

Numerical and analytical study of drug release from a biodegradable viscoelastic platform

E. Azhdari, J. A. Ferreira, Paula de Oliveira, P.M. da Silva
CMUC-Department of Mathematics, University of Coimbra.

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Abstract

A mathematical model to simulate drug delivery from a viscoelastic 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 viscoelastic behaviour, the dissolution of the solid drug and the delivery of the dissolved drug. Numerical simulations illustrating the behaviour of the model are included.

Keywords: Drug delivery; molecular weight; bulk erosion; viscoelastic behaviour; numerical simulation.

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 hydration process, that modifies the viscoelastic properties of the polymer, takes place. The molecular weight decreases and the drug starts to dissolve.

In [15] 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 [15], by considering the viscoelastic behaviour of the polymer (see for instance [1],[2], [7],[11], [16], [18]).

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

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

¹E. Azhdari, email: ebrahim@mat.uc.pt, CMUC-Department of Mathematics, University of Coimbra.

¹J. A. Ferreira, email: ferreira@mat.uc.pt, CMUC-Department of Mathematics, University of Coimbra.

¹Paula de Oliveira, email: poliveir@mat.uc.pt, CMUC-Department of Mathematics, University of Coimbra.

²P.M. da Silva, email: pascals@isec.pt, Instituto Politécnico de Coimbra, ISEC, DFM, Rua Pedro Nunes, 3030-199 Coimbra, Portugal. CMUC.

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 $-k C_W M$ represents the consumption of water in the hydrolysis of the polymer. The molecular weight loss is represented by $-\tilde{k} C_W M$ ([3],[5],[6],[8]).

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) ([15]).

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

$$\frac{\partial \sigma}{\partial t} + \frac{E}{\mu} \sigma = E \frac{\partial \epsilon}{\partial t}, \quad (2)$$

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 are proportional, that is, there exists $k_1 > 0$ such that $\epsilon = k_1 C_W$, where k_1 stands for a dimensional constant. This relation is a linear approximation of $\epsilon = f(C)$ established in [8]. 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).

Based on the results presented for instance in [1], [2], [7], [11], [16] and [18], 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 ([13]). Moreover a functional relation between the viscosity and the molecular weight represented by Mark-Houwink equation ([14]) 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 ([14],[13],[3]).

The evolution in time of the solid drug is described by the fourth equation of (1) where k_{dis} is the dissolution rate, C_{S_n} is the normalized concentration of solid drug in the polymeric matrix, C_{A_n} is the difference between the dissolved drug concentration and its maximum solubility ($C_{A_{max}}$), normalized by $C_{A_{max}}$, C_{W_n} is the normalized concentration of water ($\frac{C_W}{C_{W_{out}}}$). In this last expression $C_{W_{out}}$ 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 increase of the diffusion coefficient ([17]) 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

$$\begin{cases} C_W(0) = 0 & \text{in } \Omega, \\ \sigma(0) = \sigma_0 & \text{in } \Omega, \\ M(0) = M_0 & \text{in } \Omega, \\ C_S(0) = C_{S_0} & \text{in } \Omega, \\ C_A(0) = 0 & \text{in } \Omega, \end{cases} \quad (3)$$

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 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 ([17]).

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

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

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 a stability analysis of the mathematical model is studied. Implicit-Explicit method (IMEX) is introduced and its convergence is numerically studied in Section 3. In Section 4 the qualitative behavior of the solution is analysed. Finally in Section 5 we present some conclusions.

2 Stability analysis

In order to simplify the presentation, we assume in this section that E and μ are constant. We also assume that the diffusion tensor is only space dependent.

To gain some insight on the stability behaviour of the initial value problem (1),(3) and (4) we study in what follows the stability of a linearization of (1) for short and long times. For short times we linearize the system in the neighborhood of the initial state; for large times the system is linearized in the neighborhood of the steady state solution. Let \tilde{C}_W , \tilde{M} , \tilde{C}_A and \tilde{C}_S be a solution of (1). The linearized system at this solution can be written in the following form

$$\begin{cases} \frac{\partial C_W}{\partial t} = \nabla \cdot (D_W \nabla C_W) + \nabla \cdot (D_v \nabla \sigma) - k\tilde{C}_W M - k\tilde{M} C_W, \\ \frac{\partial \tilde{M}}{\partial t} = -k\tilde{C}_W M - k\tilde{M} C_W, \\ \frac{\partial \sigma}{\partial t} + \frac{E}{\mu} \sigma = -E \frac{\partial C_W}{\partial t}, \\ \frac{\partial \tilde{C}_S}{\partial t} = -K \left((C_{Amx} - \tilde{C}_A) \tilde{C}_W C_S - \tilde{C}_W \tilde{C}_S C_A \right. \\ \qquad \qquad \qquad \left. + \tilde{C}_S (C_{Amx} - \tilde{C}_A) C_W \right), \\ \frac{\partial \tilde{C}_A}{\partial t} = \nabla \cdot (D \nabla C_A) + K \left((C_{Amx} - \tilde{C}_A) \tilde{C}_W C_S \right. \\ \qquad \qquad \qquad \left. - \tilde{C}_W \tilde{C}_S C_A + \tilde{C}_S (C_{Amx} - \tilde{C}_A) C_W \right), \end{cases} \quad (5)$$

where $K = \frac{k_{dis}}{C_{S0} C_{Amx} C_{Wout}}$ is a constant.

