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Analytical and Numerical Study of Diffusion through Biodegradable Viscoelastic Materials

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Abstract

In this paper the transport of a drug through a viscoelastic biodegradable material is studied. The phenomenon is described by a set of three coupled partial differential equations that take into account passive diffusion, stress driven diffusion and the degradation of the material. The stability properties of the system are studied. Numerical simulations show an influence of viscoelastic and degradation parameters in agreement with the expected physical behaviour.

Key words: viscoelasticity, Young modulus, degradation

1 Introduction

In the past few decades biodegradable polymers have attracted the attention of many researchers mainly for their applications in controlled drug delivery [5]. In this paper we will consider transport of a drug through a viscoelastic and hydrolyzed polymeric matrix.

The main actors in drug delivery are the living system, the composition of drug, the polymeric matrix where it is dispersed and the external conditions of release as for example the presence of an electric field or a heat source. To obtain a predefined release profile the mechanisms of control can act essentially on the polymeric matrix and the external conditions. In this paper we study a mathematical model to predict the influence of the mechanical and chemical properties of the polymer - viscoelasticity and degradation- in

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the release rate. As degradation proceeds, the polymer molecular weight decreases and diffusional paths open through the matrix allowing solved drug molecules to leave the device [6]. Because of the increasing permeability of the system upon polymer degradation, the constant diffusion coefficient is replaced by a molecular weight dependent diffusion coefficient [7]. The viscoelastic behaviour of the polymeric matrix is described by a Maxwell fluid model [1, 2, 3].

The paper is organised as follows. In Section 2 the mathematical model is presented. In Section 3 the qualitative behaviour of the released mass is studied. A fully discrete method that mimics the properties of the continuous problem is described in Section 4 and numerical simulations are exhibited in Section 5. Finally in Section 6 some conclusions are addressed.

2 The mathematical model

We consider a polymer filling a bounded domain $\Omega \subseteq \mathbb{R}^n$ with boundary $\partial\Omega$. The diffusion of drug from this polymer is described by the following system of partial differential equations:

$$\begin{cases} \dfrac{\partial C}{\partial t} = \nabla(D(M)\nabla C) + \nabla(D_v \nabla\sigma) \ \texttt{in}\ \Omega \times (0,T], \\ \dfrac{\partial \sigma}{\partial t} + \dfrac{E}{\mu}\sigma = EC \ \texttt{in}\ \Omega \times (0,T], \\ \dfrac{\partial M}{\partial t} + \beta_1 M = \beta_2 C \ \texttt{in}\ \Omega \times (0,T], \end{cases} \tag{1}$$

where C represents the unknown concentration of the drug inside the polymer, σ is the unknown stress, M is the unknown molecular weight of the polymer. The viscoelastic influence in the drug transport is represented by the term $\nabla(D_v\nabla\sigma)$ where D_v is the so called viscoelastic diffusion coefficient. This term states that the polymer acts as a barrier to the diffusion: as the drug strains the polymer it reacts with a stress of opposite sign. To account for the increasing permeability of the system upon polymer degradation, the diffusion coefficient is defined as

$$D(M) = D_0 e^{\frac{M_0}{M+M_0}},$$

where D_0 is the diffusion coefficient of drug in the non hydrolyzed polymer and M_0 is its initial molecular weight. The second equation in (1) defines the viscoelastic behaviour of the polymer by the Maxwell fluid model [2, 3]

$$\frac{\partial \sigma}{\partial t} + \frac{E}{\mu}\sigma = E\frac{\partial \epsilon}{\partial t}$$

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where E represents the Young modulus of the material, μ its viscosity and ϵ is the strain produced by the drug molecules. If we assume that

$$\epsilon = k \int_0^t C(x,s)ds$$

where k is a positive constant we obtain the second equation in (1) where this constant has been absorbed by E. In the third equation of (1) β_1 and β_2 are constants that characterize the degradation properties of the material.

System (1) is completed with initial conditions

$$\begin{cases} C(x,0) = C_0,\ x \in \Omega, \\ \sigma(x,0) = \sigma_0,\ x \in \Omega, \\ M(x,0) = M_0,\ x \in \Omega, \end{cases}$$

and boundary conditions

$$\begin{cases} C(x,t) = 0 \ \ \texttt{on}\ \partial\Omega \times (0,T], \\ \sigma(x,t) = 0 \ \ \texttt{on}\ \partial\Omega \times (0,T], \\ M(x,t) = 0 \ \ \texttt{on}\ \partial\Omega \times (0,T], \end{cases}$$

where $\partial\Omega$ denotes the boundary of Ω.

