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Dissolution and bulk erosion in viscoelastic materials: numerical study

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Abstract

A mathematical model to simulate drug delivery from a vicoelastic erodible matrix is presented in this paper. The drug is initially distributed in the matrix which is in contact with water. The entrance of water in the material changes the molecular weight and bulk erosion can be developed depending on how fast is this entrance and how fast degradation occurs. The viscoelastic properties of the matrix also change in the presence of water as the molecular weight changes. The model is represented by a system of quasi linear partial differential equations that take into account different phenomena: the uptake of water, the decreasing of the molecular weight, the viscolestic behaviour, the dissolution of the solid drug and the delivery of the dissolved drug. Numerical simulations illustrating the behaviour of the model are included.

Key words: dissolution, diffusion, molecular weight, bulk erosion, vicoelastic polymers, IMEX method

1 Mathematical model

We consider a biodegradable viscoelastic polymeric matrix, $\Omega \subseteq \mathbb{R}^2$, with boundary $\partial\Omega$ and containing a limited amount of drug. The matrix enters in contact with water and as the water diffuses into the matrix, a hydratation process, that modifies the viscoelastic properties of the polymer, takes place. The molecular weight decreases and the drug starts to dissolve.

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In [13] a system that describes the sorption of water, by a loaded erodible matrix and the release of drug was proposed. However the viscoelastic properties of the matrix were not considered. In this paper we present a general model, which generalizes the model in [13], by considering the viscoelastic behaviour of the polymer (see for instance [1],[2], [6],[10], [14], [16]).

We consider a system of partial differential equations (PDE's) that describe the whole process: the entrance of water into the polymer and its consumption in the hydrolysis process; the decreasing of the molecular weight; the evolution of the stress and strain; the dissolution and the diffusion of the dissolved drug. The system reads

$$\begin{cases} \dfrac{\partial C_W}{\partial t} = \nabla \cdot (D_W \nabla C_W) + \nabla \cdot (D_v \nabla \sigma) - k C_W M & \text{in } \Omega \times (0,T], \\ \dfrac{\partial M}{\partial t} = -k C_W M & \text{in } \Omega \times (0,T], \\ \dfrac{\partial \sigma}{\partial t} + \dfrac{E(M)}{\mu(M)}\sigma = -E(M)\dfrac{\partial C_W}{\partial t} & \text{in } \Omega \times (0,T], \\ \dfrac{\partial C_S}{\partial t} = -k_{dis} C_{Sn} C_{An} C_{Wn} & \text{in } \Omega \times (0,T], \\ \dfrac{\partial C_A}{\partial t} = \nabla \cdot (D(M) \nabla C_A) + k_{dis} C_{Sn} C_{An} C_{Wn} & \text{in } \Omega \times (0,T]. \end{cases} \tag{1}$$

In (1) C_W, C_S and C_A represent the concentration of water, solid drug and dissolved drug in the polymeric matrix, respectively, M is the molecular weight of the polymer and σ is the stress response to the strain exerted by the water molecules.

The first diffusion-reaction equation of (1) describes the diffusion of water into the matrix and its consumption in the hydrolysis. In this equation D_W represents the diffusion tensor of water in the polymeric matrix. We consider an isotropic medium where the diffusion tensors are diagonal with equal diagonal elements. For example, $D_W = D_W I$, where I is the 2×2 identity matrix. The viscoelastic opposition to the water entrance is represented by $\nabla \cdot (D_v \nabla \sigma)$ where D_v is a viscoelastic diffusion tensor. This term states that the polymer acts as a barrier to the diffusion of water into the polymeric matrix. The term $-kC_W M$ represents the consumption of water in the hydrolysis of the polymer([7]).

Since the water diffuses into the polymeric matrix the molecules of water react with the polymer and the bounds between the polymeric chains are broken leading to a decrease in the molecular weight of the matrix. This process is described by the second equation of (1) ([13]).