For small times the concentration of water and dissolved drug is very small so we consider

$$\tilde{C}_W = 0, \tilde{C}_A = 0, \tilde{C}_S = C_{S0}, \tilde{M} = M_0. \quad (6)$$

For large times, that is when the matrix is practically degraded and the drug released, we assume

$$\tilde{M} = 0, \tilde{C}_W = C_{Wout}, \tilde{C}_S = 0, \tilde{C}_A = 0. \quad (7)$$

Solution (6) defines the state of the system as $t \rightarrow 0$. So for small times, the stability of system (1) is obtained studying the stability of (5) and (4) when (6) is considered. When $t \rightarrow +\infty$, the solution of

system (1) approaches the steady solution (7). In fact, phenomenologically, the molecular weight decreases and vanishes, the concentration of water goes to the equilibrium, that is C_{Wout} , the concentrations of solid and dissolved drug inside of the polymeric matrix vanish.

Stability for short times: To study the stability of (4) and (5), we consider the difference of two solutions, which we represent by the same notations C_W, σ, M, C_S, C_A . In this case we have

$$\begin{cases} \frac{\partial C_W}{\partial t} = \nabla \cdot (D_W \nabla C_W) + \nabla \cdot (D_v \nabla \sigma) & \text{in } \Omega \times (0, T], \\ \frac{\partial M}{\partial t} = -kM_0 C_W & \text{in } \Omega \times (0, T], \\ \frac{\partial \sigma}{\partial t} + \frac{E}{\mu} \sigma = -E \frac{\partial C_W}{\partial t} & \text{in } \Omega \times (0, T], \\ \frac{\partial C_S}{\partial t} = -\frac{k_{dis}}{C_{Wout}} C_W & \text{in } \Omega \times (0, T], \\ \frac{\partial C_A}{\partial t} = \nabla \cdot (D \nabla C_A) + \frac{k_{dis}}{C_{Wout}} C_W & \text{in } \Omega \times (0, T], \end{cases} \quad (8)$$

where $T > 0$ is fixed, with the boundary conditions

$$\begin{cases} J \cdot \eta = A_c C_W & \text{on } \partial\Omega \times (0, T], \\ C_A = 0 & \text{on } \partial\Omega \times (0, T]. \end{cases} \quad (9)$$

In what follows we use the energy method to analyze (8) and (9) complemented with the initial condition

$$\begin{cases} C_W(0) = C_{W0} & \text{in } \Omega, \\ \sigma(0) = \sigma_0 & \text{in } \Omega, \\ M(0) = M_0 & \text{in } \Omega, \\ C_S(0) = C_{S0} & \text{in } \Omega, \\ C_A(0) = C_{A0} & \text{in } \Omega. \end{cases} \quad (10)$$

From the third equation of (8) we easily get

$$\begin{aligned} \sigma = \frac{E^2}{\mu} \int_0^t e^{-\frac{E}{\mu}(t-s)} C_W(s) ds & - EC_W + EC_W(0) e^{-\frac{E}{\mu}t} \\ & + \sigma(0) e^{-\frac{E}{\mu}t}, \quad t \geq 0, \end{aligned} \quad (11)$$

and using this equality in the first equation of (8) we obtain for C_W the following equation

$$\begin{aligned} \frac{\partial C_W}{\partial t} = \nabla \cdot (D_1 \nabla C_W) + \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla \cdot (D_2 \nabla C_W(s)) ds & - kM_0 C_W \\ + E e^{-\frac{E}{\mu}t} \nabla \cdot (D_v \nabla C_W(0)) + e^{-\frac{E}{\mu}t} \nabla \cdot (D_v \nabla \sigma(0)), \end{aligned} \quad (12)$$

where

$$D_1 = D_W - ED_v, \quad D_2 = \frac{E^2}{\mu} D_v. \quad (13)$$

We assume that, in (13), D_W, D_v and D are 2×2 diagonal matrices and E and μ are such that the entries of D_1 and D_2 are positive and satisfy the following conditions:

$$D_{1,jj} \geq D_{min}, \quad D_{2,jj}, D_{v,jj} \leq D_{max}, \quad D_{jj} \geq D_0, \quad \text{for } j = 1, 2. \quad (14)$$

Let $V = H^1(\Omega) \times \left(L^2(\Omega)\right)^2 \times H_0^1(\Omega)$ and let $(C_W, M, C_S, C_A) \in V$ be such that $\frac{\partial C_W}{\partial t}, \frac{\partial M}{\partial t}, \frac{\partial C_S}{\partial t}, \frac{\partial C_A}{\partial t} \in L^2(\Omega)$ and that (10) holds. Then multiplying scalarly the equations in (8) by test functions, where the first and the third equations are replaced by (12), we have

