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

A mathematical model for controlled drug delivery in swelling polymers

José A. Ferreira[1], Mario Grassi[2], Elias Gudiño[1] and Paula de Oliveira [1]

[1] *CMUC, Department of Mathematics, University of Coimbra*

[2] *Department of Chemical Engineering, University of Trieste*

emails: ferreira@mat.uc.pt, mariog@dicamp.univ.trieste.it, egudino@gmail.com, poliveir@mat.uc.pt

Abstract

We propose a one-dimensional model to describe the sorption of a solvent by a polymeric membrane, followed by polymer swelling and drug release. We assume that the solvent diffuses into the membrane and induces a stress driven diffusion, that causes a non-Fickian mass flux. We assume that the drug is present in two states (dissolved and undissolved) and that its transport occurs by Fickian diffusion and non-linear dissolution. Polymer swelling is tracked with a volume conservation equation. The system of partial differential equations that define the model is numerically solved.

A qualitative analysis of the dependence of the solutions on the parameters of the model shows a complete agrement with the expected physical behavior.

Key words: non-Fickian, viscoelasticity, drug delivery
MSC 2000: 76Axx, 65Mxx, 35Qxx

1 Introduction

In this paper we study a one-dimensional model for the diffusion of a solvent into a polymeric membrane containing an initial drug load, followed by drug release. One of the main problems in controlled drug delivery is the accurate description of this kind of phenomena. By understanding the physical aspects of drug release, mathematical models can be obtained in order to help the design of polymeric drug carriers. In the literature several models have been proposed to predict drug release kinetics [7, 8, 11, 12, 13, 17]. The model we propose takes into consideration the viscoelastic properties of the polymer as we assume that the

 ISBN: 978-84-616-2723-3

penetrant diffuses into the membrane and causes a deformation that induces a non-Fickian mass flux. Assuming that drug release starts as soon as the solvent diffuses into the polymer we combine the non-Fickian sorption with a Fickian desorption, a non-linear dissolution and polymer swelling.

Several authors [2, 4, 14, 15, 16] agree that two main phenomena must be taken into consideration when describing the diffusion of a liquid solvent into a polymer. First the rate of diffusion of the solvent and second the change in the internal structure of the polymer. As the classical Fick's law does not take into consideration the second phenomenon, a modified flux resulting from the sum of a Fickian flux J_F and a non Fickian flux J_{NF} must be considered, that is

$$\frac{\partial C_s}{\partial t} = -\frac{\partial}{\partial x}(J_F(C_s) + J_{NF}(\sigma_s)) \ , \tag{1}$$

where C_s stands for the concentration of the solvent, σ_s stands for the stress, $J_F(C_s) = -(D(C_s)\frac{\partial}{\partial x}C_s)$ and $J_{NF}(\sigma_s) = -(D_v(C_s)\frac{\partial}{\partial x}\sigma_s)$. The functions $D(C_s)$and $D_v(C_s)$ denote the Fickian diffusion coefficient and a viscoelastic diffusion coefficient respectively.

We will introduce the strain ϵ as a third variable in (1) by considering a constitutive relationships between stress and strain. Many such relationships have been proposed in the literature [3, 5, 9, 10]. In this paper we consider a Boltzmann integral of type

$$\sigma_s(t) = -\int_0^t E(t-r)\frac{\partial \epsilon}{\partial r}(r)dr \ , \tag{2}$$

where $E(t)$ is the relaxation modulus corresponding to a Maxwell-Wiechert model [1]. In order to eliminate the strain as variable when (2) is introduced in (1), we consider a non-linear functional relation between strain and concentration

$$\epsilon = f(C_s) \ ,$$

where f will be obtained from physical considerations on polymer properties.

In Section 2 we establish a mathematical model to describe the absorbtion, swelling of the membrane and drug release. In Section 3 we propose concentration dependent functional relations for the strain and the viscoelastic diffusion coefficient. In Section 4 an implicit-explicit (IMEX) numerical method is used to numerically solve the model. In Section 5 some plots are shown to illustrate the behavior of the numerical solutions. Finally in Section 6 some conclusions are presented.