We assume that the viscoelastic behaviour of the polymer can be modelled by Maxwell fluid model

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

where E represents the Young modulus of the material, μ is its viscosity and ϵ is the strain produced by the water molecules. We assume that the strain and the concentration of water

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are proportional, that is, there $k_1 > 0$ such that $\epsilon = k_1 C_W$. As the polymer acts as a barrier to the entrance of the water, then σ and ϵ are of opposite sign, and a minus sign should be considered in the right hand side of (2) ([7]).

Based on the results presented for instance in [1], [2], [6], [10], [14] and [16], we assume that the Young modulus and the viscosity depend on the molecular weight. In fact the Young modulus varies significantly in a biodegradable polymeric matrix due to the heterogeneous nature of the hydrolysis reaction that leads to the cleavages of the polymeric chains. As the degradation processes evolves, the Young modulus decreases ([12]). Moreover a functional relation between the viscosity and the molecular weight represented by Mark-Houwink equation ([11]) is applied. The expressions used to represent the behaviours of $E(M)$ and $\mu((M))$ are $E(M) = E_0 M^\alpha$ and $\mu(M) = \mu_0 M^\beta$ where E_0, μ_0, α and β are constant ([11, 12]).

The evolution in time of the solid drug is described by the fourth equation of (1) where k_{dis} is the dissolution rate, C_{Sn} is the normalized concentration of solid drug in the polymeric matrix, C_{An} is the difference between the dissolved drug concentration and its maximum solubility (C_{Amx}), normalized by C_{Amx}, C_{Wn} is the normalized concentration of water ($\frac{C_W}{C_{Wout}}$). In this last expression C_{Wout} is the concentration of water outside of the polymeric matrix. The evolution of the concentration of dissolved drug in the matrix is defined by the last equation of (1) where Fick's law and the dissolution source were taken into account.

As the degradation occurs the molecular weight decreases and the permeability of the polymer increases. This leads to an increasing of the diffusion coefficient ([15]) that can be represented by

$$D(M) = D_A e^{\bar{k}\frac{M_0 - M}{M_0}},$$

where D_A is the diffusion coefficient of the drug in the non hydrolyzed polymer, M_0 is its initial molecular weight and $\bar{k}$ is a positive constant.

System (1) is completed with the initial conditions

$$\begin{cases} C_W(0) = 0 & \text{in } \Omega, \\ \sigma(0) = \sigma_0 & \text{in } \Omega, \\ M(0) = M_0 & \text{in } \Omega, \\ C_S(0) = C_{S0} & \text{in } \Omega, \\ C_A(0) = 0 & \text{in } \Omega, \end{cases} \tag{3}$$

where σ_0 represents the initial stress of the polymer and C_{S0} is the initial concentration of solid drug in the polymeric matrix.

Degradation of the polymeric matrix can be one of the two types: surface and bulk. Surface degradation occurs because degradation is faster than the entrance of water in

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the system. In this case the cleavage of polymeric chains occurs mainly in the outermost polymeric layers. Bulk degradation occurs when the degradation is slower than the water uptake. The entire system is rapidly hydrated and polymeric chains are cleaved through all the polymeric structure ([15]).

In what follows we assume that bulk degradation occurs and that the physical domain maintained during all diffusion process. The entrance of water occurs due to the difference of concentrations in the polymer and in the water. Then the system (1) and the initial conditions are coupled with the following boundary condition

$$\begin{cases} J \cdot \eta = A_c(C_W - C_{Wout}) & \text{on } \partial\Omega \times (0,T], \\ C_A = 0 & \text{on } \partial\Omega \times (0,T], \end{cases} \tag{4}$$

where J represents the flux defined by $J = -D_W \nabla C_W - D_v \nabla \sigma$, η is the unit outward normal to $\partial\Omega$, A_c is the permeability constant and C_{Wout} denotes the water concentration out of the polymeric matrix.

The aim of this paper is to present a numerical method to solve (1), (3) and (4) and to study the qualitative behaviour of the numerical solution. In Section 2 Implicit-Explicit method (IMEX) is introduced and its convergence is numerically studied. The qualitative behavior of the solution is analyses in Section 3. Finally in Section 4 we present some conclusions.