$$\left\{ \begin{array}{l} \left(\frac{\partial C_W}{\partial t}, v_1 \right) = -(D_1 \nabla C_W, \nabla v_1) - \int_0^t e^{-\frac{E}{\mu}(t-s)} (D_2 \nabla C_W(s), \nabla v_1) ds \\ \quad - (A_c C_W, v_1)_{\partial \Omega} - k M_0 (C_W, v_1) + e^{-\frac{E}{\mu} t} E (\nabla \cdot (D_v \nabla C_W(0)), v_1) \\ \quad + e^{-\frac{E}{\mu} t} (\nabla \cdot (D_v \nabla \sigma(0)), v_1), \quad \forall v_1 \in H^1(\Omega), \\ \left(\frac{\partial M}{\partial t}, v_2 \right) = -k (M_0 C_W, v_2), \quad \forall v_2 \in L^2(\Omega), \\ \left(\frac{\partial C_S}{\partial t}, v_3 \right) = -\frac{k_{dis}}{C_{Wout}} (C_W, v_3), \quad \forall v_3 \in L^2(\Omega), \\ \left(\frac{\partial C_A}{\partial t}, v_4 \right) = -(D \nabla C_A, \nabla v_4) \\ \quad + \frac{k_{dis}}{C_{Wout}} (C_W, v_4), \quad \forall v_4 \in H_0^1(\Omega). \end{array} \right. \quad (15)$$

In (15) the same notation is used to represent the usual inner products in $L^2(\Omega)$ and $(L^2(\Omega))^2$. We establish in what follows an estimate for the energy functional

$$\mathcal{E}(t) = E_{CM}(t) + \int_0^t \left(\|\nabla C_W(s)\|^2 + \|\nabla C_A(s)\|^2 \right) ds, \quad t \in [0, T], \quad (16)$$

with

$$E_{CM}(t) = \|C_W(t)\|^2 + \|M(t)\|^2 + \|C_S(t)\|^2 + \|C_A(t)\|^2, \quad (17)$$

where the same notation $\|\cdot\|$ was used to represent the norm induced by the usual inner products in $L^2(\Omega)$ and $(L^2(\Omega))^2$.

Theorem 1 *Let $(C_W, M, C_S, C_A) \in V$ be a solution of the variational problem (15). Then*

$$\mathcal{E}(t) \leq \frac{1}{\min \left\{ 1, 2(D_{min} - \epsilon_1^2), 2D_0 \right\}} \left(\frac{\mu}{4E\epsilon_2^2} \left(E^2 \|\nabla \cdot (D_v \nabla C_W(0))\|^2 \right. \right. \\ \left. \left. + \|\nabla \cdot (D_v \nabla \sigma(0))\|^2 \right) + E_{CM}(0) \right) e^{\bar{c}t} \quad (18)$$

where $\epsilon_1 \neq 0$ satisfies

$$D_{min} - \epsilon_1^2 > 0, \quad (19)$$

and

$$\bar{c} = \frac{\max \left\{ \frac{D_{max}\mu}{4\epsilon_1^2 E}, 2\epsilon_3^2 \left(k^2 M_0^2 + 2\frac{k_{dis}^2}{C_{Wout}^2} \right) + 4\epsilon_2^2 - 2kM_0, \frac{1}{2\epsilon_3^2} \right\}}{\min \left\{ 1, 2(D_{min} - \epsilon_1^2), 2D_0 \right\}} \quad (20)$$

being $\epsilon_2, \epsilon_3 \neq 0$ arbitrary constants.

Proof: Taking in (15) $v_1 = C_W, v_2 = M, v_3 = C_S$ and $v_4 = C_A$, we easily obtain from the first equation

$$\begin{aligned} \frac{1}{2} \frac{d}{dt} \|C_W\|^2 &= -(D_1 \nabla C_W, \nabla C_W) \\ &\quad - \int_0^t e^{-\frac{E}{\mu}(t-s)} (D_2 \nabla C_W(s), \nabla C_W) ds \\ &\quad - A_c \|C_W\|_{\partial \Omega}^2 + e^{-\frac{E}{\mu} t} E (\nabla \cdot (D_v \nabla C_W(0)), C_W) \\ &\quad + e^{-\frac{E}{\mu} t} (\nabla \cdot (D_v \nabla \sigma(0)), C_W) - k M_0 \|C_W\|^2, \end{aligned} \quad (21)$$

where $\|\cdot\|_{\partial\Omega}$ denotes the usual norm in $L^2(\partial\Omega)$. The remaining three equations of (15) lead to

$$\frac{1}{2} \frac{d}{dt} \|M\|^2 = -kM_0(C_W, M),$$

$$\frac{1}{2} \frac{d}{dt} \|C_S\|^2 = -\frac{k_{dis}}{C_{Wout}}(C_W, C_S),$$

and

$$\frac{1}{2} \frac{d}{dt} \|C_A\|^2 = -(D\nabla C_A, \nabla C_A) + \frac{k_{dis}}{C_{Wout}}(C_W, C_A).$$