2 Mathematical Model

Let us consider a polymeric membrane, with initial drug loading C_{sd}^0. As dissolved drug diffuses out, solid (undissolved) drug dissolves. The following assumptions are made in the model: (a) the transport of liquid within the membrane occurs by non-Fickian diffusion;

 ISBN: 978-84-616-2723-3

(b) the transport of drug out of the membrane occurs by Fickian diffusion and non-linear dissolution; (c) a perfect sink condition is maintained for the drug and an equilibrium concentration is maintained for the liquid.

The evolution of solvent penetration, drug diffusion and dissolution are described by the following equations in the domain $\Omega \subset \mathbb{R}$ and $t > 0$,

$$\frac{\partial C_s}{\partial t} = \frac{\partial}{\partial x}\left(D_s(C_s)\frac{\partial C_s}{\partial x} + D_v(C_s)\frac{\partial \sigma_s}{\partial x}\right) , \tag{3}$$

$$\frac{\partial C_d}{\partial t} = \frac{\partial}{\partial x}\left(D_d(C_s)\frac{\partial C_d}{\partial x}\right) + K_d\left(\frac{C_{sd} - C_d}{C_{sd}}\right)C_s , \tag{4}$$

$$\frac{\partial C_{sd}}{\partial t} = -K_d\left(\frac{C_{sd} - C_d}{C_{sd}}\right)C_s , \tag{5}$$

where C_d, C_{sd} denotes the concentration of dissolved and undissolved drug respectively, D_s, D_d the diffusion coefficients of the solvent and dissolved drug respectively and K_d the constant dissolution rate of the drug.

Equations (3)-(5) are completed with initial conditions

$$C_s = C_s^0,\ C_d = 0,\ C_{sd} = C_{sd}^0\ :\ \text{for } t = 0,\ -L_0 \le x \le L_0 , \tag{6}$$

where $C_s^0,\ C_{sd}^0 \in \mathbb{R}$ are positive constants. Symmetry conditions are applied at $x = 0$, hence we consider

$$\frac{\partial C_s}{\partial x} = \frac{\partial C_d}{\partial x} = 0 \quad : \quad \text{for } t > 0,\ x = 0 . \tag{7}$$

At the membrane surface the boundary conditions are

$$C_s = C_s^e,\ C_d = 0 :\ \text{for } t > 0,\ x = L(t) , \tag{8}$$

where $C_s^e \in \mathbb{R}$ is a positive constant representing the concentration of the liquid agent in the exterior of the membrane and $L(t)$ is the thickness of the membrane for a given t.

In order to track the moving front due to swelling, we consider the following volume conservation equation

$$L(t) = \int_0^{L(t)} \left[\frac{1}{\rho_s}C_s(x,t) + \frac{1}{\rho_d}\left(C_d(x,t) + C_{sd}(x,t)\right)\right] dx ,$$

where ρ_s and ρ_d denote the density of solvent and the drug respectively. Then taking time derivative we deduce

$$\frac{\partial L(t)}{\partial t} = \frac{1}{1 - \left(\frac{C_w^e}{\rho_s} + \frac{C_{sd}(L(t))}{\rho_d}\right)}\left[\frac{1}{\rho_s}\left(D_s(C_s^e)\frac{\partial C_s}{\partial x}(L(t),t) + D_v(C_s^e)\frac{\partial \sigma_s}{\partial x}(L(t),t)\right) + \frac{1}{\rho_d}D_d(C_s^e)\frac{\partial C_d}{\partial x}(L(t),t)\right] . \tag{9}$$

 ISBN: 978-84-616-2723-3

3 Viscoelastic behavior

In order to model the viscoelastic behavior of the polymer, we consider a Maxwell-Wiechert model [1] with $m+1$ arms in parallel as shown in figure 1. Its relaxation modulus $E(t)$ is represented by

$$E(t) = \sum_{i=1}^{m} E_i e^{\frac{-t}{\tau_i}} + E_0 \ , \tag{10}$$

where the $E_i's$ and the $\mu_i's$ respectively denote the Young modulus of the spring elements and the viscosity of the dampers. The parameters $\tau_i = \frac{\mu_i}{E_i}$ represent the relaxation times associated to each of the m Maxwell fluid arms and E_0 stands for the Young modulus of the free spring.