2 Numerical method

In this section we introduce a finite difference method to solve (1), (3), (4). Let Ω be the square $(0,L) \times (0,L)$, where L represents the thickness of the polymer. We fix $h > 0$ and we define in $\overline{\Omega}$ the grid

$$\overline{\Omega}_h = \Big\{ (x_i, y_j), i, j = 0, \ldots, N, x_0, y_0 = 0, x_N, y_N = L, \\ x_i - x_{i-1} = h, y_j - y_{j-1} = h, i, j = 1, \ldots, N \Big\}.$$

By Ω_h and $\partial\Omega_h$ we represent the mesh nodes of $\overline{\Omega}_h$ that are in Ω and on the boundary $\partial\Omega$, respectively. Let u_h and v_h be grid functions defined in $\overline{\Omega}_h$. To discretize the spatial derivatives we introduce the second order finite difference operator

$$D_x^*\big(a(v_h) D_{-x} u_h\big)(x_i, y_j) = \frac{1}{h}\Big(a(A_{h,x} v_h(x_{i+1}, y_j)) D_{-x} u_h(x_{i+1}, y_j) - a(A_{h,x} v_h(x_i, y_j)) D_{-x} u_h(x_i, y_j) \Big),$$

where D_{-x} denotes the backward finite difference operator with respect to the x-variable and $A_{h,x}$ is the following average operator

$$A_{h,x} v_h(x_\ell, y_j) = \frac{1}{2}\Big(v_h(x_\ell, y_j) + v_h(x_{\ell-1}, y_j) \Big).$$

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The finite difference operator $D_y^*\big(b(v_h)D_{-y}u_h\big)(x_i,y_j)$ is defined analogously considering the backward finite difference operator with respect to the y-variable, D_{-y}, and the average operator $A_{h,y}$. If B is a diagonal matrix with entries a and b we use the following notation

$$\nabla_h^*.\big(B(v_h)\nabla_h u_h\big) = D_x^*\big(a(v_h)D_{-x}u_h\big) + D_y^*\big(b(v_h)D_{-y}u_h\big).$$

In $[0,T]$ we consider the following time grid

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

By D_{-t} we denote the backward finite difference operator with respect to the variable t. Let $p_h^n(x_i,y_j)$ stands for an approximation of $p(x_i,y_j,t_n)$.

To solve numerically the initial boundary value problem (1), (3), (4) we consider the **IMEX** method defined by

$$\begin{cases} D_{-t}C_{W,h}^{n+1} = \nabla_h^*.\Big(D_W\nabla_h C_{W,h}^{n+1}\Big) + \nabla_h^*.\Big(D_v\nabla_h\sigma_h^n\Big) - kC_{W,h}^nM_h^n \ \text{ in}\,\Omega_h \\ D_{-t}M_h^{n+1} = -kC_{W,h}^{n+1}M_h^n \ \text{ in}\,\overline{\Omega}_h \\ D_{-t}\sigma_h^{n+1} + \dfrac{E_0(M_h^{n+1})^\alpha}{\mu_0(M_h^{n+1})^\beta}\sigma_h^n = -E_0(M_h^{n+1})^\alpha D_{-t}C_{W,h}^{n+1} \text{ in } \overline{\Omega}_h \\ D_{-t}C_{S,h}^{n+1} = -\dfrac{k_{dis}}{C_{S0}C_{Amx}C_{Wout}}C_{S,h}^n(C_{Amx}-C_{A,h}^n)C_{W,h}^{n+1} \ \text{ in}\,\overline{\Omega}_h \\ D_{-t}C_{A,h}^{n+1} = \nabla_h^*.\Big(D(M_h^{n+1})\nabla_h C_{A,h}^{n+1}\Big) + \dfrac{k_{dis}}{C_{S0}C_{Amx}C_{Wout}}C_{S,h}^{n+1}\Big(C_{Amx}-C_{A,h}^n\Big)C_{W,h}^{n+1} \ \text{ in}\,\Omega_h \end{cases} \tag{5}$$