For any non zero constants ϵ_1, ϵ_2 and ϵ_3 we have the following inequalities

$$\begin{aligned} -\int_0^t e^{-\frac{E}{\mu}(t-s)} (D_2 \nabla C_W(s), \nabla C_W) ds &\leq \epsilon_1^2 \|\nabla C_W\|^2 \\ &+ \frac{D_{max}^2 \mu}{8\epsilon_1^2 E} \int_0^t \|\nabla C_W(s)\|^2 ds, \end{aligned}$$

$$\begin{aligned} &+ e^{-\frac{E}{\mu}t} E (\nabla \cdot (D_v \nabla C_W(0)), C_W) + e^{-\frac{E}{\mu}t} (\nabla \cdot (D_v \nabla \sigma(0)), C_W) \\ &\leq \frac{1}{4\epsilon_2^2} e^{-2\frac{E}{\mu}t} \left(E^2 \|\nabla \cdot (D_v \nabla C_W(0))\|^2 + \|\nabla \cdot (D_v \nabla \sigma(0))\|^2 \right) + 2\epsilon_2^2 \|C_w\|^2, \end{aligned}$$

$$kM_0(C_W, M) \leq k^2 M_0^2 \epsilon_3^2 \|C_W\|^2 + \frac{1}{4\epsilon_3^2} \|M\|^2,$$

$$\frac{k_{dis}}{C_{Wout}}(C_W, C_S) \leq \frac{k_{dis}^2}{C_{Wout}^2} \epsilon_3^2 \|C_W\|^2 + \frac{1}{4\epsilon_3^2} \|C_S\|^2,$$

$$\frac{k_{dis}}{C_{Wout}}(C_W, C_A) \leq \frac{k_{dis}^2}{C_{Wout}^2} \epsilon_3^2 \|C_W\|^2 + \frac{1}{4\epsilon_3^2} \|C_A\|^2.$$

Summing up the preceding three equations we obtain

$$\begin{aligned} \frac{d}{dt} E_{CM} &+ 2(D_{min} - \epsilon_1^2) \|\nabla C_W\|^2 + 2D_0 \|\nabla C_A\|^2 \\ &\leq \frac{D_{max}^2 \mu}{4\epsilon_1^2 E} \int_0^t \|\nabla C_W(s)\|^2 ds \\ &+ \left(2\epsilon_3^2 \left(k^2 M_0^2 + 2\frac{k_{dis}^2}{C_{Wout}^2} \right) + 4\epsilon_2^2 - 2kM_0 \right) \|C_W\|^2 \\ &+ \frac{1}{2\epsilon_3^2} \left(\|M\|^2 + \|C_S\|^2 + \|C_A\|^2 \right) \\ &+ \frac{1}{2\epsilon_2^2} e^{-2\frac{E}{\mu}t} \left(E^2 \|\nabla \cdot (D_v \nabla C_W(0))\|^2 + \|\nabla \cdot (D_v \nabla \sigma(0))\|^2 \right), \end{aligned}$$

where E_{CM} is defined in (17). If we fix ϵ_1 satisfying (19) then

$$\begin{aligned} \mathcal{E}(t) &\leq \bar{c} \int_0^t \mathcal{E}(s) ds + \frac{1}{\min \{1, 2(D_{min} - \epsilon_1^2), 2D_0\}} \left(\frac{\mu}{4E\epsilon_2^2} \right. \\ &\left. \left(E^2 \|\nabla \cdot (D_v \nabla C_W(0))\|^2 + \|\nabla \cdot (D_v \nabla \sigma(0))\|^2 \right) + E_{CM}(0) \right), \end{aligned}$$

where \bar{c} is defined by (20). Finally by using Gronwall's Lemma we obtain (18). ■

The energy estimate (18) leads to the uniqueness of solution of the variational problem (15) and (10). It enables also to conclude the stability of such solution in bounded time intervals. These results hold provided that the initial data are smooth enough.

Stability for large times: To analyze the stability of the initial boundary value problem (1),(3) and (4) for large times we consider system (5), that arise from the linearization of system (1) in the neighborhood of the steady solution defined by (7). That is, we study the stability of the initial boundary value problem

$$\begin{cases} \frac{\partial C_W}{\partial t} = \nabla \cdot (D_W \nabla C_W) + \nabla \cdot (D_v \nabla \sigma) - k C_{Wout} M & \text{in } \Omega \times (0, T], \\ \frac{\partial M}{\partial t} = -k C_{Wout} M & \text{in } \Omega \times (0, T], \\ \frac{\partial \sigma}{\partial t} + \frac{E}{\mu} \sigma = -E \frac{\partial C_W}{\partial t} & \text{in } \Omega \times (0, T], \\ \frac{\partial C_S}{\partial t} = -\frac{k_{dis}}{C_{S0}} C_S & \text{in } \Omega \times (0, T], \\ \frac{\partial C_A}{\partial t} = \nabla \cdot (D \nabla C_A) + \frac{k_{dis}}{C_{S0}} C_S & \text{in } \Omega \times (0, T], \end{cases} \quad (22)$$

where $T > 0$ is fixed, with initial conditions

$$\begin{cases} C_W(0) = C_{W,\infty} & \text{in } \Omega, \\ \sigma(0) = \sigma_\infty & \text{in } \Omega, \\ M(0) = M_\infty & \text{in } \Omega, \\ C_S(0) = C_{S,\infty} & \text{in } \Omega, \\ C_A(0) = C_{A,\infty} & \text{in } \Omega, \end{cases} \quad (23)$$

and boundary conditions (9).

