# DRUG RELEASE FROM VISCOELASTIC SWELLING POLYMERIC PLATFORMS*

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**Abstract.** We consider a polymeric spherical platform containing a solid dispersed drug that is in contact with a solvent fluid. While swelling, a non-Fickian sorption of the solvent molecules occurs induced by the effect of the viscoelastic properties of the polymer. The solid drug in contact with the solvent fluid dissolves and a Fickian release of dissolved drug takes place. The fluid entrance, the drug dissolution, and the drug release to an external environment are described by a system of PDEs complemented with an equation for the swelling front, initial, and boundary conditions. The model includes the two major factors that govern a swelling process of a polymeric platform within a release medium: the cross-link density and the concentration of the external medium. Energy estimates for the mass of solvent fluid and of undissolved and dissolved drug in the polymeric platform are established. Numerical simulations that illustrate the theoretical results are also included.

**Key words.** drug release, viscoelastic platform, swelling, mathematical modeling, qualitative behavior, numerical simulation

**AMS subject classifications.** 35Q70, 35R09

## 1. Introduction.

Polymeric drug delivery platforms are nowadays of common use, because they can be designed with prescribed properties that lead to an optimized drug release. When a homogeneous and isotropic polymeric platform containing a homogeneously distributed drug is inside a reservoir with a solvent fluid, a set of complex phenomena occur:

(i) the solvent molecules are absorbed due to a concentration gradient;
(ii) the polymer swells and a pressure gradient arises;
(iii) the solvent molecules induce a dissolution process;
(iv) the dissolved drug molecules diffuse through the platform and leave it to the reservoir, where they continue to diffuse.

During the absorption of the fluid, the liquid strains the polymeric matrix, which, while swelling, exerts a stress that acts as a barrier to the incoming fluid. The swelling of the platform depends on the cross-link density of the polymer, which is the density of bonds between different polymeric chains per unit volume, and on the hydrophilic content of the system [19]. We assume that the molecules in the system are not charged. This means that swelling depends mainly on the Young modulus $E$ of the polymer—which is proportional to the cross-link density—and on the available amount of solvent.

* Accepted for publication (in revised form) March 14, 2018

**Funding:** This work was partially supported by the Centre for Mathematics of the University of Coimbra through grant UID/MAT/00324/2013, funded by the Portuguese Government through FCT/MEC, and cofunded by the European Regional Development Fund through the Partnership Agreement PT2020.

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As the fluid permeates the polymeric structure, the polymeric chains deform, and so stress builds up in the polymer. This stress generates an anticonvective flux on the fluid, pushing it from regions of high stress to regions of low stress. Consequently the fluid transport is driven by a concentration gradient and a stress gradient.

There is a well-established theory for diffusion in solids when the diffusion is stress-assisted. This theory extends the classical theory of diffusion by considering non-Fickian diffusion processes through deforming elastic and inelastic solids. The first unifying approach was presented in [2] and in [23]. As a departing point, the authors considered the mass and momentum conservation equations, involving the stress tensor $T_s$—of the diffusive substance in itself—and a diffusive force that measures the force exerted on the fluid by the solid platform. Considering specific forms for $T_s$ and for the diffusive force, different models have been established in the literature. In particular they obtained

$$J_\ell = -D(S, c_\ell)\nabla c_\ell + D_v(c_\ell)\nabla\sigma, \tag{1}$$

$\sigma = \text{trace}(S)$, $S = -\phi(T_s, c_\ell)$, where $\phi$ is a linear function of $T_s$ and $c_\ell$ represents the fluid concentration. We note that it was not a priori assumed by Aifantis that stress affects diffusion only through its hydrostatic component. The dependence of the flux on the stress tensor trace was obtained a posteriori in a rigorous way as a consequence of the stress-assisted diffusion theory developed in [2].

A different approach is followed by Cox and Cohen in [7]. These authors assume that the flux of the permeant fluid can be defined by

$$J_\ell = -D(c_\ell)\nabla\psi, \tag{2}$$

where $\psi$ represents the chemical potential. Then using the form of the chemical potential established experimentally by Thomas and Windle in [24], they derive an expression analogous to (1).

A large number of authors, while studying diffusion in polymeric matrices, have followed one of the two preceding approaches, using expressions of the form (1) for the flux. We mention, without being exhaustive, [4], [5], [6], [8], [9], [10], [11], [12], [13], [14], [17], and [22]. All these approaches have in common the idea that the total solvent mass flux $J_\ell$ has two main contributions: a Fickian one, depending on the concentration gradient, and a non-Fickian one proportional to the stress gradient. Accordingly the total flux is described as in (1). In [7] the authors refer to $\sigma$ as the stress, whereas in fact it represents the trace of the stress. The designation has been generally adopted by the authors working in diffusion in viscoelastic polymers. In the present manuscript when we refer to stress as a scalar; in fact, we mean the trace of the stress, which is $\sigma = \text{trace}(S)$.

Following the previous approaches, we consider that the total solvent mass flux $J_\ell$ has two main contributions: a Fickian one, depending on the concentration gradient, and a non-Fickian one proportional to the stress trace gradient defined as

$$J_\ell(x,t) = J_{\ell,F}(x,t) + J_{\ell,nF}(x,t), \quad x \in \Omega(t), t > 0, \tag{3}$$

where $\Omega(t) = B_{r(t)}(0)$ denotes a 3D polymeric sphere with radius $r(t)$ and centered at the origin, and

$$J_{\ell,F}(x,t) = -D_\ell\nabla c_\ell(x,t) \tag{4}$$

and

$$J_{\ell,nF}(x,t) = -D_v\nabla\sigma(x,t) \tag{5}$$

denote the Fickian and non-Fickian parts of the solvent mass flux, respectively. In the previous definitions $D_\ell = D_\ell(c_\ell), D_v = D_v(c_\ell)$ denote the diffusion and the viscoelastic diffusion coefficients, respectively [13], $c_\ell$ represents the solvent concentration, and $\sigma$ stands for the trace of the stress tensor.