for $n=0,\ldots,M_{\Delta t}-1$,

$$\begin{cases} C_{W,h}^0 = 0 \ \text{ in}\,\Omega_h \\ \sigma_h^0 = \sigma(0) \ \text{ in}\,\Omega_h \\ M_h^0 = M(0) \ \text{ in}\,\Omega_h \\ C_{S,h}^0 = C_S(0) \ \text{ in}\,\Omega_h \\ C_{A,h}^0 = 0 \ \text{ in}\,\Omega_h \end{cases} \tag{6}$$

and

$$\begin{cases} J_h^{n+1}.\eta = A_c(C_{W,h}^{n+1}-C_{Wout}) \ \text{ on}\ \partial\Omega_h \\ C_{A,h}^{n+1} = 0 \ \text{ on}\ \partial\Omega_h, \end{cases} \tag{7}$$

where

$$J_h^{n+1} = -D_WD_\eta C_{W,h}^{n+1} - D_vD_\eta\sigma_h^n,$$

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and D_η is the boundary operator

$$D_\eta v_h(x_i, y_j) = \begin{cases} -D_x v_h(x_0, y_j), & i = 0 \\ D_{-x} v_h(x_N, y_j), & i = N \\ -D_y v_h(x_i, y_0), & j = 0 \\ D_{-y} v_h(x_i, y_N), & j = N \end{cases}$$

for $(x_i, y_j) \in \partial\Omega_h$.

3 Qualitative behaviour of the model

In this section we illustrate the influence of the parameters on the behaviour of the model. The values of the parameters are present in Table 1 and some of them were obtained from [13]. We start by analyzing numerically the convergence properties of the numerical scheme.

Parameter	Value	Parameter	Value
D_A	5.94×10^{-2}	E_0	1×10^{-3}
D_v	2×10^{-2}	μ_0	1×10^{-1}
D_W	4.61×10^{-2}	k_{dis}	4.6×10^{-2}
k	1×10^{-2}	M_0	8.3×10^{-2}
σ_0	5×10^{-2}	C_{Wout}	5.55×10^{-1}
C_{Amx}	2.184×10^{-2}	A_c	1×10^{-2}
C_{S0}	288.42×10^{-2}	α	0.2
β	0.7	L	1
Δt	1×10^{-4}	h	0.01

Table 1: Parameter values used for the simulation.

Table 2 contains the errors for C_W and C_A defined by

$$Error(C) = \max_{n=1,\ldots,M_{\Delta t}} \max_{\Omega_h} |C_h^n - \overline{C}_h^n|,$$

where $C = C_W, C_A$ and $\overline{C}_h^n$ is a reference solution obtained with a fine grid defined by $\Delta t = 10^{-5}$ and $h = 0.001$.

h	$Error(C_W)$	$Error(C_A)$
0.01	0.0048	5.1432×10^{-8}
0.005	0.0032	4.8043×10^{-8}
0.004	0.0029	4.4917×10^{-8}
0.002	0.0017	2.9373×10^{-8}

Table 2: Errors for different step-sizes in space.

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The results of Table 2 suggest the convergence of the IMEX method.

Let the mass of water and drug, inside the matrix, be defined by

$$\mathcal{M}_i(t) = \int_\Omega C_i(t) dxdy,$$

where $i = W, A$, for $t \in [0, T]$. A numerical approximation for $M_i(t)$ is computed with the trapezoidal rule.