From the third equation of (22) we easily get an expression for the stress σ analogous to (11). Replacing then that expression in the first equation of (22) we obtain

$$\begin{cases} \frac{\partial C_W}{\partial t} = \nabla \cdot (D_1 \nabla C_W) + \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla \cdot (D_2 \nabla C_W(s)) ds \\ \quad - k C_{Wout} M + E e^{-\frac{E}{\mu}t} \nabla \cdot (D_v \nabla C_W(0)) \\ \quad + e^{-\frac{E}{\mu}t} \nabla \cdot (D_v \nabla \sigma(0)) & \text{in } \Omega \times (0, T], \\ \frac{\partial M}{\partial t} = -k C_{Wout} M & \text{in } \Omega \times (0, T], \\ \frac{\partial C_S}{\partial t} = -\frac{k_{dis}}{C_{S0}} C_S & \text{in } \Omega \times (0, T], \\ \frac{\partial C_A}{\partial t} = \nabla \cdot (D \nabla C_A) + \frac{k_{dis}}{C_{S0}} C_S & \text{in } \Omega \times (0, T], \end{cases} \quad (24)$$

where D_1 and D_2 are given by (13). The original initial boundary value problem (22), (9) and (23) is then replaced by (24), completed with (23) and (9).

In what follows we consider the weak formulation of (24), (23) and (9) defined by the variational problem:

Find $(C_W, M, C_S, C_A) \in V$ such that $\frac{\partial C_W}{\partial t}, \frac{\partial M}{\partial t}, \frac{\partial C_S}{\partial t}, \frac{\partial C_A}{\partial t} \in L^2(\Omega)$, and (23) holds and

$$\left\{ \begin{array}{l} \left(\frac{\partial C_W}{\partial t}, v_1 \right) = -(D_1 \nabla C_W, \nabla v_1) - \int_0^t e^{-\frac{E}{\mu}(t-s)} (D_2 \nabla C_W(s), \nabla v_1) ds \\ \quad - (A_c C_W, v_1)_{\partial \Omega} - k C_{Wout}(M, v_1) \\ \quad + E e^{-\frac{E}{\mu}t} (\nabla \cdot (D_v \nabla C_W(0)), v_1) \\ \quad + e^{-\frac{E}{\mu}t} (\nabla \cdot (D_v \nabla \sigma(0)), v_1), \quad \forall v_1 \in H^1(\Omega), \\ \left(\frac{\partial M}{\partial t}, v_2 \right) = -k C_{Wout}(M, v_2), \quad \forall v_2 \in L^2(\Omega), \\ \left(\frac{\partial C_S}{\partial t}, v_3 \right) = -\frac{k_{dis}}{C_{S0}}(C_S, v_3), \quad \forall v_3 \in L^2(\Omega), \\ \left(\frac{\partial C_A}{\partial t}, v_4 \right) = -(D \nabla C_A, \nabla v_4) \\ \quad + \frac{k_{dis}}{C_{S0}}(C_S, v_4), \quad \forall v_4 \in H_0^1(\Omega). \end{array} \right. \quad (25)$$

Following the proof of Theorem 1 it can be established an upper bound for $\mathcal{E}(t)$ analogous to the one defined by (16).

Theorem 2 *If $(C_W, M, C_S, C_A) \in V$ is a solution of the variational problem (25), then*

$$\begin{aligned} \mathcal{E}(t) &\leq \frac{1}{\min \left\{ 1, 2(D_{min} - \epsilon_1^2), 2D_0 \right\}} \left(E_{CM}(0) \right. \\ &\quad \left. + \frac{\mu}{4E\epsilon_2^2} \left(E^2 \left\| \nabla \cdot (D_v \nabla C_W(0)) \right\|^2 + \left\| \nabla \cdot (D_v \nabla \sigma(0)) \right\|^2 \right) \right) e^{\bar{c}t}, \quad t \geq 0, \end{aligned}$$

where ϵ_1 is fixed by (19),

$$\bar{c} = \frac{\max \left\{ \frac{\mu D_{max}^2}{4\epsilon_1^2 E}, 2k C_{Wout} \left(\frac{k C_{Wout}}{4\epsilon_2^2} - 1 \right), 2 \frac{k_{dis}}{C_{S0}} \left(\frac{k_{dis}}{C_{S0}} \epsilon_3^2 - 1 \right), \frac{1}{2\epsilon_3^2}, 6\epsilon_2^2 \right\}}{\min \left\{ 1, 2(D_{min} - \epsilon_1^2), 2D_0 \right\}},$$

and ϵ_2, ϵ_3 are arbitrary nonzero constant.

From Theorem 2 we conclude the uniqueness of the solution of (25) and (23) and its stability for bounded time intervals, provided that the initial data are smooth enough.

As the model is nonlinear we carried out a stability analysis based on a local linearization in the neighborhood of the steady state solutions for short and large times. The stability in both cases was established under the positiveness of the diagonal entries of D_1 defined in (13). This is a central issue meaning that the Fickian diffusion must dominate the non Fickian one. Due to the interpretation of viscoelasticity that we propose - as representing a barrier to the penetration of water - such assumption is physically sound.

