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DRUG RELEASE FROM A SURFACE EROSION BIODEGRADABLE VISCOELASTIC POLYMERIC PLATFORM: ANALYSIS AND NUMERICAL SIMULATION

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Abstract: In this paper a system of partial differential equations, that can be used to describe the drug release from a biodegradable viscoelastic polymeric platform, is studied from analytical and numerical point of view. The system is defined in a moving boundary domain and its stability is analysed. From numerical point of view, a numerical method is proposed and their convergence properties are established. In the context of the drug release from biodegradable polymeric platforms, the qualitative behaviour of the differential system is numerically illustrated.

Keywords: Drug delivery; biodegradable viscoelastic polymer; surface erosion; time-varying domain; stability; convergence analysis.

1. Introduction

The drug release from a biodegradable polymeric platform in contact with a fluid, where a solid drug is initially dispersed, is a cascade of phenomena:

(i) The fluid enters in the polymeric structure;
(ii) The dissolution of the solid drug takes place when the solid drug is in contact with the fluid;
(iii) The dissolved drug is transported through the polymer to the exterior;
(iv) The polymeric structure degrades.

The mathematical modeling of the drug release from biodegradable or non-biodegradable polymeric platforms has been object of intense research during the last years. Without being exhaustive we mention the papers [1], [2], [8], [9], [10], [11], [17], [18] and [19]. Viscoelastic polymeric platforms were considered in [8], [9], [10] and [11] where the non-Fickian entrance of the fluid in the viscoelastic polymeric platforms is combined with the dissolution process of the solid drug and the diffusion transport of the dissolved drug.

In what concerns the polymeric degradation, it can be one of the two types: surface or bulk (Figure 1) ([4], [14], [17], [18], [19]). Bulk degradation occurs

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when the degradation is slower than the water uptake. The entirely system is rapidly hydrated and polymer chains are cleaved through all polymer structure. Surface degradation occurs when the degradation is faster than the entrance of water in the system. The break of polymer chains occurs mainly in the outermost polymer layer. In this case, the domain changes in time that introduces new challenges in the mathematical description of the cascade of phenomena.

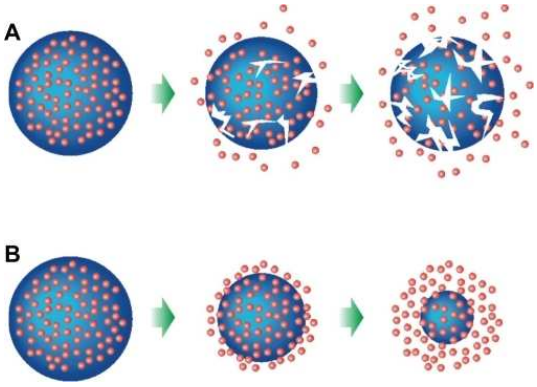

FIGURE 1. Bulk erosion (A) and surface erosion (B) ($http : //openi.nlm.nih.gov/imgs/512/203/3124394/3124394_ijn - 6 - 877f3.png$)

In [18], Rothstein et al. propose a system of partial differential equations to describe the drug release from a biodegradable polymeric matrix considering the Fickian entrance of the fluid in the structure, the evolution of the molecular weight due to the polymeric degradation that occurs due to hydrolysis reactions, the dissolution of the solid drug and the transport of the dissolved drug.

In [1], the non-Fickian drug transport through a biodegradable viscoelastic polymeric platform is studied combining the molecular weight evolution due to the degradation process ([18]) with the non-Fickian drug transport due to the viscoelastic nature of the polymeric matrix. Here, it is assumed that the fluid is in equilibrium, the drug is completely dissolved and the polymer presents bulk degradation (the spatial domain is fixed).

The aim of this work is to study a system of nonlinear partial differential equations defined in a two-dimensional moving boundary domain that can be used to describe the drug release from a biodegradable viscoelastic polymeric platform, where a solid drug is initially dispersed, involving the cascade of phenomena (i)-(iv): the non-Fickian fluid uptake, the dissolution of the solid

drug, the transport of the dissolved drug through the relaxed polymer, the surface degradation of the polymer. We assume that the erosion is due to hydrolysis reactions that lead to the reduction in time of the polymeric structure. We also assume that the mechanical characteristics of polymer chains, the Young modulus and the viscosity, depend on the polymeric molecular weight ([15], [20]). Moreover, we follow [6] to specify the moving boundary velocity considering that it depends on the fluid mass flux. The differential system is completed with convenient initial and boundary conditions and we remark that to the best of our knowledge, this system of partial differential equations was not yet object of any mathematical study. We analyse the stability of the moving boundary non-linear initial boundary value problem and we propose a numerical method that will be used to illustrate the qualitative behaviour of the fluid, solid and dissolved drug concentrations as well as the moving front of the domain. The accuracy of the spatial discretizations of the non-Fickian fluid uptake and the Fickian dissolved drug transport is established.

The paper is organized as follows: the system of partial differential equations is introduced in Section 2 considering the drug release from a biodegradable polymeric platform that is consequence of the cascade of phenomena described above. The stability analysis of the initial boundary value problem defined in a time-varying domain, that is consequence of the erosion process, is presented in Section 3. Following Oberkampf in [16], in Section 4, the moving boundary initial value problem is rewritten in a fix domain that is the basis of the numerical approach followed in Section 5. In this section, an implicit-explicit numerical scheme is proposed that is considered in Section 6 to illustrate the behaviour of the mathematical model. The convergence analysis of the discretization of the fluid uptake and the transport of the dissolved drug is presented in Section 7. We observe that the uniform boundness of the fluid approximations, that is concluded using the error estimates, has an important role in the convergence analysis of the drug approximations. Finally, in Section 8 we present some conclusions.

2. Mathematical model

We consider a two-dimensional biodegradable viscoelastic polymer $(-\ell_1(t), \ell_1(t)) \times (-\ell_2(t), \ell_2(t))$ (Figure 2). We assume that initially a solid drug is homogeneous distributed in the spatial domain and that the fluid enters through the boundaries $x = \pm\ell_1(t)$ and $y = \pm\ell_2(t)$. Consequently, it

is reasonable to assume that the fluid distribution, the solid and dissolved drug distributions in the spatial domain are symmetric with respect to the origin. These assumptions allows us to replace $(-\ell_1(t), \ell_1(t)) \times (-\ell_2(t), \ell_2(t))$ by $\overline{\Omega(t)} = [0, \ell_1(t)] \times [0, \ell_2(t)]$ which is a time-varying domain due to the polymer surface erosion.

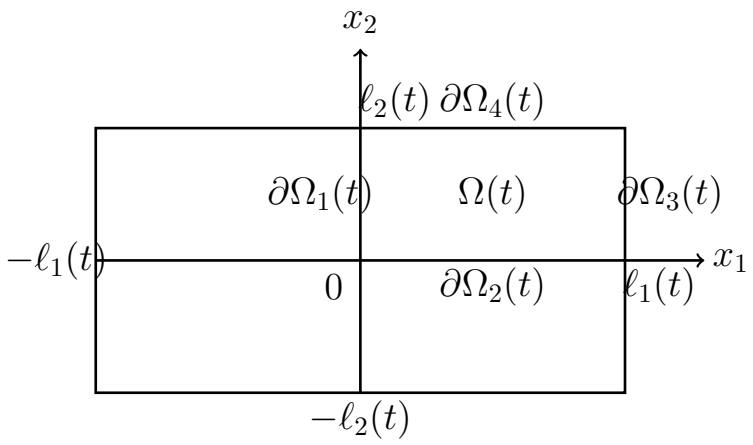

FIGURE 2. The two-dimensional domain

Let $c_w(x,t)$ denotes the fluid concentration at $x \in \Omega(t)$ at time t. We consider that the fluid transport through the viscoelastic polymeric platform is of non-Fickian type (see [10], [11])

$$\frac{\partial c_w}{\partial t} = \nabla \cdot (D_w \nabla c_w) + \nabla \cdot (D_v \nabla \sigma) - k c_w M,\ x \in \Omega(t), t \in (0,T], \quad (1)$$

where D_w represents the diffusion tensor of the solvent in the polymeric matrix, D_v is the viscoelastic diffusion tensor, σ is the stress response of the matrix to the strain exerted by the incoming molecules of solvent, M is the molecular weight of the polymer. In (1), $-kc_wM$ represents the rate of fluid consumption in the hydrolysis reactions being k the degradation rate.
As in [18], the evolution of the molecular weight of the polymer due to hydrolysis reactions that lead to the break of the polymer bonds is described by

$$\frac{\partial M}{\partial t} = -k c_w M,\ x \in \Omega(t), t \in (0,T]. \quad (2)$$

The mechanical behaviour of the viscoelastic polymer, which is specified prescribing the functional relation between the stress σ and strain ϵ, is described

by

$$\frac{\partial \sigma}{\partial t} + \frac{E(M)}{\mu(M)}\sigma = -E(M)\frac{\partial \epsilon}{\partial t},\ x \in \Omega(t), t \in (0,T],$$

(see [3]). In the last equation, E denotes the Young modulus and μ is the viscosity that we assume depending on the molecular weight ([15, 20]). As in [5] or in [7], we assume that $\epsilon = \lambda c_w$ but we remark that other expressions $\epsilon = g(c_w)$ were proposed in [10] and [11]. To simplify, we take $\lambda = 1$. Then the last equation is replaced by

$$\frac{\partial \sigma}{\partial t} + \frac{E(M)}{\mu(M)}\sigma = -E(M)\frac{\partial c_w}{\partial t},\ x \in \Omega(t), t \in (0,T]. \tag{3}$$

The kinetics of the solid drug is described by the partial differential equation

$$\frac{\partial c_s}{\partial t} = -\frac{k_{dis}}{c_{s0}c_{amx}c_{wout}}c_s(c_{amx} - c_d)c_w,\ x \in \Omega(t), t \in (0,T], \tag{4}$$

where c_s is the concentration of solid drug, c_d is the concentration of dissolved drug, k_{dis} is the dissolution rate, c_{s0} is the initial concentration of solid drug, c_{amx} is maximum solubility and c_{wout} is the concentration of water outside of the polymer matrix ([18]). Finally, the dissolved drug transport through the polymer matrix is described by

$$\begin{aligned}\frac{\partial c_d}{\partial t} &= \nabla \cdot (D(M)\nabla c_d) \\ &+ \frac{k_{dis}}{c_{s0}c_{amx}c_{wout}}c_s(c_{amx} - c_d)c_w, x \in \Omega(t), t \in (0,T],\end{aligned} \tag{5}$$

where $D(M)$ is the diffusion tensor of the dissolved drug that depends on the molecular weight and is given by

$$D(M) = D_0 e^{\bar{k}\frac{M_0 - M}{M_0}},$$

where D_0 is diffusion tensor of the drug in the non-hydrolyzed polymer, $\bar{k}$ is a positive constant, M_0 is the initial polymeric molecular weight (see in [19]).

As initially we do not have any fluid in the polymer and we have only solid drug, then the differential system (1)-(5) is completed with the initial conditions

$$c_w(0) = 0, \sigma(0) = \sigma_0, M(0) = M_0, c_s(0) = c_{s0}, c_d(0) = 0,\ \text{in } \Omega(0), \tag{6}$$

where σ_0 represents the initial stress of the molecules of polymer.