In [12] a 3D mathematical model that describes the drug release from a swelling polymeric cylinder was presented. The proposed mathematical model, defined by a system of PDEs coupled with a mathematical law for the moving domain, was numerically validated, but no mathematical analysis was included there. In the present paper we consider a closed system: a spherical polymeric matrix inside a spherical reservoir filled with a solvent fluid, suitable for simulating in vivo drug release. The physical problem is described by a set of PDEs for the drug and the solvent in the polymeric structure and for the dissolved drug in the reservoir. This system is coupled with convenient interface and boundary conditions and complemented by a moving domain condition. A theoretical analysis and a computational study are carried on. The fact that the system is closed has two main implications:

(i) the solvent content of the external medium can be viewed as a parameter and its influence on drug release can be studied;

(ii) the conservation of the total mass leads to a simple relation between the swelling rate and the permeability.

The aim of this paper is to study the drug release from a spherical viscoelastic polymeric platform $\Omega(t)$, isotropic, homogeneous with an iffnitial radius $R_0$, where a drug is initially uniformly dispersed. The device is inside another sphere, $\Omega_e = B_{\bar{R}}(0)$—which defines the closed system—of constant radius $\bar{R}$ containing a resident fluid uniformly distributed in the external medium (Figure 1).

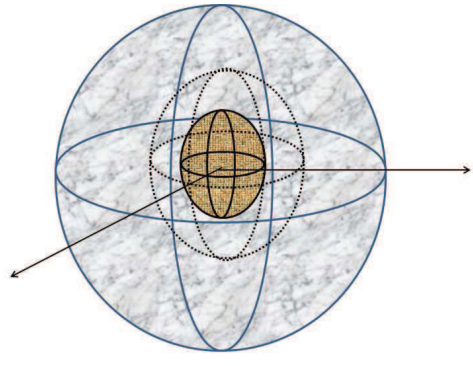

FIG. 1. *A closed system: a polymeric sphere with initial radius $R_0$ (brown color), containing dispersed drug, that swells inside a sphere with fixed radius $\bar{R}$ containing a solvent. (Color available online.)*

We assume that the polymeric platform swells upon contact with the resident solvent with radius $r(t)$. We also consider the following assumptions:

(i) the viscoelastic behavior can be described by a generalized Maxwell–Wiechert model;

(ii) the viscoelasticity induces a resistance to the solvent uptake;

(iii) the permeation of solvent in the sphere is governed by a non-Fickian diffusion;

(iv) the platform erosion is considered negligible;

(v) drug dissolution and Fickian drug diffusion take place in the swollen polymer;

(vi) drug diffusion occurs in the spherical surrounding environment.

The previous assumptions can be used to describe release from a polymeric drug delivery device that is inside an organ, as, for example, the stomach, containing a significant amount of solvent. Such a device can also be seen as an implant inside of a tissue where the solvent is the interstitial fluid that occupies the extracellular space.

Let $\Omega(t)$ be the swollen polymeric domain at time $t$. The evolution of the solvent concentration $c_\ell$, undissolved drug $c_{ud}$, and dissolved drug $c_d$ concentrations in $\Omega(t)$, for $t \in (0, T]$, $T > 0$, are described by the following system of PDEs:

$$\begin{cases} \dfrac{\partial c_\ell}{\partial t} = \nabla.(D_\ell \nabla c_\ell) + \nabla.(D_v \nabla \sigma), \\ \dfrac{\partial c_d}{\partial t} = \nabla.(D_d \nabla c_d) + f(c_{ud}, c_d, c_\ell), \\ \dfrac{\partial c_{ud}}{\partial t} = -f(c_{ud}, c_d, c_\ell). \end{cases} \tag{6}$$

In (6) the reaction term $f$ describes the kinetics of the undissolved and dissolved drugs. Assuming that the time variation of undissolved drug $c_{ud}$ is proportional to the difference between $c_{ud}$ and $c_d$, then $f$ is given by

$$f(c_{ud}, c_d, c_\ell) = H(c_{ud}) k_d \frac{c_{ud} - c_d}{c_{ud}} c_\ell, \tag{7}$$

where $H(c_{ud})$ denotes the Heaviside function, and $k_d$ denotes the dissolution constant rate of the drug [12], [18]. Otherwise, if we consider that the time variation of the undissolved drug is proportional to the difference between drug solubility $c_{sol}$ and $c_d$, then $f$ is given by a Noyes–Whitney-type relation,

$$f(c_{ud}, c_d, c_\ell) = k_d H(c_{ud}) \frac{c_{sol} - c_d}{c_{sol}} c_\ell, \tag{8}$$

where we assume that $c_{sol}$ is constant in time [6], [17], [20], [21]. Moreover, as the dissolved drug diffuses only when the solvent has permeated the matrix, we assume that its time-space evolution is described by the classical diffusion equation.

The evolution of the dissolved drug $c_{de}$ in the external medium outside the swelling platform, that is, in $\Omega_{c,e} = \Omega_e - \overline{\Omega}(t)$ for $t \in (0, T]$, is described by

$$\frac{\partial c_{de}}{\partial t} = \nabla.(D_{de} \nabla c_{de}). \tag{9}$$

The diffusion coefficients $D_\ell$, $D_d$ in (6) are given by the Fujita equation $D_\ell = D_{eq\ell} \exp\big(-\beta_\ell\big(1 - \frac{c_\ell}{c_{\ell e}}\big)\big)$, $D_d = D_{de} \exp\big(-\beta_d\big(1 - \frac{c_\ell}{c_{\ell e}}\big)\big)$, where $D_{eq\ell}$ and $D_{de}$ denote the diffusion coefficients of the liquid solvent and of the dissolved drug in the fully swollen sample, respectively; $c_{\ell e}$ denotes the solvent concentration in the exterior of $\Omega(t)$ that is assumed constant; and $\beta_\ell$, $\beta_d$ denote dimensionless positive constants [16]. We remark that when the solvent concentration is in equilibrium in the closed system, then $c_\ell = c_{\ell e}$.