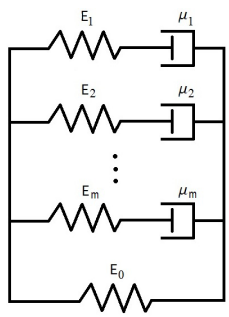

Figure 1: Maxwell-Wiechert model

To relate polymer deformation ϵ and solvent concentration C_s, we begin by assuming that the deformation ϵ occurs only in one direction, thus we have

$$\epsilon = \frac{\Delta x - \Delta x_0}{\Delta x_0} \ , \tag{11}$$

where Δx_0 stands for the thickness of Ω in the dry state and Δx for the thickness after swelling.

Let V_0 and V_s represent respectively the volume of the membrane in the dry state and the volume of solvent absorbed up to time t. From (11) it follows that $\epsilon = V_s/V_0$.

Let m_s and ρ_s denote the solvent mass and density respectively. As $V_s = m_s/\rho_s$, we deduce

$$\epsilon = \frac{m_s}{\rho_s V_0} \ , \tag{12}$$

and then considering that C_s is defined by $C_s = m_s/(V_0 + V_s)$, we obtain

$$\epsilon = f(C_s) = \frac{C_s}{\rho_s - C_s} \ . \tag{13}$$

 ISBN: 978-84-616-2723-3

Then from (10) and (13) we rewrite (2) as

$$\sigma_s = -\left(\sum_{i=0}^{m} E_i\right)\nabla f_s + \int_0^t \left(\sum_{i=1}^{m} \frac{E_i}{\tau_i} e^{-\frac{t-s}{\tau_i}}\right)\nabla f_s(s)ds \ . \tag{14}$$

To establish a functional relation for the viscoelastic diffusion coefficient D_v we begin by assuming that there exists a stress gradient $\nabla\sigma$. This implies the existence of a velocity field ν. Then the non-Fickian flux J_{NF} can be interpreted as a convective field of form

$$J_{NF} = \nu C_s \ . \tag{15}$$

The velocity field ν can be computed using the Hagen-Poiseuille equation and thus we have

$$\nu = -\frac{L^2}{8\hat{\mu}}\nabla p \ , \tag{16}$$

where L stands for the length of a virtual cross section of the polymeric sample available for the convective flux, p is the pressure drop and $\hat{\mu}$ represents the viscosity of a polymer-solvent solution characterized by a polymer concentration equal to C_s (local solvent concentration). Thus from (15), (16) and identifying the pressure p with the viscoelastic stress σ_s we conclude that

$$D_v(C_s) = \frac{L^2 C_s}{8\hat{\mu}} \ . \tag{17}$$

From (11) and (13), we have

$$V_s = \frac{C_s}{\rho_s - C_s} V_0 \ ,$$

and as $V_0 = \Delta x_0 S$, we have

$$\frac{V_s}{\Delta x_0} = \frac{C_s}{\rho_s - C_s} S \ . \tag{18}$$

The first member in (18) can be interpreted as a virtual cross section S_v available for convective flow. As $S_v = L^2$ and $S = L_0^2$ where L_0 is the length of the dry sample, we deduce from (17) and (18) that

$$D_v(C_s) = \frac{C_s^2}{\rho_s - C_s}\frac{L_0^2}{8\mu} \ . \tag{19}$$

For the Fickian diffusion coefficients $D_s(C_s)$ and $D_d(C_d)$, a Fujita-type [6] exponential dependence is assumed with

$$D_s(C_s) = D_{eq_s} exp(-\beta_s(1 - \frac{C_s}{C_s^e})) \ , \tag{20}$$

$$D_d(C_s) = D_{eq_d} exp(-\beta_d(1 - \frac{C_s}{C_s^e})) \ , \tag{21}$$

where D_{eq_s}, D_{eq_d} represent respectively the diffusion coefficient of the solvent and the dissolved drug in the fully swollen sample and β_s, β_d are positive dimensionless constants.