Let $J_w(t)$ be the fluid flux

$$J_w(t) = -D_w \nabla c_w(t) - D_v \nabla \sigma(t).$$

As we mentioned before, the symmetric conditions on $\partial\Omega_i(t)$, $i = 1, 2$, are mathematically rewritten in the following form

$$\nabla\sigma.\nu = \nabla c_w.\nu = \nabla c_d.\nu = 0, x \in \partial\Omega_1(t) \cup \partial\Omega_2(t), t \in (0, T], \tag{7}$$

where ν is the exterior unit normal $\Omega(t)$ on $\partial\Omega_1(t) \cup \partial\Omega_2(t)$.
In what follows we assume that the fluid enters into the polymer through to the boundary $\partial\Omega_3(t) \cup \partial\Omega_4(t)$ and its entrance depends on the boundary permeability A_c and on the difference between the outside fluid concentration c_{wout} and the fluid concentration at the boundary, that is

$$J_w(t).\nu_i = A_c(c_w - c_{wout}),\ x \in \partial\Omega_{i+2}(t), t \in (0, T], \tag{8}$$

where ν_i is the exterior unit normal to $\Omega(t)$ on $\partial\Omega_{i+2}(t)$, $i = 1, 2$.
All the dissolved drug that attains the boundaries $\partial\Omega_3(t) \cup \partial\Omega_4(t)$ is immediately removed, that is

$$c_d = 0,\ x \in \partial\Omega_3(t) \cup \partial\Omega_4(t), t \in (0, T]. \tag{9}$$

To close the initial boundary value problem (1)-(5) and (6)-(9) we need to specify the front degradation speed. In this work we consider a condition analogous to the one proposed by Patel in [6] for each side of the domain $\Omega(t)$:

$$\frac{d\ell_i}{dt} = \frac{1}{\ell_{i+1}(t)} \int_0^{\ell_{i+1}(t)} J_w(t).\nu_i dx_{i+1}, t \in (0, T], i = 1, 2, \tag{10}$$

where, $x_3 = x_1$, $\ell_3 = \ell_1$ and ν_1 and ν_2 denote the unitary exterior normal to $\Omega(t)$ on $\partial\Omega_3(t)$ and $\partial\Omega_4(t)$, respectively, $t \in (0, T]$.
The previous boundary conditions are summarized as follows:

$$\begin{cases} \nabla\sigma.\nu = 0, \nabla c_w.\nu = 0, \nabla c_d.\nu = 0\,, x \in \partial\Omega_1(t) \cup \partial\Omega_2(t), t \in (0, T], \\ \\ J_w(t).\nu = A_c(c_w - c_{wout}),\ c_d = 0,\ x \in \partial\Omega_3(t) \cup \partial\Omega_4(t), t \in (0, T], \\ \dfrac{d\ell_i}{dt} = \dfrac{1}{\ell_{i+1}(t)} \displaystyle\int_0^{\ell_{i+1}(t)} J_w(t).\nu_i\, dx_{i+1},\ t \in (0, T], i = 1, 2. \end{cases} \tag{11}$$

3. Stability analysis

In order to simplify the presentation, we assume in what follows that E, μ and the diffusion coefficient D are constant. Moreover, to study the stability of the initial boundary value problem (1)-(5), (6) and (11), an assumption needs to be considered in the moving front velocity.
Due to surface erosion, the degradation moving front is a decreasing function in time, then is acceptable to impose that $\ell_1(t)$ and $\ell_2(t)$ are a decreasing functions in time and their derivatives are negative. As we imposed the condition (10) and (8) also holds, then

$$\frac{d\ell_i}{dt} = \frac{1}{\ell_{i+1}(t)} \int_0^{\ell_{i+1}(t)} A_c(c_w - c_{wout})\, dx_{i+1},\ t \in (0,T], i = 1,2. \tag{12}$$

Phenomenologically, we have c_w less than c_{wout} at the degradation front, and then

$$-A_c c_{wout} \leq A_c(c_w(t) - c_{wout}) < 0,$$

being the last inequality converted in equality only when fluid is in equilibrium. It is then physically acceptable to assume that $\ell_i(t)$, $i = 1,2$, satisfy the following assumption:

Assumption 3.1. *There exists small enough γ_i, $i = 1,2$, positive constants such that*

$$\ell_i'(t) \leq -\gamma_i, t \in (0,T], i = 1,2.$$

In $L^2(\Omega(t))$ we consider the usual inner product

$$(u,v)_{\Omega(t)} = \int_{\Omega(t)} uv dx,\ u,v \in L^2(\Omega(t)),$$

and the corresponding norm is denoted by $\|.\|_{\Omega(t)}$. If $\Gamma(t)$ is a part of the boundary $\partial\Omega(t)$, then in $L^2(\Gamma(t))$ we consider the usual inner product

$$(u,v)_{\Gamma(t)} = \int_{\Gamma(t)} u(s)v(s)ds,\ u,v \in L^2(\Gamma(t)),$$

being $\|.\|_{\Gamma(t)}$ the corresponding norm.

By $H^1_{\Gamma(t)}(\Omega(t))$ we denote the space of functions in $H^1(\Omega(t))$ null on $\Gamma(t)$, for $t \in (0,T]$. For $\mathcal{C}(t) = \big(c_w(t), M(t), c_s(t), c_d(t)\big)$ we use the notation $\dfrac{d\mathcal{C}}{dt}(t) = \Big(\dfrac{dc_w}{dt}(t), \dfrac{dM}{dt}(t), \dfrac{dc_s}{dt}(t), \dfrac{dc_d}{dt}(t)\Big)$.

To gain some insight on the stability behaviour of the initial value problem (1)-(9), in what follows we study the stability of the linearization of (1)-(5) for small and large times. In order to do that, we introduce now the linearization of the previous problem in $\tilde{c}_w$, $\tilde{M}$, $\tilde{c}_d$ and $\tilde{c}_s$ which is written in the following form

$$\frac{\partial c_w}{\partial t} = \nabla \cdot (D_w \nabla c_w) + \nabla \cdot (D_v \nabla \sigma) - k\tilde{c}_w M - k\tilde{M} c_w, \tag{13}$$

$$\frac{\partial M}{\partial t} = -k\tilde{c}_w M - k\tilde{M} c_w, \tag{14}$$

$$\frac{\partial \sigma}{\partial t} + \frac{E}{\mu}\sigma = -E\frac{\partial c_w}{\partial t}, \tag{15}$$

$$\begin{aligned} \frac{\partial c_s}{\partial t} &= -K\Big((c_{amx} - \tilde{c}_d)\tilde{c}_w c_s - \tilde{c}_w \tilde{c}_s c_d \\ &+ \tilde{c}_s(c_{amx} - \tilde{c}_d)c_w\Big), \end{aligned} \tag{16}$$

$$\begin{aligned} \frac{\partial c_d}{\partial t} &= \nabla \cdot (D\nabla c_d) + K\Big((c_{amx} - \tilde{c}_d)\tilde{c}_w c_s \\ &- \tilde{c}_w \tilde{c}_s c_d + \tilde{c}_s(c_{amx} - \tilde{c}_d)c_w\Big), \end{aligned} \tag{17}$$

where $K = \dfrac{k_{dis}}{c_{s0} c_{amx} c_{wout}}$ is a constant.

Stability for large times: In the neighborhood of the steady state solution, the molecular weight decreases and vanishes, the concentration of water is in equilibrium being $c_w = c_{wout}$, the concentrations of solid and dissolved drug inside of the polymeric matrix vanish. Then, the steady solution is given by

$$\tilde{c}_w = c_{wout},\ \tilde{c}_d = 0,\ \tilde{c}_s = 0, \tilde{M} = 0. \tag{18}$$

In this case, the stability of (1)-(5) and (11) can be concluded from the stability of (13)-(17) when (18) is considered, that is

$$\frac{\partial c_w}{\partial t} = \nabla \cdot (D_w \nabla c_w) + \nabla \cdot (D_v \nabla \sigma) - k c_{wout} M, x \in \Omega(t), t \in (0, T], \tag{19}$$

$$\frac{\partial M}{\partial t} = -k c_{wout} M,\ x \in \Omega(t), t \in (0, T], \tag{20}$$

$$\frac{\partial \sigma}{\partial t} + \frac{E}{\mu}\sigma = -E\frac{\partial c_w}{\partial t},\ x \in \Omega(t), t \in (0, T], \tag{21}$$

$$\frac{\partial c_s}{\partial t} = -\frac{k_{dis}}{c_{s0}} c_s,\ x \in \Omega(t), t \in (0,T], \tag{22}$$

$$\frac{\partial c_d}{\partial t} = \nabla \cdot (D \nabla c_d) + \frac{k_{dis}}{c_{s0}} c_s,\ x \in \Omega(t), t \in (0,T], \tag{23}$$

with the boundary conditions (11).
We observe that (19)-(23) with (11) is linear. Then its stability can be concluded from energy estimates for the solution $\mathcal{C}(t) = \big(c_w(t), M(t), c_s(t), c_d(t)\big)$. In our analysis we use the integral representation of the stress σ

$$\begin{aligned} \sigma(t) = \frac{E^2}{\mu} \int_0^t e^{-\frac{E}{\mu}(t-s)} c_w(s) ds \ &- \ E c_w(t) + E c_w(0) e^{-\frac{E}{\mu} t} \\ &+ \ \sigma(0) e^{-\frac{E}{\mu} t},\ t \geq 0, \end{aligned} \tag{24}$$

that allows to obtain an useful equivalent representation for (19) and (21)

$$\begin{aligned} \frac{\partial c_w}{\partial t} \ &= \ \nabla \cdot (D_1 \nabla c_w) + \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla \cdot (D_2 \nabla c_w(s)) ds - k c_{wout} M \\ &+ \ E e^{-\frac{E}{\mu} t} \nabla . (D_v \nabla c_w(0)) + e^{-\frac{E}{\mu} t} \nabla . (D_v \nabla \sigma(0)), \end{aligned} \tag{25}$$

where

$$\sigma(0) = Constant,\ D_1 = D_w - E D_v,\ D_2 = \frac{E^2}{\mu} D_v.$$

Then the differential problem (19)-(23) with the boundary conditions (11) is replaced by the equivalent differential problem (20), (22), (23) and (25) complemented with the boundary conditions

$$\begin{cases} \nabla \sigma . \nu = 0,\ \nabla c_w . \nu = 0,\ \nabla c_d . \nu = 0 \text{ on } \partial\Omega_1(t) \cup \partial\Omega_2(t), t \in (0,T], \\ J_w(t) . \nu = A_c c_w,\ c_d = 0 \text{ on } \partial\Omega_3(t) \cup \partial\Omega_4(t), t \in (0,T], \\ \dfrac{d\ell_i}{dt}(t) = \dfrac{1}{\ell_{i+1}(t)} \displaystyle\int_0^{\ell_{i+1}(t)} J_w(t) . \nu_i \, dx_{i+1},\ t \in (0,T], i = 1,2, \end{cases} \tag{26}$$

where the fluid mass flux $J_w(t)$ is given by

$$J_w(t) = -D_1 \nabla c_w - D_2 \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla c_w(s) ds,$$

and the initial condition

$$c_w(0) = c_{w0}, M(0) = M_0, c_s(0) = c_{s0}, c_d(0) = c_{d0}, x \in \Omega(0). \tag{27}$$

In what follows we establish an upper bound for the energy functional

$$\mathcal{E}(t) = \mathcal{E}_1(t) + \mathcal{E}_2(t) + \mathcal{E}_3(t) \tag{28}$$

where

$$\mathcal{E}_1(t) = \sum_{p\in\{c_w,M,c_s,c_d\}} \|p(t)\|^2_{\Omega(t)}, \tag{29}$$

$$\mathcal{E}_2(t) = \int_0^t \left(\|\nabla c_w(\theta)\|^2_{\Omega(\theta)} + \|\nabla c_d(\theta)\|^2_{\Omega(\theta)}\right)d\theta \tag{30}$$

and

$$\mathcal{E}_3(t) = \sum_{i=3,4}\sum_{p\in\{c_w,M,c_s\}} \int_0^t \|p(\theta)\|^2_{\partial\Omega_i(\theta)}d\theta. \tag{31}$$

In $\mathcal{E}_i, i = 1, 2, 3$, we consider the solution of the following variational problem: find $\mathcal{C}(t)\in H^1(\Omega(t))\times(L^2(\Omega(t)))^2 \times H^1_{\partial\Omega_3(t)\cup\partial\Omega_4(t)}(\Omega(t))$, $t \in (0, T]$, such that $\frac{d\mathcal{C}}{dt}(t) \in \left(L^2(\Omega(t))\right)^4, t \in (0, T]$, and

$$\begin{aligned}\left(\frac{dc_w}{dt}(t), v_1\right)_{\Omega(t)} &= -(D_1\nabla c_w(t), \nabla v_1)_{\Omega(t)} - \int_0^t e^{-\frac{E}{\mu}(t-s)}(D_2\nabla c_w(\theta), \nabla v_1)_{\Omega(\theta)}d\theta \\ &- \sum_{i=3,4}(A_c c_w(t), v_1)_{\partial\Omega_i(t)} - kc_{wout}(M(t), v_1)_{\Omega(t)} \\ &+ e^{-\frac{E}{\mu}t}E(\nabla\cdot(D_v\nabla c_w(0)), v_1)_{\Omega(t)},\ \forall v_1 \in H^1(\Omega(t)),\end{aligned} \tag{32}$$

$$\left(\frac{dM}{dt}(t), v_2\right)_{\Omega(t)} = -kc_{wout}(M(t), v_2)_{\Omega(t)},\ \forall v_2 \in L^2(\Omega(t)), \tag{33}$$

$$\left(\frac{dc_s}{dt}(t), v_3\right)_{\Omega(t)} = -\frac{k_{dis}}{c_{s0}}(c_s(t), v_3)_{\Omega(t)},\ \forall v_3 \in L^2(\Omega(t)), \tag{34}$$

$$\left(\frac{dc_d}{dt}(t), v_4\right)_{\Omega(t)} = -(D\nabla c_d(t), \nabla v_4)_{\Omega(t)} + \frac{k_{dis}}{c_{s0}}(c_s(t), v_4)_{\Omega(t)}, \tag{35}$$

$$\forall v_4 \in H^1_{\partial\Omega_3(t)\cup\partial\Omega_4(t)}(\Omega(t)), \tag{36}$$

for $t \in (0, T]$.