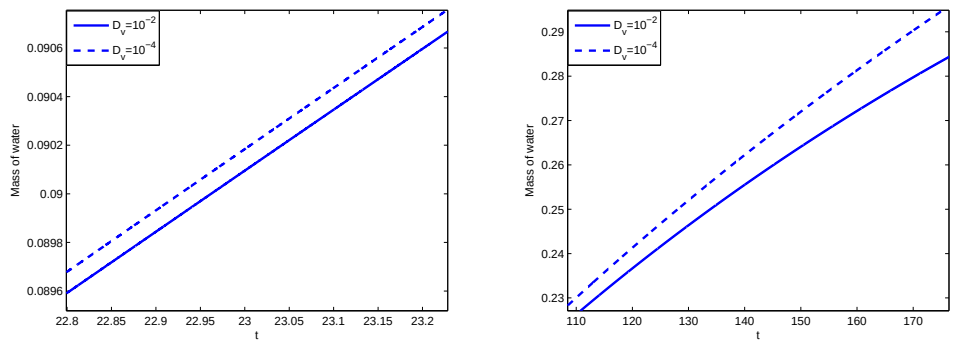

Figure 1: Influence of D_v on the mass of the water.

In Figure 1 we plot the dependence on the viscoelastic diffusion coefficient D_v of the mass of water. We observe that the polymer acts as a barrier to the entrance of water into the polymer. In other words, the non Fickian flux $-D_v \nabla \sigma$ decreases the Fickian flux, $-D_W \nabla C_W$. According to this description an increase in D_v leads to a decrease of M_W.

The influence of the Young modulus E on M_W is presented in Figure 2 (left). near $t = 2$. It is well known that the crosslink density of the polymer is proportional to the Young modulus E. Consequently as this constant increases the resistance of the polymer to the entrance of water also increases leading to a decreasing of the mass of water.

The influence of the polymer degradation rate, k, is presented in Figure 2 (right). As expected, if the degradation rate increases, then the delivery rate of the dissolved drug also increases.

The behaviour of the mass of dissolved drug is presented in Figure 3, for different thickness of the polymer. We observe that the maximum value of the mass of dissolved drug in thinner polymers is higher and less time is required to achieve this maximum.

In Figure 4 the mass of water inside the polymer, for different values of L, is plotted. In the thinner polymer more time is required for the mass to reach the steady state. We also observe that the value of the steady state in the polymer with $L = 0.1$ is 0.0555 while in the polymer with $L = 0.5$ is 0.2769.

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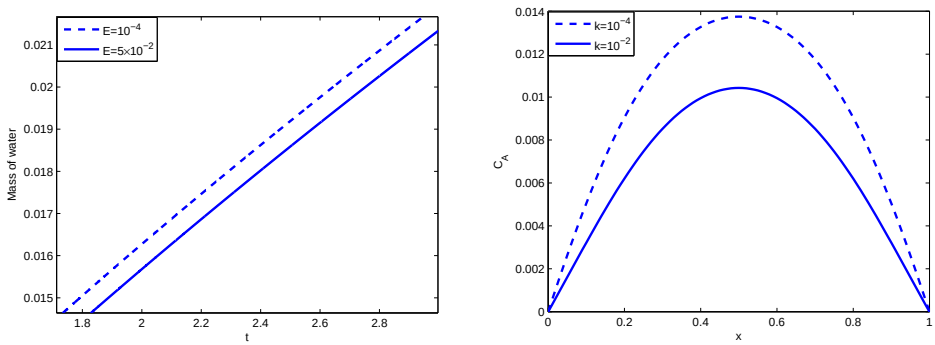

Figure 2: Mass of water for different E's (left); concentration of dissolved drug C_A for different k (right).

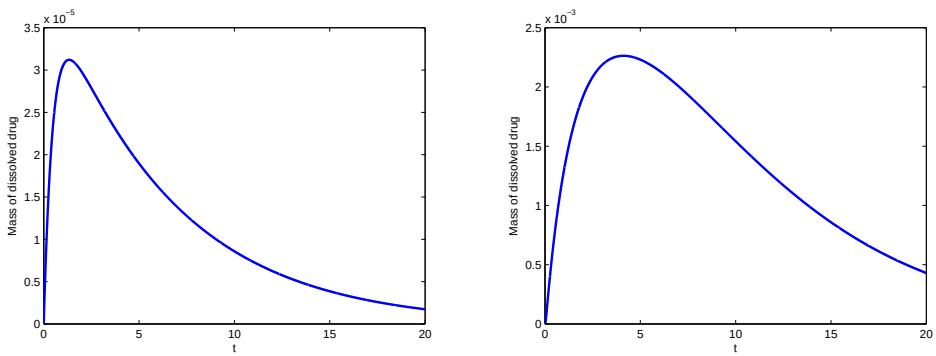

Figure 3: Mass of dissolved drug inside the polymer with $L = 0.1$ (left) and $L = 0.5$ (right).