 ISBN: 978-84-616-2723-3

4 Numerical scheme

In this section we propose a coupled IMEX method to solve the initial boundary value problem (3)-(9). We denote by C_{s_h}, C_{d_h} and C_{sd_h} the full-discrete approximations of C_s, C_d and C_{sd} respectively.

In $[0,T]$ we consider a grid $J=\{t_n, n=0,1,...,M\}$ with $t_0=0$, $t_M=T$ and $t_n-t_{n-1}=\Delta t$. We denote by D_{-t} the usual backward finite difference operator with respect to the time variable t.

To discretize the spatial domain, as the boundary is changing in time, we consider in each interval $[0,L(t_n)]$ a grid $I(t_n)=\{x_i,\ j=0,1,..,N(t_n)\}$ with $x_0=0$, $r_{N(t_n)}=L(t_n)$ and $x_j-x_{j-1}=\Delta x$. We denote by D_{-x} and D_x respectively the usual backward and forward finite difference operators with respect to the space variable x.

The IMEX method is defined by

$$\begin{aligned} D_{-t}C^n_{s_h}(x_j) &= D_x\left(D_s(M_hC^{n-1}_{s_h}(x_j))D_{-x}C^n_{s_h}(x_j)\right) \\ &\quad +D_x\left(D_v(M_hC^{n-1}_{s_h}(x_j))D_{-x}\sigma^{n-1}_{s_h}(x_j)\right)\ , \qquad (22)\\ D_{-t}C^n_{d_h}(x_j) &= D_x\left(D_d(M_hC^n_{s_h}(x_j))D_{-x}C^n_{d_h}(x_j)\right) \\ &\quad +K_d\left(\frac{C^n_{sd_h}(x_j)-C^n_{d_h}(x_j)}{C^n_{sd_h}(x_j)}\right)C^n_{s_h}(x_j)\ , \qquad (23)\\ D_{-t}C^n_{sd_h}(x_j) &= -K_d\left(\frac{C^n_{sd_h}(x_j)-C^n_{d_h}(x_j)}{C^n_{sd_h}(x_j)}\right)C^n_{s_h}(x_j)\ , \qquad (24) \end{aligned}$$

where

$$M_hu_h(x_j)=\frac{1}{2}(u_h(x_{j-1})+u_h(x_j)).$$

We couple (22)-(24) with initial conditions

$$C^0_{s_h}=C^0_s,\ C^0_{d_h}=0,\ C_{sd_h}=C^0_{sd}\ :\ \text{for } t=0,\ 0\le x_j\le L_0\ , \qquad (25)$$

and boundary conditions

$$\begin{aligned} C_{s_h}=C^e_s,\ C_{d_h}=0 &\quad :\quad \text{for } n>0,\ x_j=L(t_n)\ , \qquad (26)\\ D_xC_{s_h}=D_xC_{d_h}=0 &\quad :\quad \text{for } n>0,\ x_j=0\ . \qquad (27) \end{aligned}$$

The moving front is tracked with the following discretization of equation (9):

$$\begin{aligned} L(t_{n+1}) &= \frac{\Delta t}{1-\left(\frac{C^e_w}{\rho_s}+\frac{C_{sd}(L(t_n))}{\rho_d}\right)}\left[\frac{1}{\rho_s}D_s(C^e_s)D_{-x}C_{s_h}(L(t_n),t_n)\right. \\ &\quad \left.+\frac{1}{\rho_s}D_v(C^e_s)D_{-x}\sigma_{s_h}(L(t_n),t_n)+\frac{1}{\rho_d}D_d(C^e_s)D_{-x}C_{d_h}(L(t_n),t_n)\right]+L_0\ . \qquad (28) \end{aligned}$$

 ISBN: 978-84-616-2723-3

We compute the concentration profiles at time step t_n using the known concentration profiles at t_{n-1} with boundary conditions (26) and (27). Then we use (28) to obtain the new front position for the next time step.