To give sense to (32) we need to impose that $c_w(0) \in H^2(\Omega(t)), t \in [0,T]$ and conditions (27) hold in the following sense

$$\begin{array}{l}(c_w(0),w)_{\Omega(0)} = (c_{w0},w)_{\Omega(0)}, \forall w \in L^2(\Omega(0)),\\ (M(0),m)_{\Omega(0)} = (M_0,m)_{\Omega(0)}, \forall m \in L^2(\Omega(0)),\\ (c_s(0),s_d)_{\Omega(0)} = (c_{s0},s_d)_{\Omega(0)}, \forall s_d \in L^2(\Omega(0)),\\ (c_d(0),f_d)_{\Omega(0)} = (c_{d0},f_d)_{\Omega(0)}, \forall f_d \in L^2(\Omega(0)).\end{array}$$

Taking in (32)-(35), $v_1 = c_w, v_2 = M, v_3 = c_s$ and $v_4 = c_d$, and using the fact that

$$\begin{aligned}\frac{d}{dt}\int_{\Omega(t)} g(x_1,x_2,t)dx_1dx_2 &= \ell_2'(t)\int_0^{\ell_1(t)} g(x_1,\ell_2(t),t)dx_1\\ &+\ell_1'(t)\int_0^{\ell_2(t)} g(\ell_1(t),x_2,t)dx_2 + \int_{\Omega(t)}\frac{\partial g}{\partial t}(x_1,x_2,t)dx_1dx_2,\end{aligned}$$

we easily obtain

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|c_w(t)\|^2_{\Omega(t)} &- \frac{1}{2}\sum_{i=3,4}\ell_{i-2}'(t)\|c_w(t)\|^2_{\partial\Omega_i(t)}\\ &= -(D_1\nabla c_w(t),\nabla c_w(t))_{\Omega(t)}\\ &- \int_0^t e^{-\frac{E}{\mu}(t-s)}(D_2\nabla c_w(\theta),\nabla c_w(\theta))_{\Omega(\theta)}d\theta\\ &- \sum_{i=3,4} A_c\|c_w(t)\|^2_{\partial\Omega_i(t)}\\ &+ e^{-\frac{E}{\mu}t}E(\nabla\cdot(D_v\nabla c_w(0)),c_w(t))_{\Omega(t)}\\ &- kc_{wout}(M(t),c_w(t))_{\Omega(t)},\end{aligned} \tag{37}$$

$$\frac{1}{2}\frac{d}{dt}\|M(t)\|^2_{\Omega(t)} - \frac{1}{2}\sum_{i=3,4}\ell_{i-2}'(t)\|M(t)\|^2_{\partial\Omega_i(t)} = -kc_{wout}\|M(t)\|^2_{\Omega(t)}, \tag{38}$$

$$\frac{1}{2}\frac{d}{dt}\|c_s(t)\|^2_{\Omega(t)} - \frac{1}{2}\sum_{i=3,4}\ell_{i-2}'(t)\|c_s(t)\|^2_{\partial\Omega_i(t)} = -\frac{k_{dis}}{c_{s0}}\|c_s(t)\|^2_{\Omega(t)}, \tag{39}$$

and

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|c_d(t)\|^2_{\Omega(t)} &- \frac{1}{2}\sum_{i=3,4}\ell'_{i-2}(t)\|c_d(t)\|^2_{\partial\Omega_i(t)} \\ &= -(D\nabla c_d(t),\nabla c_d(t))_{\Omega(t)} + \frac{k_{dis}}{c_{s0}}(c_d(t),c_s(t)),\end{aligned} \tag{40}$$

where $\|c_d(t)\|^2_{\partial\Omega_i(t)} = 0$, for $i = 3, 4$.

It is easy to show that

$$\begin{aligned}-\int_0^t e^{-\frac{E}{\mu}(t-s)}(D_2\nabla c_w(\theta),\nabla c_w(t))_{\Omega(\theta)}d\theta &\leq \epsilon_1^2\|\nabla c_w(t)\|^2_{\Omega(t)} \\ &+ \frac{D_2^2\mu}{8\epsilon_1^2 E}\int_0^t\|\nabla c_w(\theta)\|^2_{\Omega(\theta)}d\theta,\end{aligned} \tag{41}$$

$$\begin{aligned}e^{-\frac{E}{\mu}t}E(\nabla\cdot(D_v\nabla c_w(0)),c_w(t))_{\Omega(t)} &\leq \tfrac{1}{4\epsilon_2^2}e^{-2\frac{E}{\mu}t}\Big(E^2\|\nabla\cdot(D_v\nabla c_w(0))\|^2_{\Omega(0)}\Big) \\ &+\epsilon_2^2\|c_w(t)\|^2_{\Omega(t)},\end{aligned} \tag{42}$$

$$kc_{wout}(M(t),c_w(t))_{\Omega(t)} \leq k^2c_{wout}^2\epsilon_3^2\|c_w(t)\|^2_{\Omega(t)} + \frac{1}{4\epsilon_3^2}\|M(t)\|^2_{\Omega(t)}, \tag{43}$$

$$\frac{\gamma_{i-2}}{2}\|c_w(t)\|^2_{\partial\Omega_i(t)} \leq \frac{\ell'_{i-2}(t)}{2}\|c_w(t)\|^2_{\partial\Omega_i(t)}, \quad i = 3, 4, \tag{44}$$

and

$$\frac{k_{dis}}{c_{s0}}(c_d(t),c_s(t)) \leq \frac{k_{dis}^2}{c_{s0}^2}\epsilon_4^2\|c_s(t)\|^2_{\Omega(t)} + \frac{1}{4\epsilon_4^2}\|c_d(t)\|^2_{\Omega(t)}, \tag{45}$$

where $\epsilon_i \neq 0, i = 1,\ldots,4$.

Summing up (37)-(40) and taking into account that (41)-(45) we obtain

$$\begin{aligned}
\frac{d}{dt}\mathcal{E}_1(t) &+ 2(D_1-\epsilon_1^2)\|\nabla c_w(t)\|^2_{\Omega(t)} + 2D\|\nabla c_d(t)\|^2_{\Omega(t)} \\
&+ \min\{\gamma_1,\gamma_2,A_c\}\sum_{i=3,4}\sum_{p\in\{c_w,M,c_s\}}\|p(t)\|^2_{\partial\Omega_i(t)} \\
&\leq \frac{D_2^2\mu}{4\epsilon_1^2E}\int_0^t\|\nabla c_w(\theta)\|^2_{\Omega(\theta)}d\theta \qquad (46)\\
&+ \Big(2\epsilon_2^2+2\epsilon_3^2k^2c_{wout}^2\Big)\|c_w(t)\|^2_{\Omega(t)} \\
&+ \frac{1}{2\epsilon_4^2}\|c_d(t)\|^2_{\Omega(t)} + \Big(\frac{2k_{dis}^2}{c_{s0}^2}\epsilon_4^2-\frac{2k_{dis}}{c_{s0}}\Big)\|c_s(t)\|^2_{\Omega(t)} \\
&+ \Big(\frac{1}{2\epsilon_3^2}-2kc_{wout}\Big)\|M(t)\|^2_{\Omega(t)} \\
&+ \frac{1}{2\epsilon_2^2}e^{-2\frac{E}{\mu}t}E^2\|\nabla\cdot(D_v\nabla c_w(0))\Big\|^2_{\Omega(0)}.
\end{aligned}$$

If we fix ϵ_1 satisfying $D_1-\epsilon_1^2>0$, then

$$\begin{aligned}
\mathcal{E}(t) &\leq \overline{c}\int_0^t\mathcal{E}(s)ds \\
&+ \frac{1}{\min\Big\{1,2(D_1-\epsilon_1^2),2D,\gamma_1,\gamma_2,A_c\Big\}}\Big(\frac{\mu E}{4\epsilon_2^2}\Big\|\nabla\cdot(D_v\nabla c_w(0)\|^2_{\Omega(0)}+\mathcal{E}_1(0)\Big),
\end{aligned}$$

where $\overline{c}$ is given by

$$\overline{c}=\frac{\max\Big\{\frac{D_2^2\mu}{4\epsilon_1^2E},(\frac{1}{2\epsilon_3^2}-2kc_{wout}),(\frac{2k_{dis}^2\epsilon_4^2}{C_{S0}^2}-\frac{2k_{dis}}{C_{S0}}),(2\epsilon_2^2+2\epsilon_3^2k^2c_{wout}^2),\frac{1}{2\epsilon_4^2}\Big\}}{\min\Big\{1,2(D_1-\epsilon_1^2),2D,\gamma_1,\gamma_2,A_c\Big\}}. \quad (47)$$

Finally by using Gronwall's Lemma ([13]) we conclude the following result:

Theorem 1. *Under Assumption 3.1, if the solution $\mathcal{C}=(c_w,M,c_s,c_d)$ of the variational problem (32)-(35) and (27) belongs to*

$$C^1\Big([0,T],\Big(L^2(\Omega(t))\Big)^4\Big)\cap C^0\Big([0,T],H^1(\Omega(t))\times\Big(L^2(\Omega(t))\Big)^2\times H^1_{\partial\Omega_3(t)\cup\partial\Omega_4(t)}(\Omega(t))\Big)$$

$c_w, M, c_s \in C^0\Big([0,T], L^2(\partial\Omega_i(t))\Big), i = 3, 4$, *and* $c_w(0) \in H^2(\Omega(0))$, *then there exist two positive constants* $C_i, i = 1, 2$, *such that*

$$\mathcal{E}(t) \leq C_1\Big(\|\nabla \cdot (D_v \nabla c_w(0))\|^2_{\Omega(0)} + \mathcal{E}_1(0)\Big)e^{C_2 t}, t \in [0,T].$$

Stability for short times: For small times, the concentration of water and dissolved drug is very small so we consider

$$\tilde{c}_w = 0,\ \tilde{c}_d = 0,\ \tilde{c}_s = c_{s_0}, \tilde{M} = M_0. \tag{48}$$

So the stability of the differential system (1)-(5) for small times can be concluded from the stability of (13)-(17) when (48) is considered, that is, from the linear differential problem

$$\frac{\partial c_w}{\partial t} = \nabla \cdot (D_w \nabla c_w) + \nabla \cdot (D_v \nabla \sigma) - kM_0 c_w,\ x \in \Omega(t), t \in (0,T], \tag{49}$$

$$\frac{\partial M}{\partial t} = -kM_0 c_w,\ x \in \Omega(t), t \in (0,T], \tag{50}$$

$$\frac{\partial \sigma}{\partial t} + \frac{E}{\mu}\sigma = -E\frac{\partial c_w}{\partial t},\ x \in \Omega(t), t \in (0,T], \tag{51}$$

$$\frac{\partial c_s}{\partial t} = -\frac{k_{dis}}{c_{wout}} c_w,\ x \in \Omega(t), t \in (0,T], \tag{52}$$

$$\frac{\partial c_d}{\partial t} = \nabla \cdot (D \nabla c_d) + \frac{k_{dis}}{c_{wout}} c_w,\ x \in \Omega(t), t \in (0,T]. \tag{53}$$

