it attains a maximum value, at $t = 30\,min$; for $t > 30\,min$ the drug concentration decreases until no drug concentration is present in the ocular implant. This qualitative behaviour is in agreement with medical data, establishing that for a duration of T months the maximum concentration of drug is attained for $\overline{T}$, where $\frac{T}{4} < \overline{T} < \frac{T}{3}$.

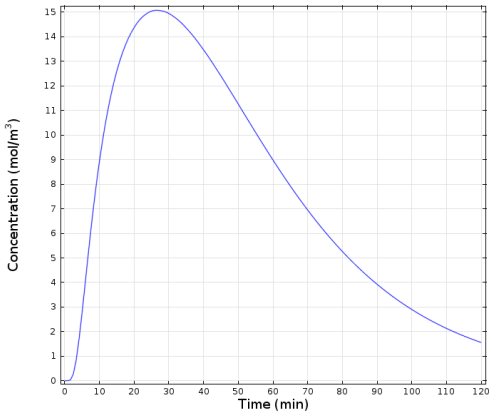

Figure 7: Drug concentration in the vitreous chamber along two hours.

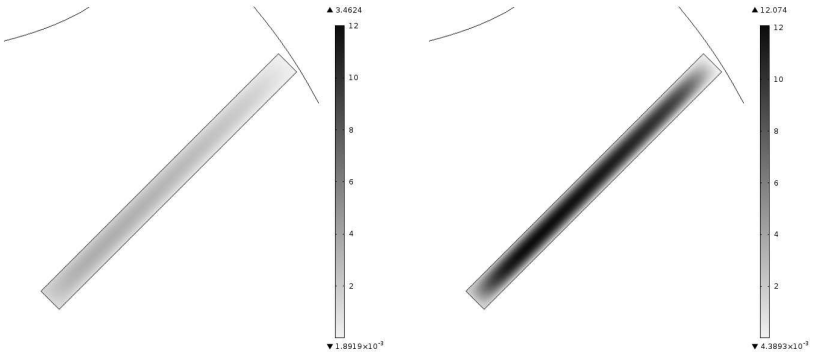

Figure 8: Drug concentration in the implant at $t = 2h$ - influence of degradation rate $\beta_1 = 5 \times 10^{-4}$ (left) and $\beta_1 = 1 \times 10^{-5}$ (right).

 ISBN: 978-84-616-2723-3

In Figure 8 the influence of the degradation rate is illustrate: a smaller value of β_1 leads to a slower degradation process and more concentration is observed inside the polymeric implant.

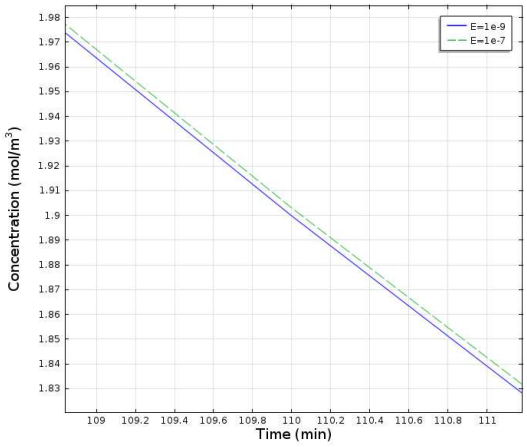

Figure 9: Drug concentration at a point of the boundary of the implant around $t = 110\,min$ - influence of E, $E = 1 \times 10^{-7}$ (top line) and $E = 1 \times 10^{-9}$ (down line).

In Figure 9 the influence of young modulus is illustrated. As expected the young modulus, E, delays the drug release once more drug concentration is observed inside the polymer. In fact as crosslinking density is proportional to E, the large is this parameter, the less elastic is the material and a more significant barrier difficult the release of drug.

5 Conclusion

A coupled model to simulate in vivo drug delivery from an intravitreal viscoelastic biodegradable implant has been developed. The whole process is described by a set of partial differential equations that take into account passive diffusion, convection resulting from the permeation of aqueous humor, stress driven diffusion and the degradation of the polymer. At the best of our knowledge the dynamics of drug desorption has not been described so far in the literature considering the simultaneous interplay between mechanical, physical and chemical effects. The numerical simulations show qualitative agreement with the physical expected behavior. The model clarifies the large influence of the degradation parameter in sustained drug delivery. The viscoelastic properties of the polymeric implant are also shown to be an effective control mechanism to delay or to speed up the release of drug. Mathematical modeling is a unique tool to explain transport mechanisms, and to help in implant design, avoiding expensive and extensive experimentation.

 ISBN: 978-84-616-2723-3

In future work physical values for all the parameters of the model should be retrieved. Also more realistic mechanical models will be considered and the heterogeneous structure of the vitreous, that is characteristic of elderly patients, should be taken into account.

Acknowledgements

This work was partially supported by the Centro de Matemática da Universidade de Coimbra (CMUC), funded by the European Regional Development Fund through the program COMPETE and by the Portuguese Government through the FCT - Fundação para a Ciência e Tecnologia under the projects PEst-C/MAT/UI0324/2011, SFR/BD/33703/2009, and by the project UTAustin/MAT/0066/2008.

References

[1] C.Hal F. Brinson, L. Catherine Brinson, *Polymer Engineering Science and Viscoelasticity: An Introduction*, Springer, 2008.

[2] C. W. Misner, K. S. Thorne and J. A. Wheeler, *Computer modeling of drug delivery to the posterior eye: effect of active transport and loss to choroidal blood flow*, Freeman, San Francisco, 1970.

[3] R. K. Balachandran and V. H. Barocas, *Computer modeling of drug delivery to the posterior eye: effect of active transport and loss to choroidal blood flow*, Pharmaceutical Research, **25** (2008) 2685-2696.

[4] S. Friedrich, Y.–L. Cheng, and B. Saville, *Finite element modeling of drug distribution in the vitreous humor of the rabbit eye*, Annals of Biomedical Engineering **25** (1997) 303-314.

[5] J. Kathawate and S. Acharya, *Computational modeling of intravitreal drug delivery in the vitreous chamber with different vitreous substitutes*,International Journal of Heat and Mass Transfer,**51**, (2008) 5598-5609.

[6] G. Pontrelli and F. de Monte, *Mass diffusion through two-layer porous media: an application to the drug-eluting stent*, International Journal of Heat and Mass Transfer, **50**, (2007) 3658-3669.

[7] M. S. Stay, J. Xu, T. W. Randolph, and V. H. Barocas, *Computer simulation of convective and diffusive transport of controlled-release drug in the vitreous humor*, Pharmaceutical Research, **20(1)**, (2003) 96-102.

 ISBN: 978-84-616-2723-3

[8] D. Cox, R. A. J. Phipps, B. Levine, A. Jacobs and D. Fowler, *Distribution of phencyclidine into vitreous humor*, Journal of Analytical Toxicology, **31**, (2007) 537-539.

[9] R. Avatar, D. Tandon, *A mathematical analysis of intravitreal drug transport*, Journal of Pharmaceutical Research, **7(1)**, (2008) 867-877.

[10] N. Haghjou, M. J. Abdekhodaie, Y. L. Cheng. M. Saadatmand, *Computer modeling of drug distribution after intravitreal administration*, W.A.S. Engineering and Tecnology, **53**, (2011) 706-716.

 ISBN: 978-84-616-2723-3