As in [12], we assume that the stress $\sigma$ in (5) is defined by the Boltzmann integral

$$\sigma(t) = -\int_0^t E(t - s) \frac{\partial \epsilon}{\partial s}(s) ds, \tag{10}$$

and the viscoelastic behavior of the polymer is described by a generalized Maxwell–Wiechert model; that is, the modulus $E(s)$ in (10) is given by

$$E(s) = E_0 + \sum_{j=1}^{m} E_j e^{-\frac{s}{\tau_j}}, \tag{11}$$

where $E_j$'s, $j = 1, \ldots, m$, are the Young modulus of the Maxwell fluid arms, the relaxation times $\tau_j$ are given by $\tau_j = \frac{\mu_j}{E_j}$, where $\mu_j$ represents the viscosity, and $E_0$ stands for the Young modulus of the free spring. For $t = 0$ the Young modulus of the polymer is $\hat{E} = \sum_{j=0}^{m} E_j$, and upon swelling it decreases steadily to $E_0$ over time.

Functional relations between the viscoelastic diffusion coefficient $D_v$ and the solvent concentration $c_\ell$ were constructed in [13], assuming that the viscoelastic effect induces a convective flux pointing outwards fromF $\Omega(t)$. In what follows we consider

$$D_v = \frac{R^2}{8\hat{\mu}} c_\ell, \tag{12}$$

where $R$ stands for the radius of a virtual cross-section of the polymeric sample available for the convective flux, and $\hat{\mu}$ represents the viscosity of a polymer-solvent solution characterized by a solvent concentration $c_\ell$.

The main idea underlying expression (12) is the following: the polymer opposes the fluid permeation through the existence of an "anticonvective" field. The non-Fickian flux $J_{NF}$ can be interpreted as being generated by this anticonvective field and is represented by

$$J_{NF} = v c_\ell,$$

where $v$ stands for the velocity. As $J_{NF}$ is induced by the scalar stress $\sigma$, we have

$$-D_v(c_\ell)\nabla\sigma = v c_\ell.$$

Then, using Darcy's law, we conclude that $D_v(c_\ell) = K c_\ell$, where $K$ represents the hydraulic conductivity (see, for instance, [3], [4], [5], [15]). Other approaches can be used to explain the non-Fickian flux, such as those presented in, for instance, [17], [18], and [19].

Let us assume that $c_\ell(0) = 0$ in $\Omega(0)$. Then from the first equation of (6), the definition of the stress $\sigma$ (10), and considering that the strain $\epsilon$ depends on the solvent concentration $c_\ell$, that is, $\epsilon = g(c_\ell)$, we deduce for the solvent concentration $c_\ell$ the following integro-differential equation:

$$\frac{\partial c_\ell}{\partial t} = \nabla.\Big(\big(D_\ell - D_v\hat{E}g'(c_\ell)\big)\nabla c_\ell + \nabla.\Big(D_v \int_0^t k_{er}(t-s)g'(c_\ell(s))\nabla c_\ell(s)\,ds\Big)\Big), \tag{13}$$

where $\hat{E} = \sum_{j=0}^{m} E_j$, $k_{er}(s) = \sum_{j=1}^{m} \frac{E_j}{\tau_j} e^{-\frac{s}{\tau_j}}$. At the moving boundary $\partial\Omega(t)$ we assume the following boundary conditions:

$$\begin{aligned} &J_\ell(c_\ell(t)).\eta = \alpha(c_\ell(t) - c_{\ell e}),\\ &J_d.\eta(c_d(t)) = J_{de}(c_{de}(t)).\eta,\\ &c_d(t) = c_{de}(t),\\ &c_{ud}(t) = 0, \end{aligned} \tag{14}$$

where $\eta$ denotes the exterior unitary normal to $\Omega(t)$, $\alpha$ represents a permeability constant, and

$$\begin{aligned} &J_\ell(c_\ell) = -\Big(D_\ell - D_v\hat{E}g'(c_\ell)\Big)\nabla c_\ell - D_v\int_0^t k_{er}(t-s)g'(c_\ell(s))\nabla c_\ell(s)\,ds,\\ &J_d(c_d) = -D_d\nabla c_d,\\ &J_{de}(c_{de}) = -D_{de}\nabla c_{de}. \end{aligned}$$

We consider that $\Omega_e$ is isolated; that is, we assume that no drug flux passes through $\partial\Omega_{c,e} - \partial\Omega(t)$,

$$J_{de}(c_{de}(t)).\eta = 0 \text{ on } \partial\Omega_{c,e} - \partial\Omega(t), \tag{15}$$

where $\eta$ denotes the exterior unitary normal to $\Omega_e$.

Summarizing, we describe the drug release by a system of PDEs defined in a time-dependent domain: the integro-differential equation (13) for the absorbed solvent concentration $c_\ell$, the second equation of (6) for the drug concentration $c_d$, and the third equation in (6) for the undissolved drug concentration $c_{ud}$. This system is coupled with the diffusion equation (9) in $\Omega_{c,e}$. The two problems are complemented by the interface conditions (14) at the interface $\partial\Omega(t)$ and the boundary condition (15) at $\partial\Omega_{c,e} - \partial\Omega(t)$. Concerning initial conditions, we assume that

$$\begin{array}{l} c_\ell(x,0) = 0,\ c_{ud}(x,0) = c_0,\ c_d(r,0) = 0,\ x \in \Omega(0), \\ c_{de}(x,0) = 0,\ c_\ell(x,0) = c_{\ell e},\ x \in \Omega_e - \overline{\Omega(0)}. \end{array} \tag{16}$$

To complete the initial boundary value problem, a moving front condition should be imposed. To define the moving front $\partial\Omega(t)$, a consequence of the swelling, we observe that the volume of the sphere $\Omega(t)$ at each time $t$ is the sum of the absorbed solvent fluid volume with the dissolved and undissolved volume of drug and the initial dry polymeric volume. Then

$$|\Omega(t)| = \int_{\Omega(t)} \Big( \frac{c_\ell(x,t)}{\rho_\ell} + \frac{c_{ud}(x,t) + c_d(x,t)}{\rho_d} \Big) dx + \frac{m_p}{\rho_p}, \tag{17}$$

where $|\Omega(t)|$ denotes the volume of the sphere $\Omega(t)$; $\rho_\ell, \rho_d, \rho_p$ represent the solvent, drug, and polymer densities; and $m_p$ represents the initial mass of dry polymeric matrix.