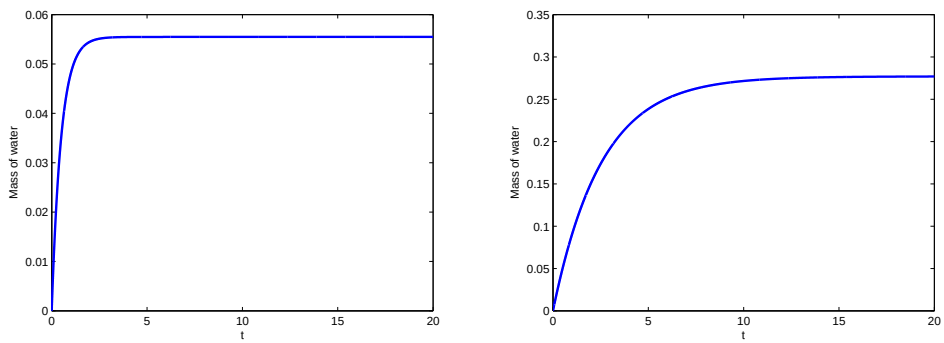

Figure 4: Mass of water inside the polymer with $L = 0.1$ (left) and $L = 0.5$ (right).

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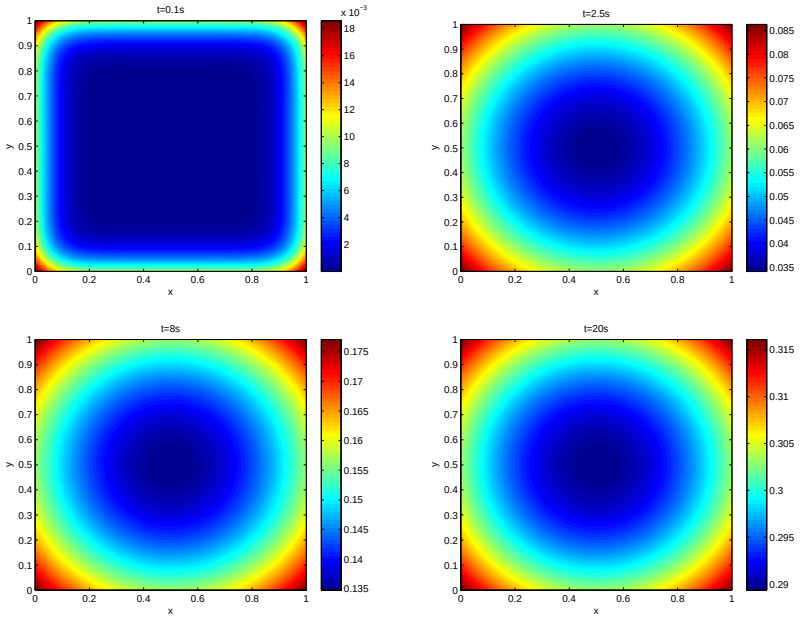

Figure 5: Concentration of water for different times.