3 Numerical method

In this section we introduce a Implicit-Explicit 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 $\bar{\Omega}$ the grid

$$\begin{aligned} \bar{\Omega}_h &= \left\{ (x_i, y_j), i, j = 0, \dots, N, x_0, y_0 = 0, x_N, y_N = L, \right. \\ &\quad \left. x_i - x_{i-1} = h, y_j - y_{j-1} = h, i, j = 1, \dots, N \right\}. \end{aligned}$$

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

second order finite difference operator

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

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

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

The finite difference operator $D_y^*(b(v_h)D_{-y}u_h)(x_i, y_j)$ 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

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

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

$$\left\{ t_n, n = 0, \dots, M_{\Delta t}, t_0 = 0, t_{M_{\Delta t}} = T, t_n - t_{n-1} = \Delta t, n = 1, \dots, M_{\Delta t} \right\}.$$

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

$$\left\{ \begin{array}{l} D_{-t}C_{W,h}^{n+1} = \nabla_h^*(D_W\nabla_h C_{W,h}^{n+1}) + \nabla_h^*(D_v\nabla_h\sigma_h^n) - kC_{W,h}^n M_h^n \quad \text{in } \Omega_h, \\ D_{-t}M_h^{n+1} = -kC_{W,h}^{n+1} M_h^n \quad \text{in } \overline{\Omega}_h, \\ D_{-t}\sigma_h^{n+1} + \frac{E_0(M_h^{n+1})^\alpha}{\mu_0(M_h^{n+1})^\beta}\sigma_h^n = -E_0(M_h^{n+1})^\alpha D_{-t}C_{W,h}^{n+1} \quad \text{in } \overline{\Omega}_h, \\ D_{-t}C_{S,h}^{n+1} = -\frac{k_{dis}}{C_{S0}C_{Amx}C_{Wout}}C_{S,h}^n(C_{Amx} - C_{A,h}^n)C_{W,h}^{n+1} \quad \text{in } \overline{\Omega}_h, \\ D_{-t}C_{A,h}^{n+1} = \nabla_h^*(D(M_h^{n+1})\nabla_h C_{A,h}^{n+1}) \\ \quad + \frac{k_{dis}}{C_{S0}C_{Amx}C_{Wout}}C_{S,h}^{n+1}(C_{Amx} - C_{A,h}^n)C_{W,h}^{n+1} \quad \text{in } \Omega_h, \end{array} \right. \quad (26)$$

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

$$\left\{ \begin{array}{l} C_{W,h}^0 = 0 \quad \text{in } \Omega_h, \\ \sigma_h^0 = \sigma(0) \quad \text{in } \Omega_h, \\ M_h^0 = M(0) \quad \text{in } \Omega_h, \\ C_{S,h}^0 = C_S(0) \quad \text{in } \Omega_h, \\ C_{A,h}^0 = 0 \quad \text{in } \Omega_h, \end{array} \right. \quad (27)$$

and

$$\left\{ \begin{array}{l} J_h^{n+1} \cdot \eta = A_c(C_{W,h}^{n+1} - C_{Wout}) \quad \text{on } \partial\Omega_h, \\ C_{A,h}^{n+1} = 0 \quad \text{on } \partial\Omega_h, \end{array} \right. \quad (28)$$

where

$$J_h^{n+1} = -D_W D_\eta C_{W,h}^{n+1} - D_v D_\eta \sigma_h^n,$$

and D_η is the boundary operator

$$D_\eta v_h(x_i, y_j) = \left\{ \begin{array}{l} -D_x v_h(x_0, y_j), \quad i = 0, \\ D_{-x} v_h(x_N, y_j), \quad i = N, \\ -D_y v_h(x_i, y_0), \quad j = 0, \\ D_{-y} v_h(x_i, y_N), \quad j = N, \end{array} \right.$$

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

Table 1: Parameter values used in the numerical simulation

Parameter (unit)	Value	Parameter (unit)	Value
D_A (mm^2/s)	5.94×10^{-2}	E_0 (Pa)	10^{-3}
D_v ($mol/(mm.s.Pa)$)	2×10^{-2}	μ_0 ($Pa.s$)	10^{-1}
D_W (mm^2/s)	4.61×10^{-2}	k_{dis} ($mol/(mm^3.s)$)	4.6×10^{-2}
k ($1/s$)	10^{-2}	M_0 (Da)	8.3×10^{-2}
\tilde{k} ($mm^3/(s.mol)$)	10^{-2}	k_1 (mm^3/mol)	1
σ_0 (Pa)	5×10^{-2}	C_{Wout} (mol/mm^3)	5.55×10^{-1}
C_{Amx} (mol/mm^3)	2.184×10^{-2}	A_c (mm/s)	10^{-2}
C_{S0} (mol/mm^3)	288.42×10^{-2}	α	2×10^{-1}
β	7×10^{-1}	L (mm)	1
Δt	10^{-4}	h	10^{-2}

Table 2: Errors and convergence orders for the concentration of water and dissolved drug

h	$Error(C_W)$	p_w	$Error(C_A)$	p_a
0.01	3.23×10^{-5}	1.38	5.29×10^{-10}	1.08
0.005	1.24×10^{-5}	1.35	2.50×10^{-10}	1.30
0.004	9.17×10^{-6}	2.01	1.87×10^{-10}	1.61
0.002	2.28×10^{-6}		6.13×10^{-11}	

4 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 presented in Table 1 and some of them were obtained from [15].