An Eulerian description of the balance laws in the two-phase domains has been used: the fluid problem is given in its natural Eulerian framework, and the solid problem is also written in Eulerian coordinates, such that both subproblems are formulated in a swelling current configuration $\Omega(t)$. Following this approach no solid velocity of the bulk polymer is included in the equations: the concentrations $c_i$, for $i = \ell, d, ud, de$, are functions of $x$ and $t$ for $x \in \Omega(t)$. With this modeling option the system is closed in the sense that we have 4 equations and 4 variables in the swollen sphere. This approach was introduced by the authors in [12] and [13].

An alternative modeling option is based on defining a velocity $v_S = \frac{\partial u}{\partial t}$, where $u$ denotes the displacement of the polymer. In this case a relation between the $u$ and $\epsilon$, such as, for example,

$$\epsilon = \frac{1}{2}(\nabla u + \nabla u^T),$$

should be used, and to close the system a relation between stress and strain should be adopted. In problems of solid mechanics, the displacements are usually represented in Lagrangian coordinates, such that the computational domain is always fixed. In this case a convective term would appear in the concentration equations. Another aspect concerning this approach is that a new unknown ($u$) is added and another equation—conservation of momentum—should be considered to close the system.

Our main goal is to study the behavior of the previous initial boundary value problem. We start our analysis by establishing in section 2 the type of dependence of the strain on the solvent concentration. A condition that relates the front velocity with

the permeability coefficient in (14) is deduced in section 3 from the mass conservation of the closed system $\overline{\Omega}_e$. In section 4 an $L^2$ energy estimate is deduced neglecting the swelling. In section 5 numerical experiments illustrating the qualitative behavior of the mathematical model, when $f$ is defined by the Noyes–Whitney expression (8), are included. Finally, in section 6 we present some conclusions, and in section 7 the proof of the $L^2$ energy estimates stated in section 4 is presented.

**2. Strain versus solvent concentration.** In this section we establish a functional relation between the strain and the solvent concentration for spherical domains $\Omega(t)$ that is different from the one introduced in [13], where $\epsilon = \frac{c_\ell}{\rho_\ell - c_\ell}$ was established for an open system composed by a swelling cylinder.

Let $V_0$ represent the volume of a local sphere with radius $r_0$ that, after swelling, due to solvent absorption, has volume $V_n$ and radius $r$. Let $V_\ell$ be the volume of the absorbed solvent. Assuming that the mixture of the polymer and the solvent occur in an ideal manner, the final volume of the swollen sphere is represented by $V_n = V_0 + V_\ell$. We observe that the correct equation is

$$V_n = V_0 + V_\ell - V_d,$$

where $V_d$ stands for the volume of the drug that has been released in the exterior medium. Due to the very small dimension of drug molecules, $V_d \ll V_0 + V_\ell$, and consequently the approximation for $V_n$ used is acceptable. As $\epsilon$ is defined by $\epsilon = \frac{r - r_0}{r_0}$ with $r_0 = \left(\frac{3}{4\pi} V_0\right)^{1/3}$ and $r = \left(\frac{3}{4\pi} V_n\right)^{1/3} = \left(\frac{3}{4\pi}(V_0 + V_\ell)\right)^{1/3}$, we obtain

$$\epsilon = \left(1 + \tilde{e}\right)^{1/3} - 1, \tag{18}$$

where $\tilde{e} = \frac{V_\ell}{V_0}$ is an approximation for the volumetric strain $e = \frac{V_n - V_0}{V_0}$.

If $m_\ell$ denotes the mass of the absorbed solvent, then $m_\ell = V_\ell \rho_\ell$, where $\rho_\ell$ represents the density of the swelling fluid. As $c_\ell = \frac{m_\ell}{V_0 + V_\ell}$, where $c_\ell$ represents the mean solvent concentration, then $m_\ell = (V_0 + V_\ell) c_\ell$. Combining the two expressions for $m_\ell$, we deduce $\tilde{e} = \frac{c_\ell}{\rho_\ell - c_\ell}$. Finally from (18) we obtain

$$\epsilon = g(c_\ell) = \left(\frac{\rho_\ell}{\rho_\ell - c_\ell}\right)^{1/3} - 1. \tag{19}$$

In what follows we assume that $g$ is defined by (19).

**3. Mass conservation and the swelling front.** To obtain an explicit expression for the moving front $\partial\Omega(t)$, it is convenient to write the differential problem in spherical coordinates. Let $r(t)$ be the radius of $\Omega(t)$ at time $t$. Then (6) and (9) admit the equivalent representation

(20)
$$\begin{cases} \dfrac{\partial c_\ell}{\partial t} = \dfrac{1}{r^2}\dfrac{\partial}{\partial r}\Big(r^2\Big(\big(D_\ell - \hat{E} D_v g'(c_\ell)\big)\dfrac{\partial c_\ell}{\partial r} + D_v \displaystyle\int_0^t k_{er}(t-s) g'(c_\ell) \frac{\partial c_\ell}{\partial r}(s)\, ds\Big)\Big), \\ \dfrac{\partial c_d}{\partial t} = \dfrac{1}{r^2}\dfrac{\partial}{\partial r}\big(r^2 D_d \dfrac{\partial c_d}{\partial r}\big) + f(c_{ud}, c_d, c_\ell), \\ \dfrac{\partial c_{ud}}{\partial t} = -f(c_{ud}, c_d, c_\ell) \end{cases}$$

for $r \in (0, r(t)), t \in (0, T]$,

$$\frac{\partial c_{de}}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\big(r^2 D_{de} \frac{\partial c_{de}}{\partial r}\big),\ r \in (r(t), \bar{R}), t \in (0, T]. \tag{21}$$