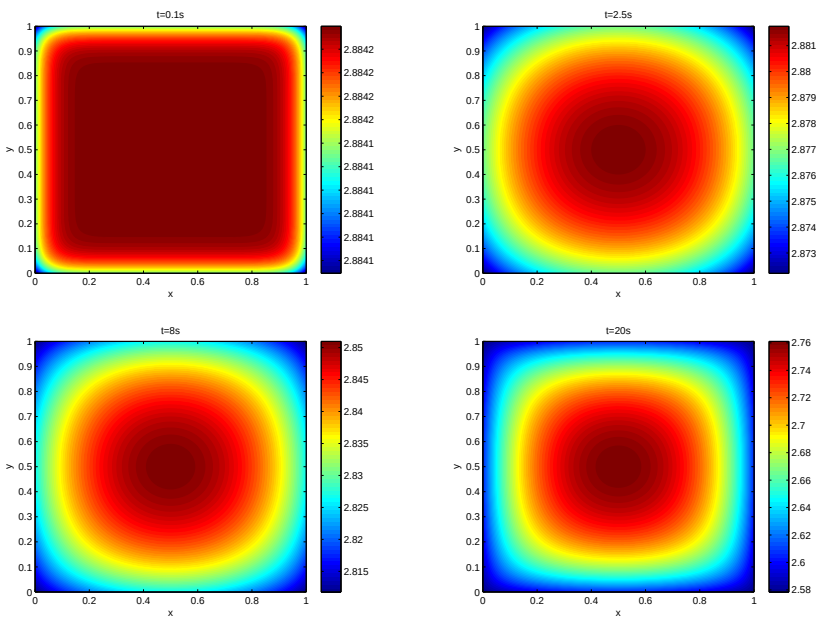

Figure 6: Concentration of solid drug for different times.

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Figure 5 illustrates the behavior of the concentration of water into the polymeric matrix at different times. We observe that the concentration increases as time increases and the behavior is homogeneous since the diffusion coefficient is constant.

The concentration of solid drug and dissolved drug, respectively, at different times are shown in Figures 6 and 7. Te regions where the concentration of water is higher, correspond to regions where the concentration of solid drug is lower. We also note that when the concentration of solid drug decreases, the concentration of dissolved drug increases.

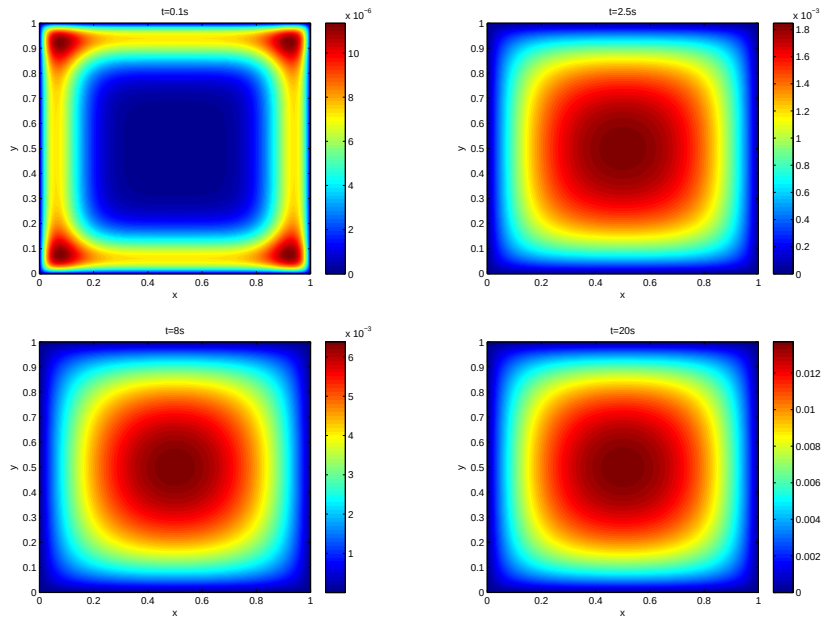

Figure 7: Concentration of dissolved drug for different times.

4 Conclusions

In this paper we describe a process of sorption of a solvent by a biodegradable polymeric matrix, when bulk erosion occurs, and the simultaneous release of a drug. Numerical results that highlight the whole process are presented. These results are physically sound. The influence of the crosslinking density of the polymer is shown to delay the drug release. In fact a larger Young modulus exerts a larger opposition to the solvent penetration. Bulk erosion which is governed by the degradation rate speeds up the release of drug. The dependence on the dimensions of the matrix is also illustrated.

The theoretical study of the initial boundary value problem (1), (3) and (4) will be object of a future work. We intent also to analyse the occurrence of surface degradation.

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