In what follows we use the energy method to analyze the stability behaviour of the (49)-(53) with the initial and boundary conditions (27) and (26), respectively. We start by remarking that from equation (24) and (49) we obtain the following equation for c_w

$$\begin{aligned} \frac{\partial c_w}{\partial t} &= \nabla \cdot (D_1 \nabla c_w) + \int_0^t e^{-\frac{E}{\mu}(t-s)} \nabla \cdot (D_2 \nabla c_w(s)) ds - kM_0 c_w \\ &+ Ee^{-\frac{E}{\mu}t} \nabla . (D_v \nabla c_w(0)),\ x \in \Omega(t), t \in (0,T]. \end{aligned} \tag{54}$$

The energy estimate is established for the solution of the variational problem: find

$$\mathcal{C}(t) = (c_w(t), M(t), c_s(t), c_d(t)) \in H^1(\Omega(t)) \times \big(L^2(\Omega(t))\big)^2 \times H^1_{\partial\Omega_3(t) \cup \partial\Omega_4(t)}(\Omega(t))$$

and $\frac{d\mathcal{C}}{dt}(t) \in \left(L^2(\Omega(t))\right)^4$, $t \in (0,T]$, such that

$$\begin{aligned}(\frac{dc_w}{dt}(t), v_1)_{\Omega(t)} &= -(D_1\nabla c_w(t), \nabla v_1)_{\Omega(t)} - \int_0^t e^{-\frac{E}{\mu}(t-s)}(D_2\nabla c_w(s), \nabla v_1)_{\Omega(s)}ds \\ &- \sum_{i=3,4}(A_c c_w(t), v_1)_{\partial\Omega_i(t)} - kM_0(c_w(t), v_1)_{\Omega(t)} \\ &+ e^{-\frac{E}{\mu}t}E(\nabla\cdot(D_v\nabla c_w(0)), v_1)_{\Omega(t)},\ \forall v_1 \in H^1(\Omega(t)),\end{aligned} \tag{55}$$

$$(\frac{dM}{dt}(t), v_2)_{\Omega(t)} = -kM_0(c_w(t), v_2)_{\Omega(t)},\ \forall v_2 \in L^2(\Omega(t)), \tag{56}$$

$$(\frac{dc_s}{dt}(t), v_3)_{\Omega(t)} = -\frac{k_{dis}}{c_{wout}}(c_w(t), v_3)_{\Omega(t)},\ \forall v_3 \in L^2(\Omega(t)), \tag{57}$$

$$(\frac{dc_d}{dt}(t), v_4)_{\Omega(t)} = -(D\nabla c_d(t), \nabla v_4)_{\Omega(t)} + \frac{k_{dis}}{c_{wout}}(c_w(t), v_4)_{\Omega(t)}, \tag{58}$$

$$\forall v_4 \in H_0^1(\Omega(t)), \tag{59}$$

for $t \in (0,T]$, with the initial condition (27).

Following the proof of Theorem 1, it can be shown the following result:

Theorem 2. *Under Assumption 3.1, if the solution $\mathcal{C} = (c_w, M, c_s, c_d)$ of the variational problem (55)-(58) and (27) belongs to*

$$C^1\Big([0,T], \Big(L^2(\Omega(t))\Big)^4\Big) \cap C^0\Big([0,T], H^1(\Omega(t)) \times \big(L^2(\Omega(t))\big)^2 \times H^1_{\partial\Omega_3(t)\cup\partial\Omega_4(t)}(\Omega(t))\Big)$$

$c_w, M, c_s \in C^0\Big([0,T], L^2(\partial\Omega_i(t))\Big), i = 3,4$, *and* $c_w(0) \in H^2(\Omega(0))$, *then there exist two positive constants* $C_i, i = 1,2$, *such that*

$$\mathcal{E}(t) \le C_1\Big(\|\nabla\cdot(D_v\nabla c_w(0))\|^2_{\Omega(0)} + \mathcal{E}_1(0)\Big)e^{C_2 t}, t \in [0,T].$$

Theorems 1 and 2 allow us to conclude the stability of the linearization of the initial boundary value problem (1)-(9) in the large and short times for bounded time intervals.

4. Tracking the degradation fronts

In what follows we rewrite the IBVP (1)-(6) and (11) in a fixed domain $\overline{\Omega} = [0,1] \times [0,1]$ considering a convenient coordinate transformation. Let $(\xi, \eta) \in \overline{\Omega}$ be the new space variables. Following Oberkampf in [16] we take

$$\xi = \frac{x_1}{\ell_1(t)}, \eta = \frac{x_2}{\ell_2(t)}.$$

We observe that if $\phi(\xi, \eta, t) = \phi(x_1, x_2, t)$ then we have

$$\frac{\partial \phi}{\partial \xi}(\xi, \eta, t) = \ell_1(t) \frac{\partial \phi}{\partial x_1}(x_1, x_2, t), \ \frac{\partial \phi}{\partial \eta}(\xi, \eta, t) = \ell_2(t) \frac{\partial \phi}{\partial x_2}(x_1, x_2, t), \tag{60}$$

and

$$\frac{\partial \phi}{\partial t}(x_1, x_2, t) = \frac{\partial \phi}{\partial t}(\xi, \eta, t) - \xi \frac{\ell_1'(t)}{\ell_1(t)} \frac{\partial \phi}{\partial \xi}(\xi, \eta, t) - \eta \frac{\ell_2'(t)}{\ell_2(t)} \frac{\partial \phi}{\partial \eta}(\xi, \eta, t). \tag{61}$$

We use $\nabla_{\xi,\eta}$ to denote the gradient operator with respect to the new variables and $\partial\Omega_1 = \{(0, \eta), \eta \in (0,1)\}$, $\partial\Omega_2 = \{(\xi, 0), \xi \in (0,1)\}$, $\partial\Omega_3 = \{(1, \eta), \eta \in (0,1)\}$ and $\partial\Omega_4 = \{(\xi, 1), \xi \in (0,1)\}$.
To simplify, we use the same notation for the dependent variables defined now in the fixed domain. Considering the last relations (60) and (61), the IBVP (1)-(6) and (11) is now rewritten in the fixed domain $\overline{\Omega}$ as follows:

$$\begin{aligned} \frac{\partial c_w}{\partial t} &= \nabla_{\xi,\eta} . \Big(D_w L_1 \nabla_{\xi,\eta} c_w \Big) + \nabla_{\xi,\eta} . \Big(D_v L_1 \nabla_{\xi,\eta} \sigma \Big) \\ &\quad + L_2 \nabla_{\xi,\eta} c_w - k c_w M \text{ in } \Omega \times (0, T], \end{aligned} \tag{62}$$

where L_1 and L_2 are diagonal matrices with entries $\frac{1}{\ell_i^2}, i = 1, 2$, and $\frac{\ell_1'}{\ell_1}\xi, \frac{\ell_2'}{\ell_2}\eta$, respectively,

$$\frac{\partial M}{\partial t} = L_2 \nabla_{\xi,\eta} M - k c_w M \text{ in } \Omega \times (0, T], \tag{63}$$

$$\frac{\partial \sigma}{\partial t} + \frac{E(M)}{\mu(M)} \sigma = E(M) L_2 \nabla_{\xi,\eta} c_w + L_2 \nabla_{\xi,\eta} \sigma - E(M) \frac{\partial c_w}{\partial t} \text{ in } \Omega \times (0, T], \tag{64}$$

$$\frac{\partial c_s}{\partial t} = L_2 \nabla_{\xi,\eta} c_s - \frac{k_{dis}}{c_{s0} c_{amx} c_{wout}} c_s (c_{amx} - c_d) c_w \text{ in } \Omega \times (0, T], \tag{65}$$

$$\begin{aligned}\frac{\partial c_d}{\partial t} &= \nabla_{\xi,\eta}.\Big(D(M)L_1\nabla_{\xi,\eta}c_d\Big) + L_2\nabla_{\xi,\eta}c_d \\ &+ \frac{k_{dis}}{c_{s0}c_{amx}c_{wout}}c_s(c_{amx}-c_d)c_w \text{ in } \Omega\times(0,T], \end{aligned} \tag{66}$$

$$c_w(0)=0, \sigma(0)=\sigma_0, M(0)=M_0, c_s(0)=c_{s0}, c_d(0)=0 \text{ in } \Omega, \tag{67}$$

and

$$\begin{cases} \nabla_{\xi,\eta}\sigma.\nu=0,\ \nabla_{\xi,\eta}c_w.\nu=0,\ \nabla_{\xi,\eta}c_d.\nu=0 \text{ on } (\partial\Omega_1\cup\partial\Omega_2)\times(0,T], \\ J_{w\xi,\eta}(t).\nu=\ell_\nu(t)A_c(c_w-c_{wout}),\ c_d=0 \text{ on } (\partial\Omega_3\cup\partial\Omega_4)\times(0,T], \\ \dfrac{d\ell_1}{dt}=\dfrac{1}{\ell_1(t)}\displaystyle\int_0^1 J_{w\xi,\eta}(1,\eta).\nu_1\,d\eta,\ t\in(0,T], \\ \dfrac{d\ell_2}{dt}=\dfrac{1}{\ell_2(t)}\displaystyle\int_0^1 J_{w\xi,\eta}(\xi,1).\nu_2\,d\xi,\ t\in(0,T], \end{cases} \tag{68}$$

respectively, where $J_{w\xi,\eta}(t)=-D_w\nabla_{\xi,\eta}c_w-D_v\nabla_{\xi,\eta}\sigma$ and $\ell_{\nu_i}=\ell_i(t), i=1,2$.

As before, from the third and last equations of (68), we have

$$\frac{d\ell_1}{dt}=\frac{1}{\ell_1(t)}\int_0^1 A_c(c_w(1,\eta)-c_{wout})\,d\eta, \quad t\in(0,T], \tag{69}$$

$$\frac{d\ell_2}{dt}=\frac{1}{\ell_2(t)}\int_0^1 A_c(c_w(\xi,1)-c_{wout})\,d\xi, \quad t\in(0,T]. \tag{70}$$

5. Numerical scheme

In this section we propose a coupled Implicit-Explicit (IMEX) method to solve the initial boundary value problem (62)-(68).

In $[0,T]$ we consider the grid $\{t_n, n=0,\dots,M\}$, with $t_0=0, t_M=T$ and $t_n-t_{n-1}=\Delta t$. We fix $\Delta\xi=\Delta\eta=h>0$, and we define in $\overline{\Omega}$ the grid

$$\begin{aligned}\overline{\Omega}_h &= \{(\xi_i,\eta_j), i,j=0,\dots,N,\ \xi_0,\eta_0=0,\ \xi_N,\eta_N=1, \xi_i-\xi_{i-1}=h, \\ &\quad \eta_j-\eta_{j-1}=h, i,j=1,\dots,N\}.\end{aligned}$$

As we are dealing with an initial boundary problem with boundary conditions on the spatial derivatives defined on the boundary, and to obtain discrete approximations with higher precision, we introduce the auxiliary points $\xi_{-1}=-h=\eta_{-1}, \xi_{N+1}=\eta_{N+1}=1+h$. Let $\overline{\Omega}_h^*$ be the set of grid points defined by $\overline{\Omega}_h^*=\overline{\Omega}_h\cup\{(\xi_r,\eta_j),(\xi_j,\eta_r), r=-1,N+1, j=0,\dots,N\}$. The space of grid functions defined in $\overline{\Omega}_h$ (or $\overline{\Omega}_h^*$) is represented by W_h (or W_h^*). Let $D_{-\xi}$ and $D_{-\eta}$ be the backward finite difference operators in ξ and η directions, respectively. By D_ξ and D_η we denote the forward finite difference operators

in ξ and η directions, respectively. By $D_{2,\xi}$ we represent the second order finite difference operator

$$D_{2,\xi}u_h(\xi_i,\eta_j)=\frac{1}{h^2}\big(u_h(\xi_{i+1},\eta_j)-2u_h(\xi_i,\eta_j)+u_h(\xi_{i-1},\eta_j)\big),$$

for $i,j=0,\ldots,N$ and $u_h\in W_h^*$. The operator $D_{2,\eta}$ is defined analogously. By $D_{c,\xi}$ we denote the first order finite difference operator

$$D_{c,\xi}u_h(\xi_i,\eta_j)=\frac{1}{2h}\big(u_h(\xi_{i+1},\eta_j)-u_h(\xi_{i-1},\eta_j)\big),$$

for $i,j=0,\ldots,N, u_h\in W_h^*$. The operator $D_{c,\eta}$ is defined analogously. We also need to introduce the average operator

$$A_{h,\xi}u_h(\xi_i,\eta_j)=\frac{1}{2}(u_h(\xi_{i-1},\eta_j)+u_h(\xi_i,\eta_j)),$$

being $A_{h,\eta}$ defined analogously.