From (14), at the moving interface $r = r(t)$ we have

$$
\begin{aligned}
&J_\ell(r(t),t) = \alpha(c_\ell(r(t),t) - c_{\ell e}),\\
&J_d(r(t),t) = J_{de}(r(t),t),\\
&c_d(r(t),t) = c_{de}(r(t),t),\\
&c_{ud}(r(t),t) = 0,\ t>0,
\end{aligned}
\tag{22}
$$

with

$$
\begin{aligned}
J_\ell(r(t),t) = &-\big(D_\ell - \hat{E}D_v g'(c_\ell(r(t),t))\big)\frac{\partial c_\ell}{\partial r}(r(t),t)\\
&-D_v\int_0^t k_{er}(t-s)g'(c_\ell(r(s),s))\frac{\partial c_\ell}{\partial r}(r(s),s)\,ds,\\
J_d(r(t),t) = &-D_d\frac{\partial c_d}{\partial r}(r(t),t),\\
J_{de}(r(t),t) = &-D_{de}\frac{\partial c_{de}}{\partial r}(r(t),t).
\end{aligned}
$$

At $r = 0$, we consider the following symmetry conditions:

$$
\frac{\partial c_\ell}{\partial r}(0,t) = \frac{\partial c_d}{\partial r}(0,t) = 0, \quad t>0. \tag{23}
$$

The boundary condition (15) is equivalent to the following condition at $r = \overline{R}$:

$$
J_{de}(\overline{R},t) = 0, \quad t>0. \tag{24}
$$

The initial conditions (16) can be written in the following form:

$$
\begin{aligned}
&c_\ell(r,0) = 0,\ c_{ud}(r,0) = c_0,\ c_d(r,0) = 0, \quad r\in(0,R_0),\\
&c_{de}(r,0) = 0,\ c_\ell(r,0) = c_{\ell e}, \quad r\in(R_0,\overline{R}).
\end{aligned}
\tag{25}
$$

To define the moving front $r(t)$, a consequence of the swelling, we observe that condition (17) is equivalent to

$$
\frac{4}{3}\pi r^3(t) = 4\pi\int_0^{r(t)} r^2\Big(\frac{c_\ell(r,t)}{\rho_\ell} + \frac{c_{ud}(r,t)+c_d(r,t)}{\rho_d}\Big)dr + \frac{m_p}{\rho_p}. \tag{26}
$$

In spherical coordinates, the evolution of $c_\ell, c_{ud}, c_d$, and $c_{de}$ is defined by the integro-differential system (20) in $(0,r(t))$, the diffusion equation (21) in $(r(t),\overline{R})$, the interface condition (22) at $r = r(t)$, the boundary condition (23) at $r = 0$, the condition (24) at $r = \overline{R}$, and the initial conditions (25).

It should be remarked that $\sigma$ is in equilibrium with a certain function $F$ that can be seen as a force induced by the solvent permeation. In fact, we observe that the first equation of (20) can be rewritten in the following equivalent form:

$$
\frac{\partial c_\ell}{\partial t}(r,t) = \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\Big(D_\ell(c_\ell(r,t))\frac{\partial c_\ell}{\partial r}(r,t) + D_v(c_\ell(r,t))\frac{\partial \sigma}{\partial r}(r,t)\Big)\Big).
$$

Then, integrating this last equation in $[0,r]$, we obtain successively

$$
\begin{aligned}
\frac{\partial \sigma}{\partial r}(r,t) &= \frac{1}{D_v(c_\ell(r,t))}\Big(\frac{1}{r^2}\int_0^r w^2\frac{\partial c_\ell}{\partial t}(w,t)dw - D_\ell(c_\ell(r,t))\frac{\partial c_\ell}{\partial r}(r,t)\Big)\\
&= -F.
\end{aligned}
$$

The conservation of mass in the closed system $\overline{\Omega}_e = \bar{B}_{\bar{R}}(0)$ leads to a relationship between the mass transfer coefficient $\alpha$ and the front velocity $r'(t)$. This relation is established in what follows.

Let $M$ be the total mass in $\Omega_e$. Then

$$M(t) = \int_{\Omega(t)} \Big(c_\ell(x,t) + c_{ud}(x,t) + c_d(x,t)\Big)dx + \int_{\Omega_{c,e}(t)} \Big(c_{\ell e} + c_{de}\Big)dx,$$

which, in spherical coordinates, admits the representation

$$M(t) = 4\pi \int_0^{r(t)} r^2\Big(c_\ell + c_{ud} + c_d\Big)dr + 4\pi \int_{r(t)}^{\bar{R}} r^2\Big(c_{\ell e} + c_{de}\Big)dr. \tag{27}$$

From (27), as $c_{\ell e}$ is assumed constant, we obtain

$$\begin{aligned} M'(t) &= 4\pi r^2(t) r'(t)\Big(c_\ell(r(t),t) + c_{ud}(r(t),t) + c_d(r(t),t)\Big) \\ &\quad + 4\pi \int_0^{r(t)} r^2\Big(\frac{\partial c_\ell}{\partial t} + \frac{\partial c_{ud}}{\partial t} + \frac{\partial c_d}{\partial t}\Big)dr \\ &\quad - 4\pi r^2(t) r'(t)\Big(c_{\ell e} + c_{de}(r(t),t)\Big) + 4\pi \int_{r(t)}^{\bar{R}} r^2 \frac{\partial c_{de}}{\partial t} dr. \end{aligned} \tag{28}$$

Now, combining (28) with the interface conditions (14) and the differential equations (20) and (21), we establish

$$\begin{aligned} M'(t) &= 4\pi r^2(t) r'(t)\Big(c_\ell(r(t),t) - c_{\ell e}\Big) - 4\pi \int_0^{r(t)} \frac{\partial}{\partial r}\Big(r^2(J_\ell + J_d)\Big)dr \\ &\quad - 4\pi \int_{r(t)}^{\bar{R}} \frac{\partial}{\partial r}\Big(r^2 J_{de}\Big)dr, \end{aligned}$$

that is,

$$\begin{aligned} M'(t) &= 4\pi r^2(t) r'(t)\Big(c_\ell(r(t),t) - c_{\ell e}\Big) - 4\pi\Big(r^2(t)(J_\ell(r(t),t) + J_d(r(t),t))\Big) \\ &\quad - 4\pi\Big(\bar{R}^2 J_{de}(\bar{R},t) - r^2(t) J_{de}(r(t),t)\Big). \end{aligned} \tag{29}$$

Taking into account again the interface conditions (14) and the boundary condition (24), we finally deduce

$$M'(t) = 4\pi r^2(t)\Big(r'(t) - \alpha\Big)\Big(c_\ell(r(t),t) - c_{\ell e}\Big). \tag{30}$$

From (30) we conclude the following result.