We start by analyzing numerically the convergence properties of the numerical scheme. Table 2 contains the errors for C_W and C_A at time $T = 0.001$ defined by,

$$Error(C) = \|C_h^n - \bar{C}_h^n\|_{L^2(\Omega_h)} = \left(\sum_{P \in \bar{\Omega}_h} q_1(P) (C_h^n(P) - \bar{C}_h^n(P))^2 \right)^{1/2},$$

where $q_1(P) = h^2$ on Ω_h , $q_1(P) = \frac{h^2}{2}$ on $\partial\Omega_h - C_h$ and $q_1(P) = \frac{h^2}{4}$ on C_h , with $C_h = \{(x_i, y_j) : i, j = 0, N\}$, using a reference solution \bar{C}_h^n obtained with a fine grid defined by $\Delta t = 10^{-5}$ and $h = 0.001$. In the same table we also present estimations for the convergence orders, using the following formula

$$p = \frac{\ln \left(\frac{Error_{h_1}(C)}{Error_{h_2}(C)} \right)}{\ln \left(\frac{h_1}{h_2} \right)},$$

where h_1 and h_2 represent two consecutive step sizes. The results suggest the convergence of the IMEX method (26)-(28) with second convergence rate in space.

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

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

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

In Figure 1 we plot the dependence on the viscoelastic diffusion coefficient D_v of the mass of water inside the polymeric matrix. In this figure as well as in the following the time is measured in seconds. We observe that the polymer acts as a barrier to the entrance of water. In other words, the non Fickian flux

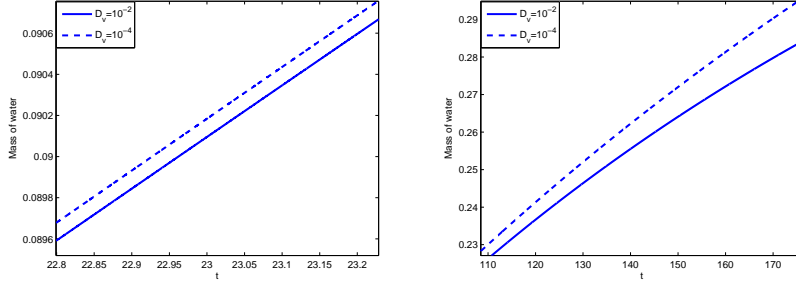


Figure 1: Influence of D_v on the mass of the water inside the polymeric matrix.

$-D_v \nabla \sigma$ decreases the Fickian flux, $-D_W \nabla C_W$. According to this description an increase in D_v leads to a increase 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.

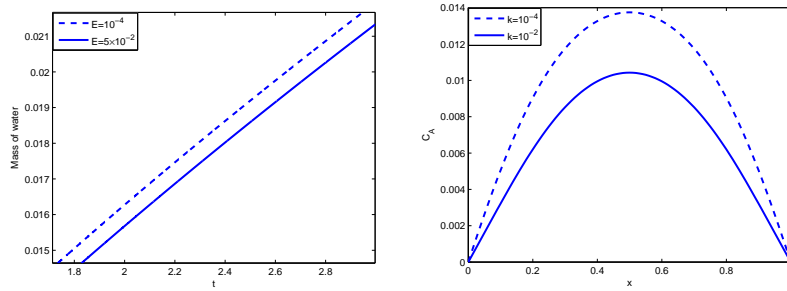


Figure 2: Mass of water for different E 's (left); concentration of dissolved drug C_A for different k (right).

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 lower and less time is required to achieve this maximum. The amount of dissolved drug results from a balance between the dissolution process and the release of drug. The instant when the maximum occurs, represents the time when the delivery process dominates the dissolution process.

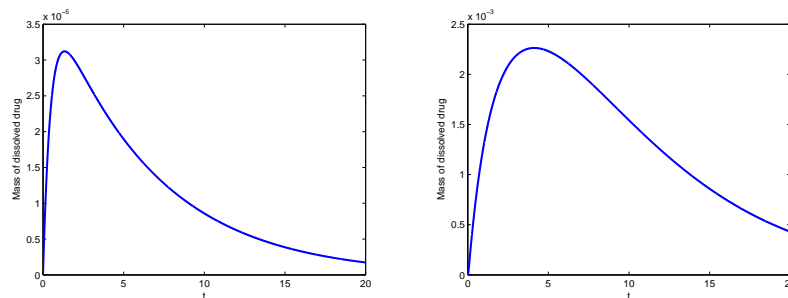


Figure 3: Mass of dissolved drug inside the polymer with $L = 0.1$ (left) and $L = 0.5$ (right).

In Figure 4 the mass of water inside the polymer, for different values of L , is plotted. In the thicker

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.

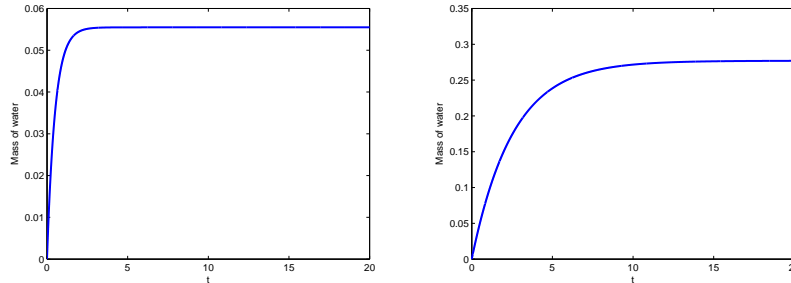


Figure 4: Mass of water inside the polymer with $L = 0.1$ (left) and $L = 0.5$ (right).