3 Qualitative behaviour of a mass related functional

In this section we study the qualitative behaviour of the mass related functional

$$M(t) = \int_\Omega C^2(t)dx, \quad t \geq 0.$$

From the second equation of (1) we easily get

$$\sigma(t) = E \int_0^t e^{-\frac{E}{\mu}(t-s)} C(s)ds + \sigma(0)e^{-\frac{E}{\mu}t}, \quad t \geq 0.$$

Replacing in the first equation of (1) we obtain for C

$$\frac{\partial C}{\partial t} = \nabla(D(M)\nabla C) + E \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla(D_v \nabla C(s))ds \ \ in \ \ \Omega \times (0,T]. \tag{2}$$

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As $\frac{1}{2}M'(t) = \int_\Omega C(t)\frac{\partial C}{\partial t}(t)dx$ we deduce, considering (2)

$$\frac{1}{2}M'(t) = -\left\|\sqrt{D(M)}\nabla C(t)\right\|^2 - \left(E\int_0^t e^{-\frac{E}{\mu}(t-s)}D_v\nabla C(s)ds, \nabla C(t)\right), \tag{3}$$

where $(.,.)$ stands for the scalar product in $L^2(\Omega)$. From (3) we have

$$\frac{1}{2}M'(t) + \overline{D}_0\left\|\nabla C(t)\right\|^2 \leq \frac{D_v^2}{4\epsilon^2}E^2\left\|\int_0^t e^{-\frac{E}{\mu}(t-s)}\nabla C(s)ds\right\|^2 + \epsilon^2\left\|\nabla C(t)\right\|^2,$$

where $\overline{D}_0 \leq D$ and $\epsilon \neq 0$. Consequently we deduce

$$\frac{1}{2}M'(t) + (\overline{D}_0 - \epsilon^2)\left\|\nabla C(t)\right\|^2 \leq \frac{D_v^2}{4\epsilon^2}E^2\int_0^t e^{-2\frac{E}{\mu}(t-s)}ds\int_0^t\left\|\nabla C(s)\right\|^2 ds,$$

and then

$$M(t) + 2(\overline{D}_0 - \epsilon^2)\int_0^t\left\|\nabla C(s)\right\|^2 ds \leq \frac{D_v^2}{2\epsilon^2}\frac{E^2}{2\frac{E}{\mu}}\int_0^t\int_0^s\left\|\nabla C(\mu)\right\|^2 d\mu ds + M(0).$$

If ϵ^2 is such that

$$\overline{D}_0 - \epsilon^2 > 0$$

we obtain

$$\begin{aligned} M(t) + \int_0^t\left\|\nabla C(s)\right\|^2 ds &\leq \frac{D_v^2E^2}{\max\{1, 2(\overline{D}_0 - \epsilon^2)\}4\epsilon^2\frac{E}{\mu}}\int_0^t\int_0^s\left\|\nabla C(\mu)\right\|^2 d\mu ds \\ &+ \frac{1}{\max\{1, 2(\overline{D}_0 - \epsilon^2)\}}M(0). \end{aligned}$$

Finally Gronwall's Lemma [4] leads to

$$M(t) + \int_0^t\left\|\nabla C(s)\right\|^2 ds \leq \frac{1}{\max\{1, 2(\overline{D}_0 - \epsilon^2)\}}M(0)e^{\frac{D_v^2E^2}{\max\{1,2(\overline{D}_0-\epsilon^2)\}4\epsilon^2\frac{E}{\mu}}t}. \tag{4}$$

This last inequality establishes that $M(t)$ and $\int_0^t\left\|\nabla C(s)\right\|^2 ds$ are bounded for bounded intervals of time. We note that (4) can be improved by eliminating the exponential factor in its right hand side [8]. A stability result of type

$$M(t) + \int_0^t e^{-2\gamma(t-s)}\left\|\nabla C(s)\right\|^2 ds \leq M(0)$$

can then be stated for a convenient choice of the parameters of the model.