PROPOSITION 1. *The total mass $M$ is constant in the isolated system $\overline{\Omega}_e$ if and only if $r'(t) = \alpha$, and in this case*

$$M = \frac{4}{3}\pi\Big(R_0^3 c_{ud}(0) + (\bar{R}^3 - R_0^3)c_{\ell e}\Big), \quad t \geq 0. \tag{31}$$

If we consider the open system $\Omega(t)$, then the second and third conditions in (22) are replaced by $J_d = \beta c_d$, where $\beta$ denotes a permeability constant. If $M_s(t)$ denotes

the total mass in this system, then, proceeding as before to establish the expression of $M'(t)$, we easily obtain

$$M_s'(t) = 4\pi r^2(t) r'(t)\Big(c_\ell(r(t),t) + c_d(r(t),t)\Big) - 4\pi r^2(t)\Big(J_\ell(r(t),t) + J_d(r(t),t)\Big),$$

which leads to

$$\begin{aligned} M_s'(t) = 4\pi r(t)^2 r'(t)\Big(c_\ell(r(t),t) + c_d(r(t),t)\Big) - 4\pi r(t)^2\Big(\alpha\big(c_\ell(r(t),t) \\ -c_{\ell e}(r(t),t)\big) + \beta c_d(r(t),t)\Big). \end{aligned} \tag{32}$$

From (26) it can be shown that the front speed is given by

$$r'(t) = -\frac{\frac{\alpha}{\rho_\ell}\big(c_\ell(r(t),t) - c_{\ell e}\big) + \beta\frac{c_d(r(t),t)}{\rho_d}}{1 - \big(\frac{c_\ell(r(t),t)}{\rho_\ell} + \frac{c_d(r(t),t)}{\rho_d}\big)}. \tag{33}$$

Inserting (33) into (32), we get

$$M_s'(t) = v_1(t) + v_2(t) - v_3(t) - v_4(t), \tag{34}$$

where

$$\begin{aligned} v_1(t) &= 4\pi r(t)^2\alpha\big(c_{\ell e} - c_\ell(r(t),t)\big), \\ v_2(t) &= 4\pi r(t)^2\frac{\alpha}{\rho_\ell}\big(c_{\ell e} - c_\ell(r(t),t)\big)\frac{c_\ell(r(t),t) + c_d(r(t),t)}{1 - \big(\frac{c_\ell(r(t),t)}{\rho_\ell} + \frac{c_d(r(t),t)}{\rho_d}\big)}, \\ v_3(t) &= 4\pi r(t)^2\beta c_d(r(t),t), \\ v_4(t) &= \beta\frac{c_d(r(t),t)}{\rho_d}\frac{c_\ell(r(t),t) + c_d(r(t),t)}{1 - \big(\frac{c_\ell(r(t),t)}{\rho_\ell} + \frac{c_d(r(t),t)}{\rho_d}\big)}. \end{aligned}$$

From (34) we can interpret the time variation of the mass in the sphere $\Omega(t)$ as the result of four components: the solvent fluid entrance ($v_1(t)$) and its correction due to the increasing volume ($v_2(t)$), the drug amount that crosses the boundary $\Omega(t)$ ($v_3(t)$), and the corresponding correction due to the swelling ($v_4(t)$).

**4. Energy estimates.** This section aims to provide a stability analysis when the swelling is instantaneous. The study of stability for a moving boundary problem remains an open question that we intend to study in the near future. Let $\Omega(t)$ be time independent, that is, $\Omega(t) = \Omega$. The evolution of the complete system is defined in $\Omega$ by the integro-differential equation (13) for the absorbed solvent concentration $c_\ell$, the second and the third equations of (6) for $c_d$ and $c_{ud}$, respectively; in $\Omega_{c,e} = \Omega_e - \overline{\Omega}$ the drug evolution is defined by the diffusion equation (9). We remark that in our analysis we take $m = 1$, and the sets $\Omega$ and $\Omega_e$, not necessarily open spheres, can be open domains with $\Omega \subset \Omega_e$. The two problems are complemented by the interface conditions (14) at the interface $\partial\Omega$, the boundary conditions (15), and the initial conditions (16). To simplify the presentation, constant diffusion coefficients are considered. The generalization for non–constant diffusion coefficients is straightforward.

We begin by introducing some notation. By $(.,.)_{L^2(B}$, $\|.\|_{L^2(B)}$, $(.,.)_{L^2(B)\times L^2(B)}$, and $\|.\|_{L^2(B)\times L^2(B)}$ we denote the usual inner products and corresponding norms. We recall that the so-called trace inequality holds: there exists a positive constant $C_{tr}$ such that for all $v \in H^1(\Omega)$, $\|v\|_{L^2(\partial\Omega)} \leq C_{tr}\|v\|_1$, where $\|.\|_1$ represents the usual norm in the Sobolev space $H^1(\Omega)$. Let $L^\infty(0,T,L^2(\Omega))$ be the space of functions $v$ defined

from $[0,T]$ into $L^2(\Omega)$ such that $\operatorname{ess\,sup}_{[0,T]} \|v(t)\|_{L^2(\Omega)} < \infty$, and $\|v\|_{L^\infty(0,T,L^2(\Omega))} = \operatorname{ess\,sup}_{[0,T]} \|v(t)\|_{L^2(\Omega)}$. The previous norm is denoted by $\|.\|_{L^\infty(L^2)}$.