5 Numerical Results

In this section we exhibit numerical results for the IBVP (3)-(9) using the method (22)-(28). In the Maxwell-Wiechert model we consider $m = 3$, that is three Maxwell fluid arms in parallel with a free spring. The following values for the parameters have been considered,

$$
\begin{aligned}
L_0 &= 1 \times 10^{-3}\ m,\ D_{eq_s} = 3.74 \times 10^{-9}\ m^2/s,\ D_{eq_d} = 2.72 \times 10^{-9}\ m^2/s,\ \beta_s = 0.5,\\
\beta_d &= 0.6,\ \hat{\mu} = 1 \times 10^5\ Pas,\ E_1 = 1000\ Pa,\ E_2 = 600\ Pa,\ E_3 = 400\ Pa,\ E_0 = 1000\ Pa,\\
\mu_1 &= 5\ Pas,\ \mu_2 = 3\ Pas,\ \mu_3 = 2\ Pas,\ \rho_l = 1000\ kg/m^3,\ \rho_p = 1175\ kg/m^3,\\
\rho_d &= 1400\ kg/m^3,\ C_s^e = 450\ Kg/m^3,\ C_s^0 = 0\ Kg/m^3,\ C_{sd}^0 = 400\ Kg/m^3,\\
K_d &= 1 \times 10^{-1}\ s^{-1},\ \Delta t = 0.015\ s \text{ and } \Delta x = 1 \times 10^{-5}\ m\ .
\end{aligned}
$$

In Figure 2 we plotted the behavior of the concentration of the solvent as it diffuses into the membrane for different values of t. The left part of the domain correspond to the inner part of the membrane where symmetry conditions were considered. The right part correspond to the swelling front where the constant source of concentration C_s^e is assume. We observe that the solutions develop from low levels of concentration to high levels of concentration as expected, since the transport occurs from right to left in the plot. Also the amount of solvent inside the membrane increases with time.

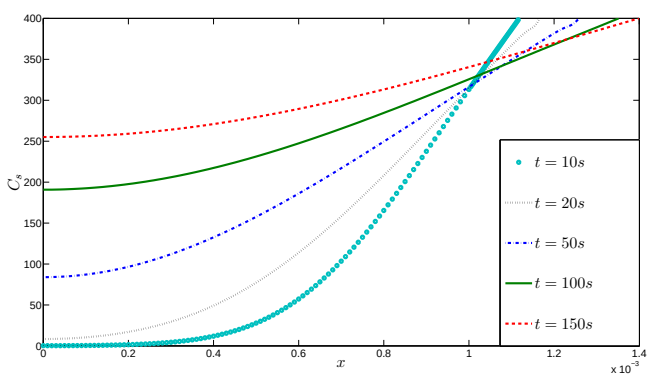

Figure 2: C_s for different values of t

 ISBN: 978-84-616-2723-3

In Figure 3 we show a plot of the concentration of dissolved drug inside of the membrane for different values of t. As before, the left part of the domain correspond to the inner part of the membrane where symmetry conditions were considered. The right part correspond to the swelling front where a perfect sink condition is assumed. We observe that as expected regions where the concentration of dissolved drug is high correspond to regions where the concentration of the solvent is high. As we are removing the dissolved drug that reaches the moving front, we also observe that after some time the amount of dissolved drug inside of the membrane decreases, since the initial drug load C_{sd}^0 is constant.

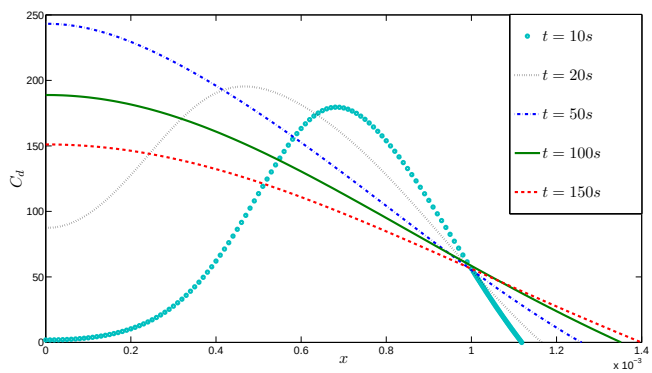

Figure 3: C_d for different values of t

In Figure 4 we present a plot of the concentration of solid drug inside of the membrane for different values of t. We observe that the solutions are consistent with the plots of the concentration for the solvent and dissolved drug. Regions where the concentration of solid drug is low correspond to regions where the concentration of solvent and dissolved drug are high and vice versa.