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4 A discrete model

In order to simplify the presentation we consider in what follows $\Omega = (0,1)$. We fix $h > 0$ and we introduce in $\overline{\Omega}$ the grid

$$I_h = \{x_i, i = 0, \ldots, N, x_0 = 0, x_N = 1, x_i - x_{i-1} = h, i = 1, \ldots, N\}.$$

Discretizing the spatial derivative using the second order finite difference discretization

$$\frac{\partial}{\partial x}(D(M)\frac{\partial C}{\partial x})(x_i,t) \simeq \frac{D(\frac{M(x_i,t)+M(x_{i+1},t)}{2})D_{-x}C(x_{i+1},t) - D(\frac{M(x_i,t)+M(x_{i-1},t)}{2})D_{-x}C(x_i,t)}{h},$$

where D_{-x} represents the backward finite difference operator. We replace (1) by the following ordinary differential system

$$\begin{cases} \dfrac{dC_i(t)}{dt} = \dfrac{1}{h}\left(D(A_hM_i(t))D_{-x}C_{i+1}(t) - D(A_hM_{i-1}(t))D_{-x}C_i(t)\right) + D_vD_{2,h}\sigma_i(t), \\ \dfrac{d\sigma_i(t)}{dt} + \dfrac{E}{\mu}\sigma_i(t) = EC_i(t), \\ \dfrac{dM_i(t)}{dt} + \beta_1 M_i(t) = \beta_2 C_i(t), \end{cases} \tag{5}$$

and where, for $i = 1, \ldots, N-1$, $C_i(t)$, $\sigma_i(t)$ and $M_i(t)$ stand for semi-discrete approximation of $C(t)$, $\sigma(t)$ and $M(t)$, respectively. In (5) A_h represents the average operator

$$A_hv(x_i) = \frac{1}{2}(v(x_i) + v(x_{i+1})),$$

and $D_{2,h}$ is the second-order finite difference operator

$$D_{2,h}u(x_i) = \frac{u(x_{i+1}) - 2u(x_i) + u(x_{i-1})}{h^2}, \quad i = 1, \ldots, N-1.$$

To solve system (5) we use the discretized boundary conditions

$$C_0(t) = C_N(t) = \sigma_0(t) = \sigma_N(t) = M_0(t) = M_N(t) = 0,$$

and the initial conditions

$$C_i(0) = C_0, \sigma_i(0) = \sigma_0, M_i(0) = M_0, \quad i = 1, \ldots, N.$$

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The time integration of (5) is performed considering as implicit-explicit approach, defined by

$$\begin{cases} \dfrac{C_i^{n+1}-C_i^n}{\Delta t} = \dfrac{1}{h}\left(D(A_hM_i^n)D_{-x}C_{i+1}^{n+1} - D(A_hM_{i-1}^n)D_{-x}C_i^{n+1}\right) + D_vD_{2,h}\sigma_i^n, \\ \dfrac{\sigma_i^{n+1}-\sigma_i^n}{\Delta t} + \dfrac{E}{\mu}\sigma_i^n = EC_i^{n+1}, \\ \dfrac{M_i^{n+1}-M_i^n}{\Delta t} + \beta_1 M_i^n = \beta_2 C_i^{n+1}. \end{cases} \tag{6}$$

In (6) C_i^n, σ_i^n, and M_i^n for $i = 1, ..., N$ stand for time for approximations of $C_i(t_n)$, $\sigma_i(t_n)$ and $M_i(t_n)$ in the time grid defined by

$$\{t_n, n = 0, \ldots, M, t_0 = 0, t_M = T, t_n - t_{n-1} = \Delta t, n = 1, \ldots, M-1\}.$$

System (6) is completed with the following conditions

$$C_0^n = C_N^n = \sigma_0^n = \sigma_N^n = M_0^n = M_N^n = 0, \quad n = 0, \ldots, M.$$

It can be shown that method (6) is second order consistent in space and first order in time. In the numerical simulations, that we present in Section 5, we consider the drug released mass defined by

$$M(t) = \int_\Omega C(x,0)dx - \int_\Omega C(x,t)dx, \tag{7}$$

for each $t \in [0, T]$.

5 Numerical results

In this section we illustrate the use of the numerical scheme (6). We take $C_0 = 1, M_0 = 0.5, \sigma_0 = 0.5, D_0 = 0.01, D_v = -1 \times 10^{-4}, \mu = 1 \times 10^{-2}, E = 1 \times 10^{-3}, \beta_1 = 0.1, \beta_2 = 1 \times 10^{-3}$, $\Delta t = 5 \times 10^{-4}, h = 1 \times 10^{-2}$. The units of the concentration are mol/mm^3. The units of other variables and parameters are such that the equations are dimensionally correct.