Let $E_n(t)$ be the functional energy defined by

$$E_n(t) = \sum_{i=\ell,d,ud} \|c_i(t)\|^2_{L^2(\Omega)} + \|c_{de}(t)\|^2_{L^2(\Omega_{c,e})}. \tag{35}$$

The energy $E_n(t)$ is defined for weak solutions of the problem:

find $(c_\ell(t), c_d(t), c_{ud}(t), c_{de}(t)) \in (H^1(\Omega))^2 \times L^2(\Omega) \times H^1(\Omega_{c,e})$ such that

(36)

$$\sum_{j\in\{\ell,ud,d\}} \Big(\frac{\partial c_j}{\partial t}(t), v_j\Big)_{L^2(\Omega)} + \Big(\frac{\partial c_{de}}{\partial t}(t), v_{d,e}\Big)_{L^2(\Omega_{c,e})} = -(\alpha(c_\ell(t) - c_{\ell e}), v_\ell)_{L^2(\partial\Omega)}$$

$$+ (J_\ell(c_\ell(t)), \nabla v_\ell)_{L^2(\Omega)\times L^2(\Omega)} + (J_d(c_d(t)), \nabla v_d)_{L^2(\Omega)\times L^2(\Omega)}$$

$$+ (J_{d,e}(c_{de}(t)), \nabla v_{d,e})_{L^2(\Omega_{c,e})\times L^2(\Omega_{c,e})} + (f(c_{ud}(t), c_d(t), c_\ell(t)), v_d - v_{ud})_{L^2(\Omega)}$$

for all $v_\ell, v_d \in H^1(\Omega), v_{ud} \in L^2(\Omega), v_{d,e} \in H^1(\Omega_{c,e})$.

The energy estimates are established assuming that to have an effective solvent uptake, the Fickian diffusion should dominate the non-Fickian diffusion and the transference through the boundary $\partial\Omega$, that is,

$$D_{f,nf} = D_d - \hat{E} D_v \|g'(c_\ell)\|_{L^\infty(L^2)} - \alpha C_{tr}^2 > 0. \tag{37}$$

Let $\epsilon_i, i = 1, 2$, be such that

$$\gamma_1(c_\ell) = D_{f,nf} - \epsilon_1^2 C_{tr}^2 - \epsilon_2^2 > 0. \tag{38}$$

In the next result we establish upper bounds for the energy $E_n(t)$ depending on the dissolution reaction. The proof is given in the appendix.

PROPOSITION 2. *For $t \in (0,T]$, let $(c_\ell(t), c_d(t), c_{ud}(t), c_{de}(t))$ in $(H^1(\Omega))^2 \times L^2(\Omega) \times H^1(\Omega_{c,e})$ be such that the boundary conditions* (14) *and* (15) *hold on $\partial\Omega$ and $\partial\Omega_{c,e} - \partial\Omega$, respectively, and* (16) *and* (36) *are satisfied. If $g'(c_\ell) \in L^\infty(0,T,L^2(\Omega))$ and conditions* (37), (38) *hold, then there exist positive constants $C_i, i = 1, 2$, such that for $E_n(t)$ defined by* (35) *we have*

$$\begin{aligned} &\frac{1}{2}\frac{d}{dt}\Big(\sum_{i=d,ud} \|c_i(t)\|^2_{L^2(\Omega)} + \|c_{de}(t)\|^2_{L^2(\Omega_{c,e})}\Big) \\ &= -D_d \|\nabla c_d(t)\|^2_{L^2(\Omega)\times L^2(\Omega)} - D_{d,e} \|\nabla c_{de}(t)\|^2_{L^2(\Omega_{c,e})\times L^2(\Omega_{c,e})} \\ &+ (F(t), c_d(t) - c_{ud}(t))_{L^2(\Omega)}, \end{aligned} \tag{39}$$

*where $F(t) = f(c_{ud}(t), c_d(t), c_\ell(t))$.*

1. *If $f$ is given by* (7), *then $(F(t), c_d(t) - c_{ud}(t))_{L^2(\Omega)} \le 0$ and*

$$\begin{aligned} &E_n(t) + \int_0^t \|\nabla c_\ell(s)\|^2_{L^2(\Omega)\times L^2(\Omega)} ds + 2D_d \int_0^t \|\nabla c_d(s)\|^2_{L^2(\Omega)\times L^2(\Omega)} ds \\ &+ 2D_{d,e} \int_0^t \|\nabla c_{de}(s)\|^2_{L^2(\Omega_{c,e})\times L^2(\Omega_{c,e})} ds \\ &\le C_1 e^{C_2 t} (\alpha c_{\ell e} |\partial\Omega|)^2 t + \|c_{ud}(0)\|^2_{L^2(\Omega)},\ t \in [0,T]. \end{aligned} \tag{40}$$

2. *If $f$ is given by* (8), *then*

$$
\begin{aligned}
&E_n(t) + \int_0^t \|\nabla c_\ell(s)\|^2_{L^2(\Omega)\times L^2(\Omega)} ds + 2D_d \int_0^t \|\nabla c_d(s)\|^2_{L^2(\Omega)\times L^2(\Omega)} ds \\
&+ 2D_{d,e} \int_0^t \|\nabla c_{de}(s)\|^2_{L^2(\Omega_{c,e})\times L^2(\Omega_{c,e})} ds \\
&\leq e^{k_d\left(1+\frac{1}{c^2_{sol}}\right)\sqrt{C_1}\alpha|\partial\Omega|c_{\ell e}\int_0^t \sqrt{s}e^{\frac{C_2}{2}s}ds} \\
&\left(\|c_{ud}(0)\|^2_{L^2(\Omega)} + k_d\sqrt{C_1}\alpha|\partial\Omega|c_{\ell e}\int_0^t \sqrt{s}e^{\frac{C_2}{2}s}ds\right) \\
&+ C_1 e^{C_2 t}(\alpha c_{\ell e}|\partial\Omega|)^2 t,\ t\in[0,T].
\end{aligned}
\tag{41}
$$

Note that when the dissolution reaction is defined by (7), then $\sum_{i\in\{ud,d\}} \|c_i(t)\|^2_{L^2(\Omega)}$ is a decreasing function in $t$. However, if the dissolution reaction is given by (8), then we just prove that this term is bounded. Numerically we will illustrate that, for a large set of parameters used in the experiments, $E_n(t)$ is a decreasing function also in this last case.

Proposition 2 implies the stability with respect to the initial conditions of the initial boundary value problem (14), (15), (16), and (36). The uniqueness of the weak solution is also a consequence of this result.