In Figure 5 we plotted the dimensionless movement in time of the swelling front defined by $L(t)/L_0$. We observe that the initial solvent absorption causes an initial rapid growth of the swelling followed by the reach of an equilibrium state.

By $M_d/M_{sd_0}(t)$ we represent the relative drug release at time t, defined as

$$M_d/M_{sd_0}(t) = 1 - \frac{1}{L_0 C_{sd}^0} \int_0^{L(t)} \left(C_d(x,t) + C_s(x,t)\right)\ dx\ .$$

and by $M_s/M_\infty(t)$ the mass of the liquid solvent inside of the matrix at time t, defined as

$$M_s/M_\infty(t) = \frac{1}{L_0 C_s^e} \int_0^{L(t)} C_s(x,t) dr\ dx\ .$$

 ISBN: 978-84-616-2723-3

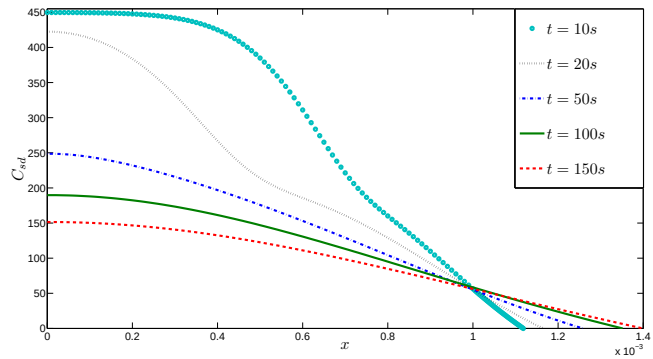

Figure 4: C_{sd} for different values of t

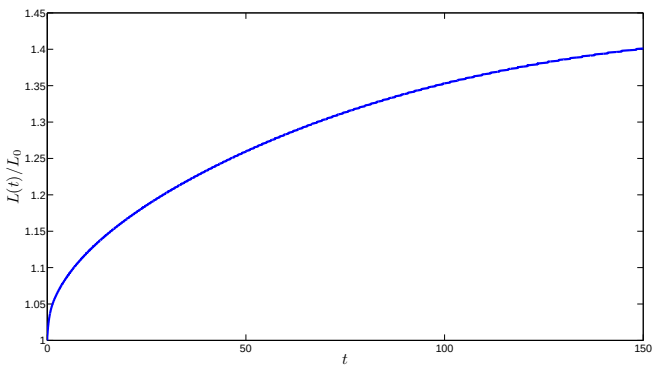

Figure 5: Swelling front

In Figures (6) and 7 we show respectively plots of $L(t)/L_0$ and M_d/M_{sd_0} as functions of E_0. We observe that $L(t)/L_0$ is a decreasing function of E_0. As the swelling is decreases, more dissolved drug accumulates at the moving front where the perfect sink condition is assumed. Then as we observe in Figure 7 the relative drug release is an increasing function of E_0.