To simplify the presentation we consider the following notation: for $u_h\in W_h^*$ we consider $\Delta_h u_h=(D_{2,\xi}u_h,D_{2,\eta}u_h)$, $\nabla_{c,h}u_h=(D_{c,\xi}u_h,D_{c,\eta}u_h)$.

Discretizing the spatial derivatives of (62)-(66) using the introduced finite difference operators, we obtain the following semi-discrete initial value problem

$$\begin{aligned}\frac{dc_{w,h}}{dt}(t) &= D_wL_1\Delta_hc_{w,h}(t)+D_vL_1\Delta_h\sigma_h(t)\\ &+ L_{2,h}\nabla_{c,h}c_{w,h}(t)-kc_{w,h}(t)M_h(t),\end{aligned}\tag{71}$$

where $L_{2,h}$ is the diagonal matrix with diagonal entries $\frac{\ell_1'}{\ell_1}a_h$, $\frac{\ell_2'}{\ell_2}b_h$ with $a_h(\xi_i,\eta_j)=\xi_i$ and $b_h(\xi_i,\eta_j)=\eta_j$,

$$\frac{dM_h}{dt}(t)=L_{2,h}\nabla_{c,h}M_h(t)-kc_{w,h}(t)M_h(t),\tag{72}$$

$$\begin{aligned}\frac{d\sigma_h}{dt}(t)+\frac{E(M_h(t))}{\mu(M_h(t))}\sigma_h(t) &= E(M_h(t))L_{2,h}\nabla_{c,h}c_{w,h}(t)+L_{2,h}\nabla_{c,h}\sigma_h(t)\\ &- E(M_h(t))\frac{dc_{w,h}}{dt}(t),\end{aligned}\tag{73}$$

$$\frac{dc_{s,h}}{dt}(t)=L_{2,h}\nabla_{c,h}c_{s,h}(t)-\frac{k_{dis}}{c_{s0}c_{amx}c_{wout}}c_{s,h}(t)(c_{amx}-c_{d,h}(t))c_{w,h}(t),\tag{74}$$

$$\begin{aligned}\frac{dc_{d,h}}{dt}(t) &= \nabla_{-h}.\Big(L_1\hat{D}(M_h(t))\nabla_h c_{d,h}(t)\Big) + L_{2,h}\nabla_{c,h}c_{d,h}(t)\\ &+ \frac{k_{dis}}{c_{s0}c_{amx}c_{wout}}c_{s,h}(t)(c_{amx}-c_{d,h}(t))c_{w,h}(t),\end{aligned} \tag{75}$$

where $\nabla_{-h} = (D_{-\xi}, D_{-\eta})$, $\nabla_h = (D_\xi, D_\eta)$ and $\hat{D}(M_h(t))$ is a diagonal matrix with entries $D(A_{h,\xi}M_h(t)), D(A_{h,\eta}M_h(t))$. This ordinary differential problem is complemented with the boundary conditions

$$\begin{cases} D_{c,\xi}\sigma_h(0,\eta_j,t)=0, D_{c,\xi}c_{w,h}(0,\eta_j,t)=0, D_{c,\xi}c_{d,h}(0,\eta_j,t)=0, j=0,\dots,N,\\ D_{c,\eta}\sigma_h(\xi_i,0,t)=0, D_{c,\eta}c_{w,h}(\xi_i,0,t)=0, D_{c,\eta}c_{d,h}(\xi_i,0,t)=0, i=0,\dots,N,\\ J_{h,\xi}(1,\eta_j,t)=A_c\ell_1(t)(c_{w,h}(1,\eta_j,t)-c_{wout}), j=0,\dots,N,\\ J_{h,\eta}(\xi_i,1,t)=A_c\ell_2(t)(c_{w,h}(\xi_i,1,t)-c_{wout}), i=0,\dots,N,\\ \\ c_{d,h}(\xi_i,\eta_j,t)=0, i=N, j=0,\dots,N, i=0,\dots,N-1, j=N,\\ \dfrac{d\ell_1}{dt}=\dfrac{1}{\ell_1(t)}A_c\Big(h\big(\dfrac{1}{2}c_{w,h}(1,0,t)+\displaystyle\sum_{j=1}^{N-1}c_{w,h}(1,\eta_j,t)+\dfrac{1}{2}c_{w,h}(1,1,t)\big)-c_{wout}\Big),\\ \dfrac{d\ell_2}{dt}=\dfrac{1}{\ell_2(t)}A_c\Big(h\big(\dfrac{1}{2}c_{w,h}(0,1,t)+\displaystyle\sum_{i=1}^{N-1}c_{w,h}(\xi_i,1,t)+\dfrac{1}{2}c_{w,h}(1,1,t)\big)-c_{wout}\Big), \end{cases} \tag{76}$$

for $t \in (0,T]$, and the following initial conditions

$$c_{w,h}(0)=0, \sigma_h(0)=\sigma_{0,h}, M_h(0)=M_{0,h}, c_{s,h}(0)=c_{0,s,h}, c_{d,h}(0)=0 \text{ in } \overline{\Omega}_h. \tag{77}$$

In (76) the following notation was used

$$J_{h,\xi}(1,\eta_j,t) = -D_w D_{c,\xi}c_{w,h}(1,\eta_j,t) - D_v D_{c,\xi}\sigma_h(1,\eta_j,t),$$

and

$$J_{h,\eta}(\xi_i,1,t) = -D_w D_{c,\eta}c_{w,h}(\xi_i,1,t) - D_v D_{c,\eta}\sigma_h(\xi_i,1,t).$$

The IMEX method is now obtained integrating the last semi-discrete problem using the implicit-explicit Euler's method that leads to

$$\begin{aligned}\frac{c_{w,h}^{n+1}-c_{w,h}^n}{\Delta t} &= D_w L_1(t_n)\Delta_h c_{w,h}^{n+1} + D_v L_1(t_n)\Delta_h\sigma_h^n\\ &+ L_{2,h}^{n+1,n}\nabla_{c,h}c_{w,h}^{n+1} - kc_{w,h}^n M_h^n,\end{aligned} \tag{78}$$

where $L_{2,h}^{n+1,n}$ is the diagonal matrix with entries $\frac{\ell_1^{n+1}-\ell_1^n}{\Delta t \ell_1^n} a_h$ and $\frac{\ell_2^{n+1}-\ell_2^n}{\Delta t \ell_2^n} b_h$,

$$\frac{M_h^{n+1}-M_h^n}{\Delta t} = L_{2,h}^{n+1,n} \nabla_{c,h} M_h^n - k c_{w,h}^{n+1} M_h^n, \tag{79}$$

$$\begin{aligned} \frac{\sigma_h^{n+1}-\sigma_h^n}{\Delta t} + \frac{E(M_h^{n+1})}{\mu(M_h^{n+1})}\sigma_h^n &= E(M_h^{n+1}) L_{2,h}^{n+1,n} \nabla_{c,h} c_{w,h}^{n+1} + L_{2,h}^{n+1,n} \nabla_{c,h} \sigma_h^n \\ &- E(M_h^{n+1}) \frac{c_{w,h}^{n+1}-c_{w,h}^n}{\Delta t}, \end{aligned} \tag{80}$$

$$\frac{c_{s,h}^{n+1}-c_{s,h}^n}{\Delta t} = L_{2,h}^{n+1,n} \nabla_{c,h} c_{s,h}^n - \frac{k_{dis}}{c_{s0} c_{amx} c_{wout}} c_{s,h}^n (c_{amx} - c_{d,h}^n) c_{w,h}^{n+1}, \tag{81}$$

$$\begin{aligned} \frac{c_{d,h}^{n+1}-c_{d,h}^n}{\Delta t} &= \nabla_{-h}.\Big(L_1(t_n) \hat{D}(M_h^{n+1}) \nabla_h c_{d,h}^{n+1}\Big) + L_{2,h}^{n+1,n} \nabla_{c,h} c_{d,h}^{n+1} \\ &+ \frac{k_{dis}}{c_{s0} c_{amx} c_{wout}} c_{s,h}^{n+1} (c_{amx} - c_{d,h}^n) c_{w,h}^{n+1}, \end{aligned} \tag{82}$$

for $n = 0, \ldots, M-1$, complemented with the boundary conditions, for $p = 0, \ldots, M-1$,

$$\begin{cases} D_{c,\xi} \sigma_h^p(0,\eta_j) = 0, D_{c,\xi} c_{w,h}^p(0,\eta_j) = 0, D_{c,\xi} c_{d,h}^p(0,\eta_j) = 0, j = 0, \ldots, N, \\ D_{c,\eta} \sigma_h^p(\xi_i,0) = 0, D_{c,\eta} c_{w,h}^p(\xi_i,0) = 0, D_{c,\eta} c_{d,h}^p(\xi_i,0) = 0, i = 0, \ldots, N, \\ J_{h,\xi}^p(1,\eta_j) = A_c \ell_1^p (c_{w,h}^p(1,\eta_j) - c_{wout}), j = 0, \ldots, N, \\ J_{h,\eta}^p(\xi_i,1) = A_c \ell_2^p (c_{w,h}^p(\xi_i,1) - c_{wout}), i = 0, \ldots, N, \\ \\ c_{d,h}^p(\xi_i,\eta_j) = 0, i = N, j = 0, \ldots, N, i = 0, \ldots, N-1, j = N, \\ \frac{\ell_1^{p+1}-\ell_1^p}{\Delta t} = \frac{1}{\ell_1^p} A_c \Big(h\big(\frac{1}{2} c_{w,h}^p(1,0) + \sum_{j=1}^{N-1} c_{w,h}^p(1,\eta_j) + \frac{1}{2} c_{w,h}^p(1,1)\big) - c_{wout}\Big), \\ \frac{\ell_2^{p+1}-\ell_2^p}{\Delta t} = \frac{1}{\ell_2^p} A_c \Big(h\big(\frac{1}{2} c_{w,h}^p(0,1) + \sum_{i=1}^{N-1} c_{w,h}^p(\xi_i,1) + \frac{1}{2} c_{w,h}^p(1,1)\big) - c_{wout}\Big), \end{cases} \tag{83}$$

and with initial conditions

$$c_{w,h}^0 = 0, \sigma_h^0 = \sigma_{0,h}, M_h^0 = M_{0,h}, c_{s,h}^0 = c_{0,s,h}, c_{d,h}^0 = 0 \text{ in } \overline{\Omega}_h. \tag{84}$$

In (83)

$$J^p_{h,\xi}(1,\eta_j) = -D_w D_{c,\xi} c^p_{w,h}(1,\eta_j) - D_v D_{c,\xi} \sigma^p_h(1,\eta_j),$$

and

$$J^p_{h,\eta}(\xi_i,1) = -D_w D_{c,\eta} c^p_{w,h}(\xi_i,1) - D_v D_{c,\eta} \sigma^p_h(\xi_i,1).$$

6. Numerical Results

In what follows we exhibit some numerical results for the initial-boundary value problem (62)-(68) using the method (78)-(84). The following values for the parameters have been considered:

D_w	$= 4.61 \times 10^{-2} mm^2/s,$	D_v	$= 10^{-4} mol/(mm.s.Pa)$	c_{wout}	$= 5.55 \times 10^{-1} mol/mm^3$
σ_0	$= 5 \times 10^{-2} Pa$	A_c	$= 10^{-2} mm/s$	M_0	$= 8.3 \times 10^{-2} Da$
k	$= 1 \times 10^{-2} 1/s$	c_{s_0}	$= 288.42 \times 10^{-2} mol/mm^3$	k_{dis}	$= 4.6 \times 10^{-2} mol/(mm^3.s)$
c_{amx}	$= 2.184 \times 10^{-2} mol/mm^3$	D_A	$= 5.94 \times 10^{-2} mm^2/s$	E_0	$= 10^{-4} Pa$
μ_0	$= 1 \times 10^{-1} Pa.s$	α	$= 2 \times 10^{-1}$	β	$= 7 \times 10^{-1}$

In Figure 3 we plot the concentration of the water as it diffuses into the polymeric matrix at $T = 0.5$, $T = 4$, $T = 30$ and $T = 65$. As expected, we observe a solution that presents high values in the outermost regions and low values at the center of the polymer. The shrinking of the polymer is clearly observed from the last figure.