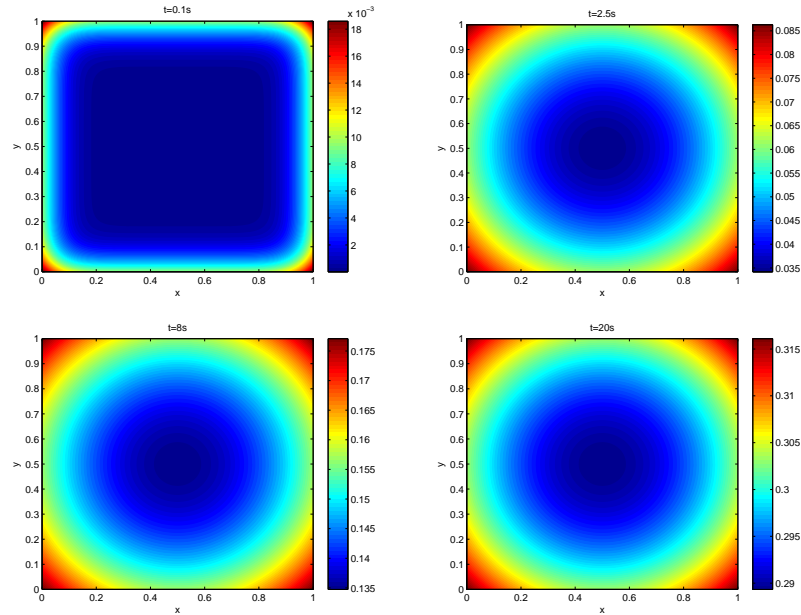


Figure 5: Concentration of water for different times.

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. The 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.

5 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. The stability analysis of the mathematical model was studied. 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

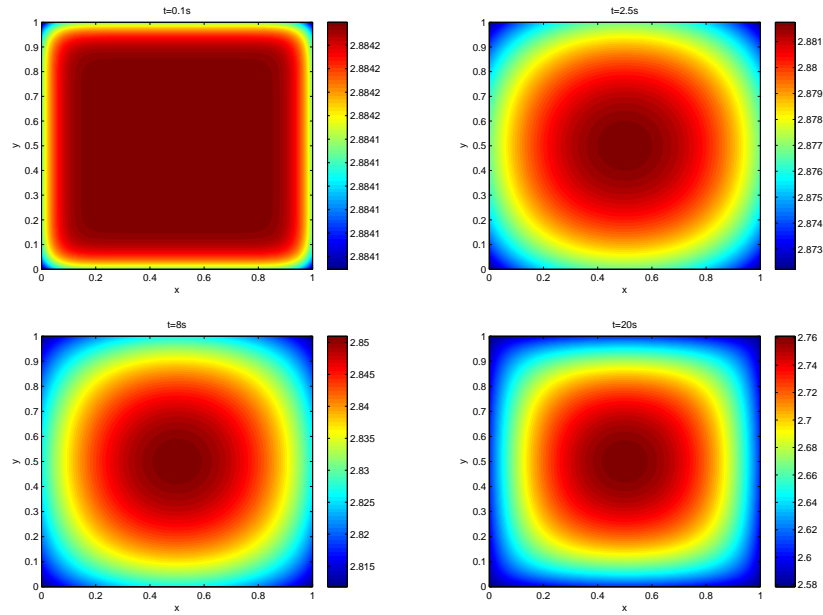


Figure 6: Concentration of solid drug for different times.

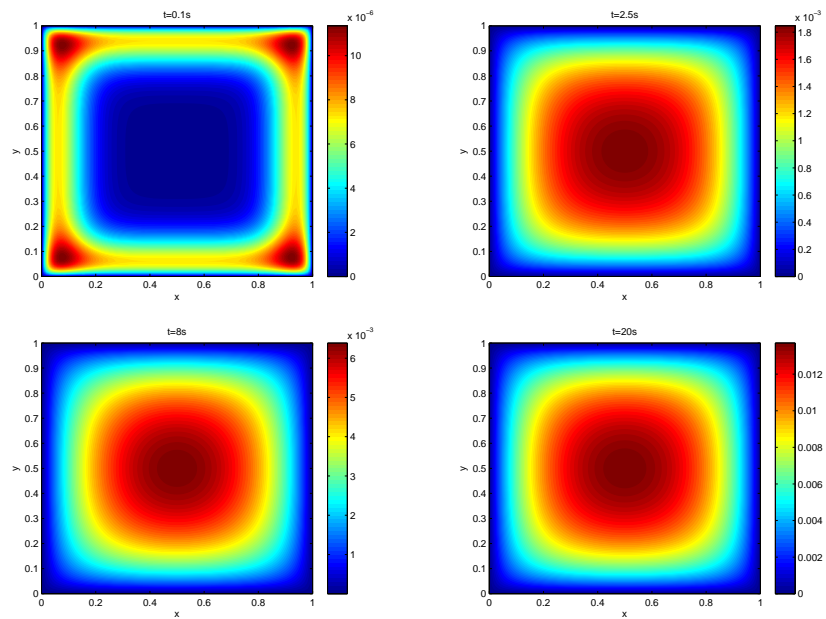


Figure 7: Concentration of dissolved drug for different times.

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.

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