In order to compare the effects of swelling on the drug release in what follows we consider that the boundary is fixed, that is $L(t) = L_0$ for all t. In Figures (8) and 9 we plotted respectively M_s/M_∞ and M_d/M_{sd_0} as functions of E_0. We observe that M_s/M_∞ is a decreasing function of E_0. As less solvent diffuses into the matrix, a smaller amount of dissolved drug is present inside of the membrane. Since the effect of swelling is not considered, the amount of drug that accumulates at the moving front decreases. Then as

 ISBN: 978-84-616-2723-3

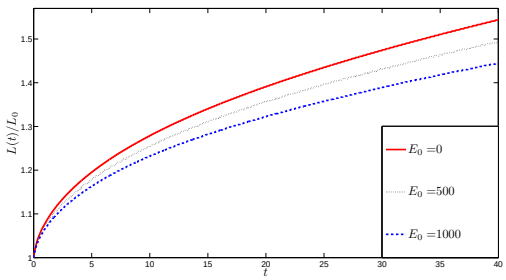

Figure 6: Swelling front, $L(t)/L_0$ as a function of E_0

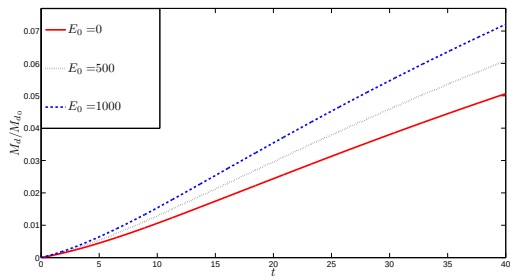

Figure 7: Relative mass of drug released, M_d/M_{sd_0} as a function of E_0

we observe in Figure 9 the relative drug release is a decreasing function of E_0.

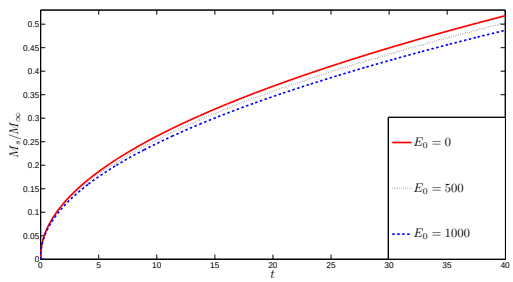

Figure 8: Mass of solvent inside of the membrane, M_s/M_∞ as a function of E_0 with $L(t) = L_0$

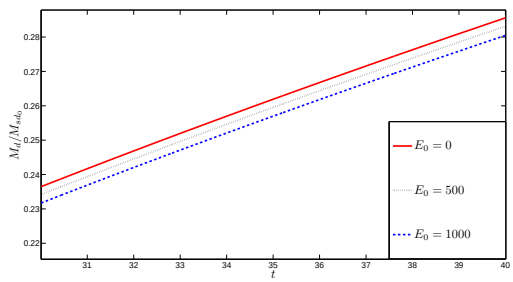

Figure 9: Relative mass of drug released, M_d/M_{sd_0} as a function of E_0 with $L(t) = L_0$

In order to illustrate the effects of drug release in the swelling we consider that no dispersed drug is present in the membrane, that is $C^0_{sd} = 0$. In Figures 10 and 11 we plotted respectively M_s/M_∞ and $L(t)/L_0$ as functions of E_0. We observe that in both cases they are decreasing functions of E_0. If we compare Figures 10 and 8 we observe that the effects of E_0 over the solutions are more significant when we consider swelling. Comparing Figures 6 and 11 we observe that when no drug is present the membrane shows more swelling for the same values of E_0.

6 Conclusions

In this paper, the drug release from a polymeric membrane is described by a mathematical model consisting of a system of partial differential equations coupled with initial conditions over a moving boundary that represents the swelling of the polymer. The viscoelastic

 ISBN: 978-84-616-2723-3

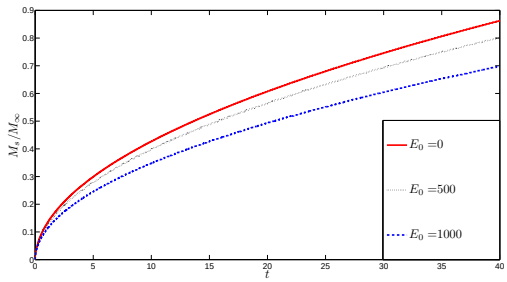

Figure 10: Mass of solvent inside of the membrane, M_s/M_∞ as a function of E_0 with $C^0_{sd} = 0$