The behaviour of the dissolved drug is illustrated in Figure 4 where we include the plots of the c_d at $T = 0.5$, $T = 4$, $T = 30$ and $T = 65$. We observe that regions where the concentration of the water is high correspond to regions where the concentration of dissolved drug is also high. The concentration of dissolved drug increases at initial times and then decreases due to the effect of the boundary condition $c_d = 0$ at the external boundary.

In Figure 5 we include plots of the concentration of solid drug c_s at $T = 0.5$, $T = 4$, $T = 30$ and $T = 65$. From these plots we conclude that the solid drug concentration decreases as time increases.

Figure 6 intents to illustrate the behaviour of the erosion front in time. We observe an initial rapid decreasing of the degradation front position. This fact can be justified by the rapid initial fluid uptake that induces a rapid decreasing of the polymeric molecular weight and consequently a rapid decreasing of the domain.

The behaviour of the front position as function of D_v is illustrated in Figure 7. As D_v increases, increases the position of the degradation front. This behaviour is physically sound, since an increase in D_v corresponds to an

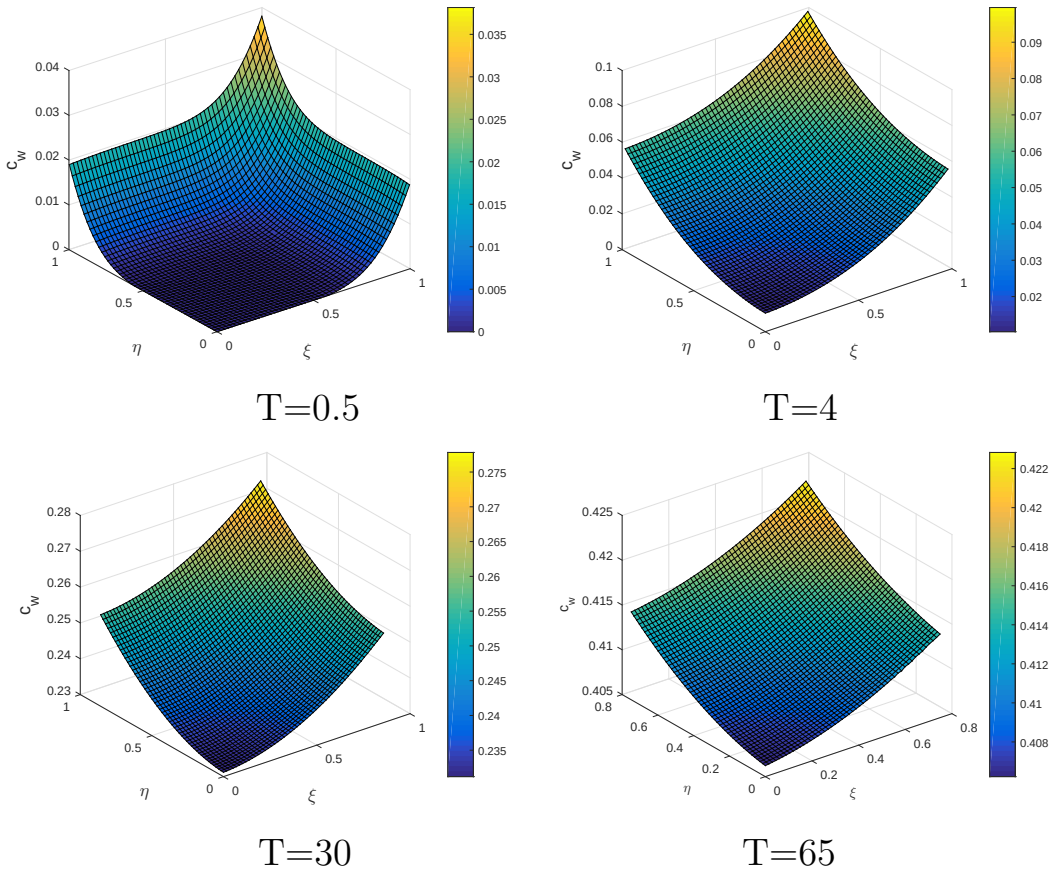

FIGURE 3. Concentration of water, c_w, at different times.

increase in the resistance of the polymeric chains to the fluid entrance. Consequently lower decrease in the molecular weight is observed that leads to a lower decrease in the degradation front position.

By $M_w(t)$, $M_s(t)$ and $M_d(t)$ we represent the masses of water, solid drug and dissolved drug, respectively, inside the polymeric matrix at time t, and which is given by

$$M_i(t) = \int_0^{\ell_2(t)} \int_0^{\ell_1(t)} c_i(t) dx dy,$$

where $i = w, s, d$. Let $M_T(t)$ represents the dimensionless total mass of drug released at time t that is defined by

$$M_T(t) = 1 - \frac{1}{c_{s0}}(M_s(t) + M_d(t)).$$

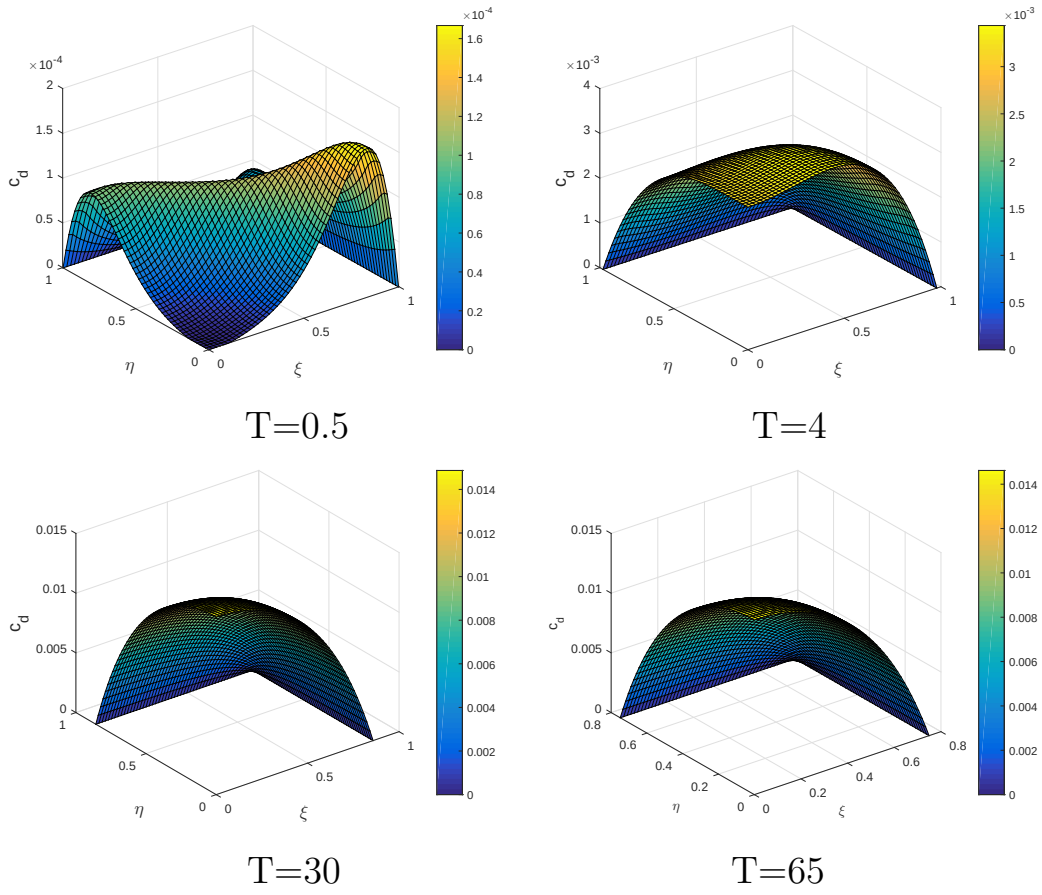

FIGURE 4. Concentration of dissolved drug, c_d, for different times.

In Figures 8 and 9 we include the plots of M_w and c_w, respectively, for different values of D_v. Figure 8 illustrates the behaviour M_w when D_v increases. As D_v increases, increases the polymeric resistance to the fluid uptake, and consequently a decreasing in total mass of fluid is absorbed. This behaviour is highlighted in Figure 9 where we plot the fluid concentration c_w at $T = 300$ for two different values of D_v. An increasing of D_v leads to a decreasing in the fluid concentration inside the polymeric platform.

To conclude the numerical study of the qualitative behaviour of the IBVP (1)-(5), (6) and (11), we would like to compare surface erosion with bulk erosion. To simulate this last situation we consider that $\ell_i(t)$, $i = 1, 2$, are fixed.

In Figures 10 and 11 we include the plots of M_w and M_d, respectively, to compare the fluid uptake by the polymeric platform and the dissolved drug in the polymer for both situations: surface and bulk erosions. The amount of fluid absorbed by the polymer decreases for surface degradation. This fact

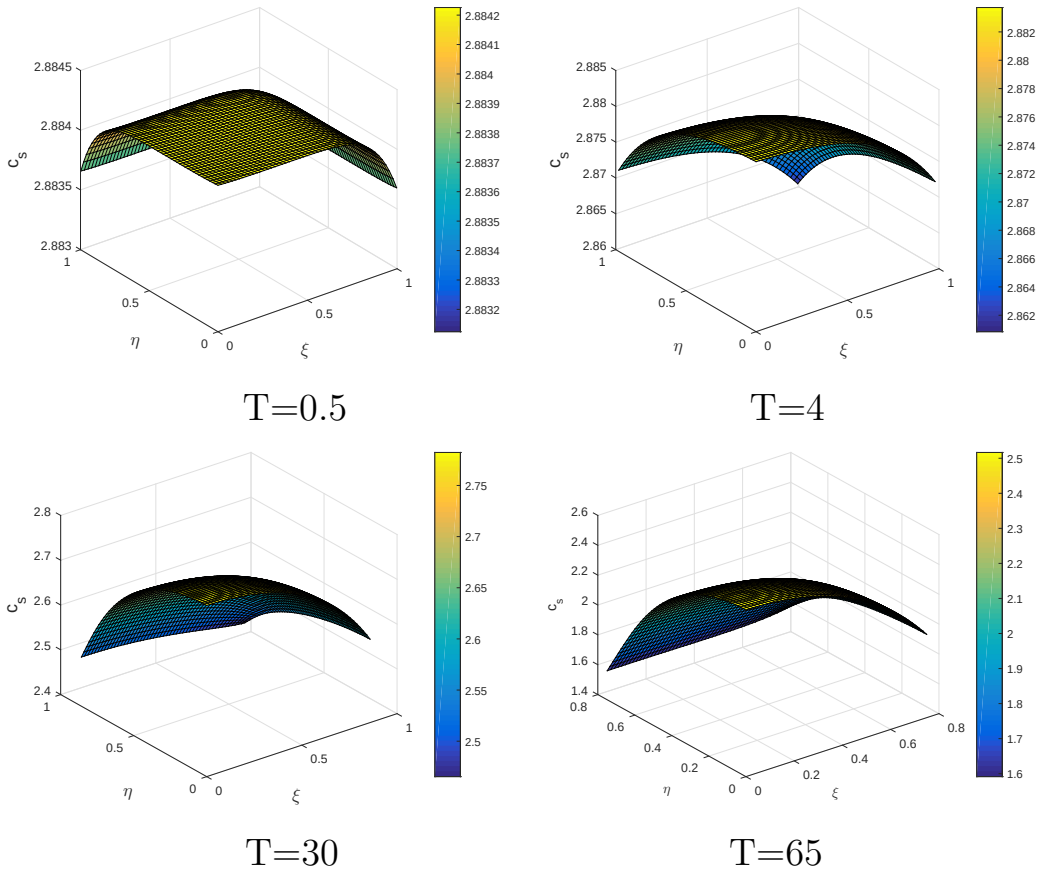

FIGURE 5. Concentration of solid drug, c_s, for different times.