In Figure 1 the evolution of C in time is illustrated. As expected the drug concentration decreases in time. The evolution of M is plotted in Figure 2, where the decrease in time of the molecular weight is consequence of the polymer degradation. In order to see that the evolution inside the polymer is not spatially homogeneous, a plot of the molecular weight at $t = 4$ is presented in Figure 2(right).

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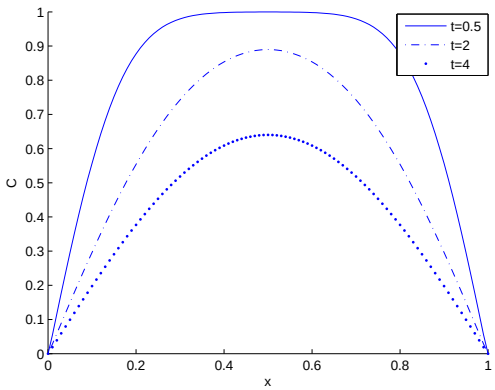

Figure 1: Concentration at different times.

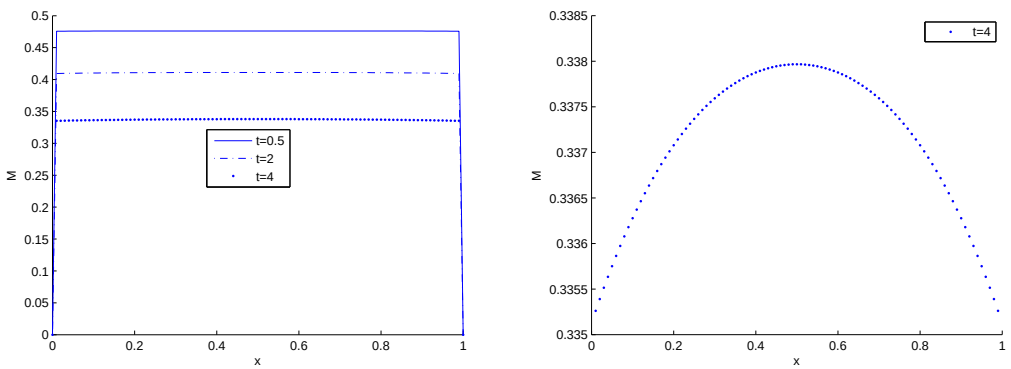

Figure 2: Molecular weight (left) at different times and a zoom of molecular weight at $t = 4$ (right).

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In Figure 3 the influence of diffusion on released mass and molecular weight are shown for $t = 0.5$, 2, 4. As D_0 increases the released mass increases because the diffusion process becomes faster. Consequently as D_0 increases the concentration inside the polymer decreases and from the third equation in (1) we conclude that the molecular weight decreases. Obviously that taking into account the non linear character of the problem this argument is naive and it can not be considered a general result. However in Figure 3 (right) we illustrate this ansatz for the data used in our simulations.

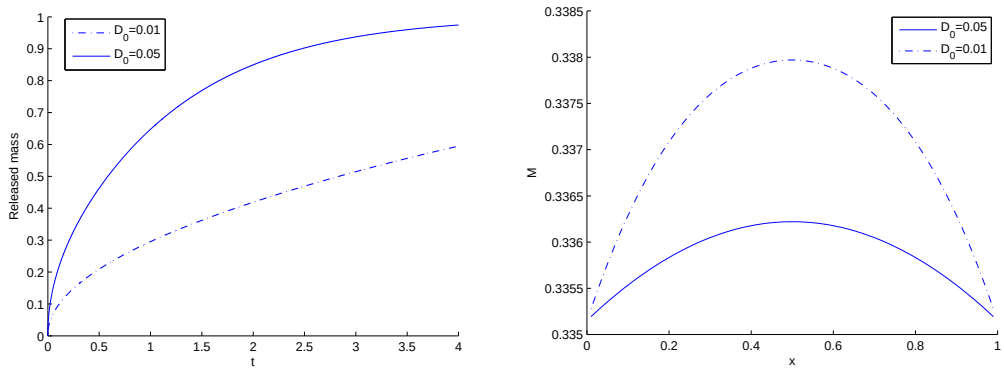

Figure 3: Influence of the diffusion on the released mass (left) and the molecular weight (right).