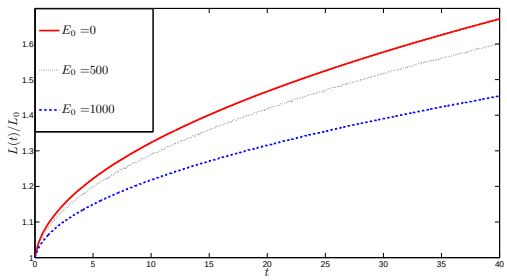

Figure 11: Swelling front, $L(t)/L_0$ as a function of E_0 with $C^0_{sd} = 0$

behavior of the polymer is defined by considering that the transport of solvent into the membrane occurs by non-Fickian diffusion. The swelling associated to solvent uptake is tracked with a volume conservation equation and the drug release is described with an equation that combines Fickian drug diffusion (associated to solvent uptake) and non-linear dissolution. The qualitative behavior of the model is in agreement with expected physical behavior. The model can be used to predict drug release kinetics and help in drug delivery design.

Acknowledgements

This work was partially supported by the Centro de 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, UTAustin/MAT/0066/2008 and by Fondo PRIN 2010-2011 (20109PLMH2).

References

[1] H. F. Brinson and L. C. Brinson, *Polymer Engineering Science and Viscoelasticity, An Introduction*, Springer, New York, 2008.

[2] G. Camera-Roda and G. C. Sarti, *Mass transport with relaxation in polymers*, AIChE J. **36** (1990) 851–860.

[3] D. S. Cohen and D. A. Edwards, *A mathematical model for a dissolving polymer*, AIChE J. **41** (1995) 2345–2355.

 ISBN: 978-84-616-2723-3

[4] D. S. Cohen and A. B. White Jr., *Sharp fronts due to diffusion and viscoelastic relaxation in polymers*, SIAM J. Appl. Math. **51** (1991) 472–483.

[5] D. A. Edwards, *Non-Fickian Diffusion in thin polymer films*, J. Polym. Sci. Part B Polym. Phys. **34** (1996) 981–997.

[6] H. Fujita, *Diffusion in polymer-diluent systems*, Fortschr. Hochpolym. Forsch. **3** (1961) 1–47.

[7] M. Grassi and G. Grassi, *Mathematical modeling and controlled drug delivery: matrix systems*, Curr. Drug Deliv., **2** (2005) 97–116.

[8] M. Grassi, G. Grassi, R. Lapasin and I. Colombo, *Understanding Drug Release and Absorption Mechanisms: A Physical and Mathematical Approach*, CRC Press, Boca Raton, 2006.

[9] Q. Liu and D. De Kee, *Modeling of diffusion through polymeric membranes*, Rheol. Acta **44** (2005) 287–294.

[10] Q. Liu, X. Wang and D. De Kee, *Mass transport through swelling membranes*, Int. J. Eng. Sci. **43** (2005) 1464–1470.

[11] D. R. Paul and S. K. McSpadden, *Diffusional release of a solute from a polymer matrix*, J. Membr. Sci. **1** (1976) 33–48.

[12] D. E. Pelinovsky and W. Zhao, *Multilevel computations of dispersed drug release*, Numer. Methods Partial Diff. Equations, **29** (2013) 1391–1415.

[13] F.A. Radu, M. Bause, P. Knabner, G.W. Lee and W.C Friess, *Modeling of drug release from collagen matrices*, J. Pharm. Sci. **91(4)** (2002) 964–72.

[14] L. N. Thomas and A. H. Windle, *A deformation model for case II diffusion*, Polym. **21** (1980) 613–619.

[15] L. N. Thomas and A. H. Windle, *Diffusion mechanics of the system PMMA-methano*, Polym. **22** (1981) 627–639.

[16] L. N. Thomas and A. H. Windle, *A theory of case II diffusion*, Polym., **23** (1982) 529–542.

[17] X. Y. Wu and Y. Zhou, *Studies of diffusional release of a dispersed solute from polymeric matrices by finite element method*, J. Pharm. Sci, **88** (1999) 1050–1057.

 ISBN: 978-84-616-2723-3