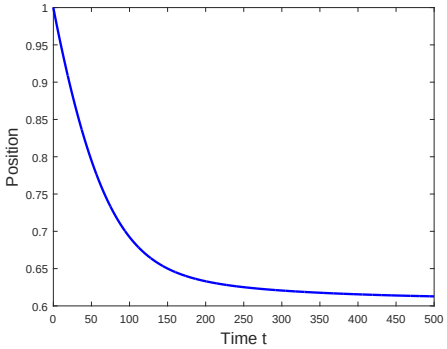

FIGURE 6. Shrinking in the axials ξ and η direction.

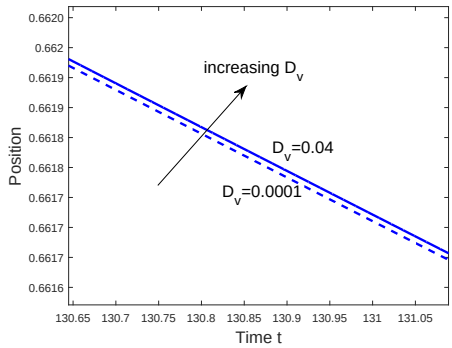

FIGURE 7. Axial shrinking, as a function of D_v.

is consequence of the reduction of the polymeric domain. The dissolved drug

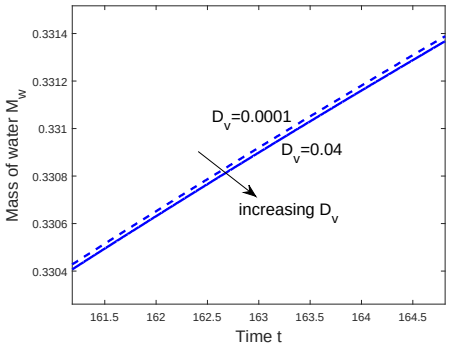

FIGURE 8. Fluid mass for different values of D_v.

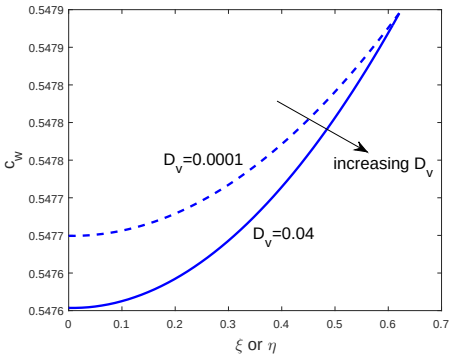

FIGURE 9. Fluid concentration c_w for different values of D_v at time $T = 300$.

mass inside of the polymer increases for bulk erosion because increases the time needed to the dissolved drug to leave the platform.

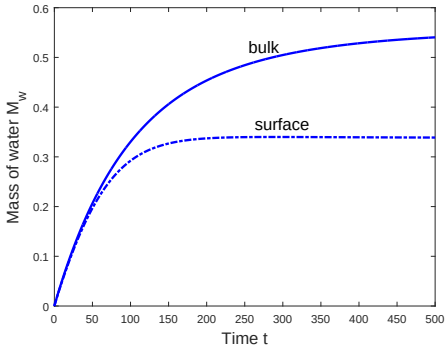

FIGURE 10. Mass of water absorbed by the polymeric platform for surface and bulk erosion.

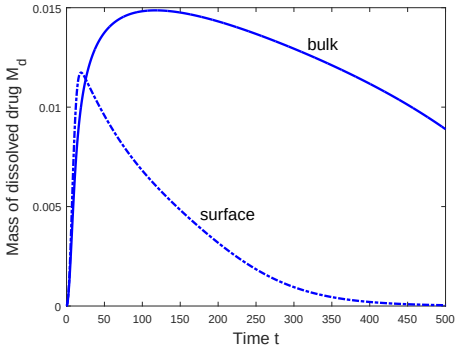

FIGURE 11. Mass of dissolved drug in the polymeric platform for surface and bulk erosion.

7. Error analysis

To justify the behaviour of the numerical method (78)-(84), in what follows we study the spatial discretization considering only the fluid concentration c_w without the polymeric reaction for the fluid entrance and the dissolved drug concentration c_d. In this scenario, we analyze the convergence behaviour of

the solution of the differential problem

$$\begin{cases} \dfrac{dc_{w,h}}{dt}(\xi_i,t) = D_w D_{2,\xi} c_{w,h}(t) + a_h(\xi_i,t) D_{c,\xi} c_{w,h}(\xi_i,t), i = 0,\dots,N, \\ D_{c,\xi} c_{w,h}(\xi_0,t) = 0,\ -D_w D_{c,\xi} c_{w,h}(\xi_N,t) = \alpha(t)\big(c_{w,h}(\xi_N,t) - c_{wout}\big)\ ,\ t \in (0,T], \\ c_{w,h}(0) = 0, \end{cases} \tag{85}$$

coupled with the following differential system

$$\begin{cases} \dfrac{dc_{d,h}}{dt}(\xi_i,t) = D_d D_{2,\xi} c_{d,h}(\xi_i,t) + b_h(\xi_i,t) D_{c,\xi} c_{d,h}(\xi_i,t) \\ +(\gamma_1 - \gamma_2 c_{d,h}(\xi_i,t)) c_{w,h}(\xi_i,t), i = 0,\dots,N-1, \\ D_{c,\xi} c_{d,h}(\xi_0,t) = 0,\ c_{d,h}(\xi_N,t) = 0\ ,\ t \in (0,T], \\ c_{d,h}(0) = 0, \end{cases} \tag{86}$$

where $a_h(t), b_h(t) : \overline{\Omega}_h \to \mathbb{R}$ are bounded and $\gamma_i, i = 1,2$, are positive constants.

For $h \le h_0$, let $R_h : C([-h_0, 1+h_0]) \to W_h^*$ and $\hat{R}_h : C([-h_0,1]) \to W_{h,0}^*$ be the restriction operators, where $W_{h,0}^*$ denotes the space of grid functions u_h defined in $\{\xi_i, i = -1,\dots,N\}$ and $u_h(x_N) = 0$. Let $E_{w,h}(t) = R_h c_w(t) - c_{w,h}(t)$ and $E_{d,h}(t) = \hat{R}_h c_d(t) - c_{d,h}(t)$ be the semi-discretization errors induced by the spatial discretizations (85) and (86), respectively, and let $T_{w,h}(t)$ and $T_{d,h}(t)$ be the corresponding truncation errors. We have

$$\begin{cases} \dfrac{dE_{w,h}}{dt}(\xi_i,t) = D_w D_{2,\xi} E_{w,h}(t) + a_h(\xi_i,t) D_{c,\xi} E_{w,h}(\xi_i,t) + T_{w,h}(\xi_i,t), i = 0,\dots,N, \\ D_{c,\xi} E_{w,h}(\xi_0,t) = T_{w,lef}(t),\ -D_w D_{c,\xi} E_{w,h}(\xi_N,t) = \alpha(t) E_{w,h}(\xi_N,t) + T_{w,rig}(t), \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad t \in (0,T], \\ E_{w,h}(0) = 0, \end{cases} \tag{87}$$

and

$$\begin{cases} \dfrac{dE_{d,h}}{dt}(\xi_i,t) = D_d D_{2,\xi} E_{d,h}(\xi_i,t) + b_h(\xi_i,t) D_{c,\xi} E_{d,h}(\xi_i,t) \\ \qquad +\gamma_1 E_{w,h}(\xi_i,t) - \gamma_2\big(c_d(\xi_i,t) c_w(\xi_i,t) - c_{d,h}(\xi_i,t) c_{w,h}(\xi_i,t)\big) \\ \qquad +T_{d,h}(\xi_i,t), i = 0,\dots,N-1, \\ D_{c,\xi} E_{d,h}(\xi_0,t) = T_{d,lef}(t),\ E_{d,h}(\xi_N,t) = 0,\ t \in (0,T], \\ E_{d,h}(0) = 0. \end{cases} \tag{88}$$

If we assume that $c_w(t) \in C^4([-h_0, 1+h_0])$ and $c_d(t) \in C^4([-h_0,1])$, then

$$\|T_{\ell,h}(t)\|_\infty \le Ch^2, |T_{\ell,k}(t)| \le Ch^2,\ \ell = w, k = lef, rig, \ell = d, k = lef. \tag{89}$$

In W_h we introduce the inner product

$$(u_h, v_h)_h = \frac{1}{2}h \sum_{i=0,N} u_h(\xi_i)v_h(\xi_i) + h\sum_{i=1}^{N-1} u_h(\xi_i)v_h(\xi_i),$$

and the corresponding norm is denoted by $\|.\|_h$. We use the following notation

$$\|D_{-\xi}u_h\|_+ = \Big(\sum_{i=1}^{N} h(D_{-\xi}u_h(\xi_i))^2\Big)^{1/2}.$$

We establish now a result which is an important tool to prove the main convergence results.

Theorem 3. *If $u_h \in W_h^*$ then*

$$(D_{2,\xi}u_h, u_h)_h = -hD_{c,\xi}u_h(x_0)u_h(x_0) - \|D_{-\xi}u_h\|_+^2 + hD_{c,\xi}u_h(x_N)u_h(x_N). \quad (90)$$

In the next result we obtain an estimate for the error $E_{w,h}(t)$ that will be used to get an estimate for $E_{d,h}(t)$.

Theorem 4. *If $c_w(t) \in C^4([-h_0, 1+h_0])$, then the error $E_{w,h}(t)$ satisfies the following*

$$\begin{aligned} &\|E_{w,h}(t)\|_h^2 + 2(D_w - \epsilon^2)\int_0^t e^{\int_s^t (3+\frac{1}{2\epsilon^2}\|a_h(\mu)\|_\infty^2)d\mu}\|D_{-\xi}E_{w,h}(s)\|_+^2 ds \\ &\qquad \le \int_0^t e^{\int_s^t (3+\frac{1}{2\epsilon^2}\|a_h(\mu)\|_\infty^2)d\mu} g_h(s)ds,\ t \in [0,T], \end{aligned} \quad (91)$$

for $h \le h_0$, where $\epsilon \neq 0$, and

$$g_h(s) = h(T_{w,lef}(s)^2 + T_{w,rig}(s)^2) + \|T_{w,h}(s)\|_h^2.$$

Proof: From the differential equation of (87) we get

$$\begin{aligned} \tfrac{1}{2}\tfrac{d}{dt}\|E_{w,h}(t)\|_h^2 &= (D_w D_{2,\xi}E_{w,h}(t), E_{w,h}(t))_h + (a_h(t)D_{c,\xi}E_{w,h}(t), E_{w,h}(t))_h \\ &\quad +(T_{w,h}(t), E_{w,h}(t))_h. \end{aligned} \quad (92)$$

From (90) and (87) we get

$$\begin{aligned} (D_w D_{2,\xi}E_{w,h}(t), E_{w,h}(t))_h &= -hD_w D_{c,\xi}E_{w,h}(\xi_0,t)E_{w,h}(\xi_0,t) \\ &\quad -D_w\|D_{-\xi}E_{w,h}(t)\|_+^2 + hD_w D_{c,\xi}E_{w,h}(\xi_N,t)E_{w,h}(\xi_N,t) \\ &= -hT_{w,lef}(t)E_{w,h}(\xi_0,t) - D_w\|D_{-\xi}E_{w,h}(t)\|_+^2 \\ &\quad -h\alpha(t)E_{w,h}(\xi_N,t)^2 - hT_{w,rig}(t)E_{w,h}(\xi_N,t) \end{aligned}$$

that leads to

$$\begin{aligned}(D_w D_{2,\xi} E_{w,h}(t), E_{w,h}(t))_h &\leq -D_w \|D_{-\xi} E_{w,h}(t)\|_+^2 \\ &\quad + \frac{1}{2} h (T_{w,lef}(t)^2 + T_{w,rig}(t)^2) + \|E_{w,h}(t)\|_h^2. \end{aligned} \tag{93}$$

For $(a_h(t) D_{c,\xi} E_{w,h}(t), E_{w,h}(t))_h$, it can be shown the following estimate

$$|(a_h(t) D_{c,\xi} E_{w,h}(t), E_{w,h}(t))_h| \leq \frac{1}{4\epsilon^2} \|a_h(t)\|_\infty^2 \|E_{w,h}(t)\|_h^2 + \epsilon^2 \|D_{-\xi} E_{w,h}(t)\|_+^2, \tag{94}$$

for $\epsilon \neq 0$.