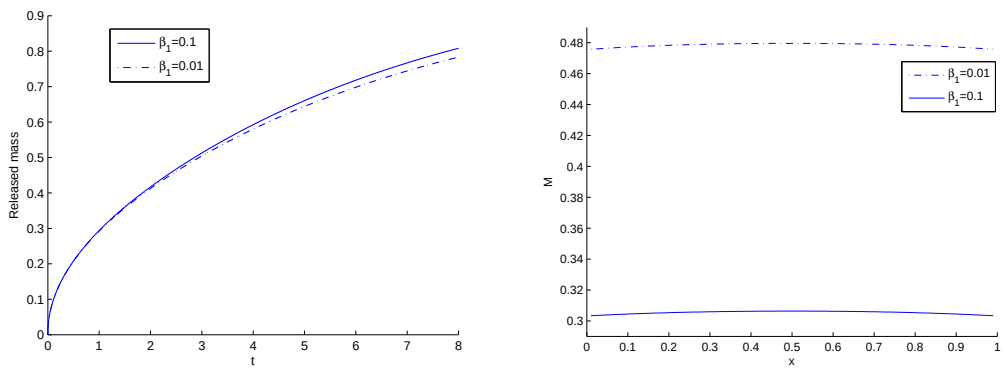

Figure 4: Influence of the degradation rate on the released mass (left) and molecular weight at $t = 8$ (right).

The influence of the degradation rate is presented in Figure 4. As expected if the degradation rate increases the rate delivery of the drug also increases. In the right of Figure

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4 we observe that the increase of the degradation rate is closely related with loss of molecular weight.

In Figure 5 we study the dependance of released mass on the viscoelastic diffusion coefficient D_v. We observe that the polymer acts as a barrier that difficults drug diffusion. The drug molecules strain the polymer and it exerts a stress of opposite sign. The non Fickian flux $-D_v(\nabla\sigma)$ is, in a certain sense a antiflux which decreases the Fickian flux $-D(\nabla C)$. From a mathematical point of view we represent this interpretation by considering $D_v < 0$. In agreement with this description the increase of $\mid D_v \mid$ leads to a delay of release.

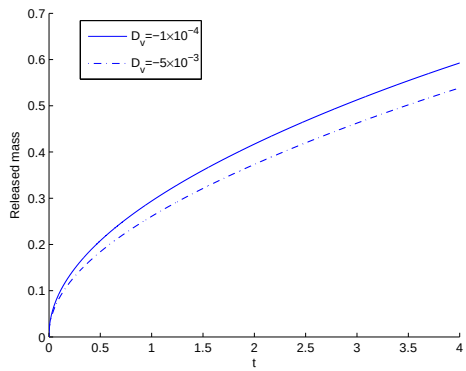

Figure 5: Influence of parameter D_v on the released mass.

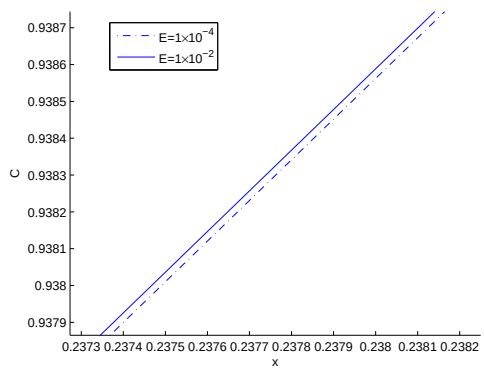

Figure 6: Influence of parameter E in the drug concentration at $t = 0.5$.

In Figure 6 the influence of Young modulus, E, in the drug concentration inside the polymer is presented at $t = 0.5$. The crosslink density of the polymer is proportional to

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Young modulus E and consequently as this constant increases the polymer offers more resistance to the exit of the drug, which is delayed.

6 Conclusion

A model to simulate transport through a biodegradable viscoelastic material is studied. The analytical treatment of the system of partial differential equations lead to the establishment of stability results. The influence of mechanical and degradation parameters is analysed, showing agreement with physical behaviour. We believe that with future improvements the model can be used as a tool to design biodegradable polymers with predefined properties.

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