As for $(T_{w,h}(t), E_{w,h}(t))_h$ we have

$$|(T_{w,h}(t), E_{w,h}(t))_h| \leq \frac{1}{2} \|T_{w,h}(t)\|_h^2 + \frac{1}{2} \|E_{w,h}(t)\|_h^2,$$

taking in (92) the estimates (93) and (94) we obtain

$$\begin{aligned}\tfrac{d}{dt}\|E_{w,h}(t)\|_h^2 \; &+2(D_w - \epsilon^2)\|D_{-\xi} E_{w,h}(t)\|_+^2 \leq \|T_{w,h}(t)\|_h^2 \\ &+(3 + \frac{1}{2\epsilon^2}\|a_h(t)\|_\infty^2)\|E_{w,h}(t)\|_h^2 \\ &+h(T_{w,lef}(t)^2 + T_{w,rig}(t)^2),\end{aligned}$$

that can be rewritten in the following equivalent form

$$\begin{aligned}&\tfrac{d}{dt}\Big(e^{-\int_0^t (3+\frac{1}{2\epsilon^2}\|a_h(\mu)\|_\infty^2) d\mu} \|E_{w,h}(t)\|_h^2 \\ &\quad +2(D_w - \epsilon^2) \int_0^t e^{-\int_0^s (3+\frac{1}{2\epsilon^2}\|a_h(\mu)\|_\infty^2) d\mu} \|D_{-\xi} E_{w,h}(s)\|_+^2 ds \\ &\quad - \int_0^t e^{-\int_0^s (3+\frac{1}{2\epsilon^2}\|a_h(\mu)\|_\infty^2) d\mu} g_h(s) ds \Big) \leq 0,\end{aligned} \tag{95}$$

for $t \in (0, T]$. Finally, from (95) we conclude (91).

■

Corollary 1. *Under the assumptions of Theorem 4, there exists a positive constant C, h and t-independent, such that*

$$\|E_{w,h}(t)\|_h^2 + \int_0^t \|D_{-\xi} E_{w,h}(s)\|_+^2 ds \leq C h^4, \; t \in [0, T], \tag{96}$$

for $h \leq h_0$.

We remark that the next result leads to the uniform boundness of $c_{w,h}(t)$ with respect to $t \in [0, T]$ and $h \leq h_0$. This result has an important role in the convergence analysis of $c_{d,h}(t)$.

Corollary 2. *Under the assumptions of Theorem 4, there exists a positive constant C, h and t-independent, such that*

$$\|c_{w,h}(t)\|_\infty \leq C, t \in [0,T], h \leq h_0. \tag{97}$$

Proof: As we have successively

$$\begin{aligned}\|c_{w,h}(t)\|_\infty &\leq \|E_{w,h}(t)\|_\infty + \|R_h c_w(t)\|_\infty \\ &\leq \frac{1}{h}\|E_{w,h}(t)\|_h + \|R_h c_w(t)\|_\infty,\end{aligned}$$

from (96) we conclude

$$\|c_{w,h}(t)\|_\infty \leq Ch + \|R_h c_w(t)\|_\infty,$$

that leads to (97).

■

Theorem 5. *If $c_d(t) \in C^4([-h_0,1])$, then the error $E_{d,h}(t)$ satisfies the following*

$$\begin{aligned}&\|E_{d,h}(t)\|_h^2 + 2(D_d - \epsilon^2)\int_0^t e^{\int_s^t (3+\gamma_1+\frac{1}{2\epsilon^2}\|b_h(\mu)\|_\infty^2 + 2\gamma_2\|c_{w,h}(\mu)\|_\infty)d\mu}\|D_{-\xi}E_{d,h}(s)\|_+^2 ds \\ &\quad\leq \int_0^t e^{\int_s^t (3+\gamma_1+\frac{1}{2\epsilon^2}\|b_h(\mu)\|_\infty^2 + 2\gamma_2\|c_{w,h}(\mu)\|_\infty)d\mu} \\ &\quad\quad\Big(g_h(s) + \big(\gamma_1 + \gamma_2^2\|c_d(s)\|_\infty^2\big)\|E_{w,h}(s)\|_h^2\Big)ds,\ t \in [0,T],\end{aligned} \tag{98}$$

for $h \leq h_0$, where $\epsilon \neq 0$, and

$$g_h(s) = hT_{d,lef}(s)^2 + \|T_{d,h}(s)\|_h^2.$$

Proof: From the differential equation of (88) we get

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|E_{d,h}(t)\|_h^2 &= (D_d D_{2,\xi}E_{d,h}(t), E_{d,h}(t))_h + (b_h(t)D_{c,\xi}E_{d,h}(t), E_{d,h}(t))_h \\ &\quad + (T_{d,h}(t), E_{d,h}(t))_h + \gamma_1(E_{w,h}(t), E_{d,h}(t))_h \\ &\quad - \gamma_2(c_d(t)c_w(t) - c_{d,h}(t)c_{w,h}(t), E_{d,h}(t))_h.\end{aligned} \tag{99}$$

As it can be shown that

$$\begin{aligned}(D_d D_{2,\xi}E_{d,h}(t), E_{d,h}(t))_h &= -hT_{d,lef}(t)E_{d,h}(\xi_0,t) - D_d\|D_{-\xi}E_{d,h}(t)\|_+^2 \\ &\leq \tfrac{1}{2}hT_{d,lef}(t)^2 + \tfrac{1}{2}\|E_{d,h}(t)\|_h^2 - D_d\|D_{-\xi}E_{d,h}(t)\|_+^2,\end{aligned}$$

$$|(b_h(t)D_{c,\xi}E_{d,h}(t), E_{d,h}(t))_h| \leq \frac{1}{4\epsilon^2}\|b_h(t)\|_\infty^2\|E_{d,h}(t)\|_h^2 + \epsilon^2\|D_{-\xi}E_{d,h}(t)\|_+^2,$$

where $\epsilon \neq 0$,

$$|(T_{d,h}(t), E_{d,h}(t))_h| \leq \frac{1}{2}\|T_{d,h}(t)\|_h^2 + \frac{1}{2}\|E_{d,h}(t)\|_h^2,$$

$$\gamma_1|(E_{w,h}(t), E_{d,h}(t))_h| \leq \frac{\gamma_1}{2}\|E_{w,h}(t)\|_h^2 + \frac{\gamma_1}{2}\|E_{d,h}(t)\|_h^2,$$

and

$$\begin{aligned}
&-\gamma_2(c_d(t)c_w(t) - c_{d,h}(t)c_{w,h}(t), E_{d,h}(t))_h \\
&\quad = -\gamma_2(R_h c_d(t)E_{w,h}(t) + c_{w,h}(t)E_{d,h}(t), E_{d,h}(t))_h \\
&\quad \leq \gamma_2\big(\|c_d(t)\|_\infty\|E_{w,h}(t)\|_h + \|c_{w,h}(t)\|_\infty\|E_{d,h}(t)\|_h\big)\|E_{d,h}(t)\|_h \\
&\quad \leq \frac{1}{2}\gamma_2^2\|c_d(t)\|_\infty^2\|E_{w,h}(t)\|_h^2 \\
&\quad + \big(\frac{1}{2} + \gamma_2\|c_{w,h}(t)\|_\infty\big)\|E_{d,h}(t)\|_h^2,
\end{aligned}$$

from (99) we obtain

$$\begin{aligned}
&\frac{d}{dt}\|E_{d,h}(t)\|_h^2 + 2(D_d - \epsilon^2)\|D_{-\xi}E_{d,h}(t)\|_+^2 \\
&\quad \leq \|T_{d,h}(t)\|_h^2 + \big(\gamma_1 + \gamma_2^2\|c_d(t)\|_\infty^2\big)\|E_{w,h}(t)\|_h^2 \\
&\quad + \big(3 + \gamma_1 + \frac{1}{2\epsilon^2}\|b_h(t)\|_\infty^2 + 2\gamma_2\|c_{w,h}(t)\|_\infty\big)\|E_{d,h}(t)\|_h^2 + hT_{d,lef}(t)^2,
\end{aligned}$$

for $t \in (0, T]$, that leads to (98).

■

Corollary 2 guarantees that under the assumptions of Theorem 4, we have the uniform boundness of $\|c_{w,h}(t)\|_\infty$, with respect to $t \in [0, T]$ and $h \leq h_0$. Then we conclude the following convergence result:

Corollary 3. *Under the assumptions of Theorems 4 and 5, there exists a positive constant C, h and t independent, such that*

$$\begin{aligned}
\|E_{w,h}(t)\|_h^2 + \int_0^t \|D_{-\xi}E_{w,h}(s)\|_+^2 ds &\leq Ch^4, \\
\|E_{d,h}(t)\|_h^2 + \int_0^t \|D_{-\xi}E_{d,h}(s)\|_+^2 ds &\leq Ch^4,
\end{aligned}$$

for $t \in [0, T]$ and $h \leq h_0$.

In what follows we illustrate the last result - Corollary 3. Table 1 presents the convergence rates

$$p(c_w) = \frac{\ln\left(\frac{E_{h_1}(c_w)}{E_{h_2}(c_w)}\right)}{\ln\left(\frac{h_1}{h_2}\right)}$$

where $E_h(c_w)$ is defined by

$$E_h(c_w) = \max_{n=1,\ldots,M} \left(\|E^n_{w,h}\|^2_h + \Delta t \sum_{j=1}^{n} \|D_{-\xi} E^j_{w,h}\|^2_+ \right),$$

being $E_h(c_d)$ defined analogously. These convergence rates were obtained for the numerical approximations computed with the one-dimensional version of the method (78)-(84) and the reference solution defined by $h = \Delta\xi = 0.001$ and $\Delta t = 2 \times 10^{-7}$. These results illustrate the second convergence order stated in Corollary 3.

TABLE 1. Convergence rates $p(c_w)$ and $p(c_d)$.

$\Delta\xi$	$E_h(c_w)$	$p(c_w)$	$E_h(c_d)$	$p(c_d)$
0.01	4.9679×10^{-9}	2.98	4.4411×10^{-17}	3.75
0.005	6.2942×10^{-10}	3.16	3.2799×10^{-18}	4.09
0.004	3.1072×10^{-10}	3.99	1.3160×10^{-18}	4.14
0.002	1.9554×10^{-11}	——	7.4576×10^{-20}	——

8. Conclusion

A system of partial nonlinear differential equations complemented with boundary and initial conditions defined in a moving boundary domain (1)-(5) and (6)-(9) is analysed from analytical and numerical point of view. We point out that the boundary moving law (10) used here is analogous to the one proposed by Patel in [6]. This system can be used to describe the drug release from a biodegradable viscoelastic polymeric platform that presents surface erosion and where a drug is initially dispersed in the solid state([11], [18]). To solve numerically the last moving boundary problem, an equivalent IBVP (62)-(68) defined in a fixed domain is established.

The stability of the moving boundary domain (1)-(5) and (6)-(9) is studied for large and short times in Theorems 1 and 2, respectively. The properties of the spatial discretization of the problem (62)-(68) that leads to the

one-dimensional version of the numerical scheme (78)-(84) is established in Theorems 4, 5 and Corollaries 2 and 3 considering only the main phenomena: fluid uptake and dissolved drug transport. In the convergence analysis, the uniform boundness of the sequence of approximations for the fluid concentration is a main tool.

Finally, the numerical simulation presented illustrates the qualitative behaviour of the solution of differential problem (1)-(5) and (6)-(9) as well as the influence of the main parameters in such behaviour.

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