## 5. Numerical simulation.

**5.1. Discrete model.** In what follows we introduce a finite difference discretization of the initial boundary value problem defined by

(i) the integro-differential system (20) for the evolution of $c_\ell, c_{ud}, c_d$;
(ii) the kinetics of the undissolved and dissolved drugs as defined by (8);
(iii) the diffusion equation (21) for $c_{de}$;
(v) the interface conditions (22) at $r = r(t)$;
(vi) the boundary conditions (23) at $r = 0$ and (24) at $r = \overline{R}$;
(vii) the initial conditions (25);
(viii) the moving front defined by (26).

We follow the approach used in [14] and [12]. We start by introducing in the spatial domain $[0, \bar{R}]$ an initial grid $\{r_i(0), i = 0, \ldots, N(0), \ldots, \bar{N}(0)\}$, $r_0(0) = 0, r_{N(0)} = R_0, r_{\bar{N}}(0) = \bar{R}$, with stepsize $h(0)$.

In $[0,T]$ we introduce a uniform grid $\{t_n, n = 0, \ldots, M\}$, with $t_0 = 0, t_M = T$ and stepsize $\Delta t$. As in each time step $t_n$ the swelling front occupies a new position $r_{N(t_n)}$, we introduce in $[0, r_{N(t_n)}]$ and $[r_{N(t_n)}, \bar{R}]$ new grids $\{r_i(t_n), i = 0, \ldots, N(t_n)\}$ and $\{r_i(t_n), i = N(t_n), \ldots, \overline{N}(t_n)\}$, respectively, that can be nonuniform, with stepsize $h_i(t_n) = r_i(t_n) - r_{i-1}(t_n)$, where $r_{-1}(t_n) = -r_1(t_n)$ and $r_{\bar{N}+1}(t_n) = \bar{R} + h_{\bar{N}}(t_n)$.

By $M_h$ we represent the average operator $M_h v_h(r_i) = \frac{1}{2}(v_h(r_{i-1}) + v_h(r_i))$. We also consider the finite difference operator

$$
D^*_h(v_h)(r_i) = \frac{v_h(r_{i+1/2}) - v_h(r_{i-1/2})}{r_{i+1/2} - r_{i-1/2}}, \qquad D_h(v_h)(r_{i-1/2}) = \frac{v_h(r_i) - v_h(r_{i-1})}{r_i - r_{i-1}},
$$

where $r_{i+1/2} = r_i + \frac{h_{i+1}}{2}$, $r_{i-1/2} = r_i - \frac{h_i}{2}$. By $D_{-t}$ we denote the time backward finite difference operator.

Let $c^n_{\ell,i}, c^n_{d,i}, c^n_{ud,i}, c^n_{de,i}$ be the numerical approximations for the correspondent variables at $(r_i(t_n), t_n)$. To introduce the discretization of the diffusion equations in

(20) we observe that the integro-differential equation in this system can be rewritten in the following equivalent form:

$$\frac{\partial c_\ell}{\partial t}(r,t) = \frac{1}{r^2}\frac{\partial}{\partial r}\Big(r^2\Big(D_\ell(c_\ell(r,t))\frac{\partial c_\ell}{\partial r}(r,t) + D_v(c_\ell(r,t))\frac{\partial \sigma}{\partial r}(r,t)\Big)\Big).$$

This equation is replaced by the following implicit-explicit finite difference equation:

$$D_{-t}c_{\ell,i}^{n+1} = \frac{1}{r_i(t_n)^2}D_h^*\Big(M_h(r_i(t_n)^2)\Big(D_{\ell,i}^n D_h c_{\ell,i}^{n+1} + D_{v,i}^n D_h \sigma_{\ell,i}^n\Big)\Big), \tag{42}$$

and $D_{\ell,i}^n = D_\ell(M_h(c_{\ell,i}^n)), D_{v,i}^n = D_v(M_h(c_{\ell,i}^n))$ for $i = 0,\dots,N(t_{n+1})-1$. In the last finite difference equation we take $c_{\ell,i}^n = 0$ for $i = N(t_n),\dots,N(t_{n+1})$ and $r_{-1}^j = -r_1^j$, $j = n, n+1$.

The diffusion equation in (20) for dissolved drug concentration $c_d$ in $\Omega(t_{n+1})$ is replaced by the finite difference equation

$$D_{-t}c_{d,i}^{n+1} = \frac{1}{r_i(t_n)^2}D_h^*\Big(M_h(r_i(t_n)^2)D_{d,i}^n D_h c_{\ell,i}^{n+1}\Big) + f(c_{ud,i}^n, c_{d,i}^n, c_{\ell,i}^{n+1}), \tag{43}$$

for $i = 0,\dots,N(t_{n+1})-1$, where $c_{d,i}^n = 0$, for $i = N(t_n),\dots,N(t_{n+1})$, and $r_{-1}^j = -r_1^j, j = n, n+1$.

Finally, to compute $c_{ud,i}^n$ we solve the finite difference equation

$$D_{-t}c_{d,i}^{n+1} = -f(c_{ud,i}^{n+1}, c_{d,i}^{n+1}, c_{\ell,i}^{n+1}) \tag{44}$$

for $i = 1,\dots,N(t_{n+1})-1$, where $c_{d,i}^n = 0$ for $i = N(t_n),\dots,N(t_{n+1})$.

The approximation for the drug concentration in the surrounding sphere is given by

$$D_{-t}c_{de,i}^{n+1} = \frac{1}{r_i(t_n)^2}D_h^*\Big(M_h(r_i(t_n)^2)D_{de}D_h c_{\ell,i}^{n+1}\Big) \tag{45}$$

for $i = N(t_{n+1})+1,\dots,\overline{N}-1$.

To compute $c_{\ell,i}^n$ in (43) we should first compute $\sigma_i^n$. We remark that from (10), (11), and (19) we have

$$\sigma(r(t),t) = -g(c_\ell(r(t),t))\hat{E} + \int_0^t E'(t-s)g(c_\ell(r(s),s))\,ds,$$

which leads to

$$\begin{aligned}\sigma(r_i(t_n),t_n) = -g(c_\ell(r_i(t_n),t_n))\hat{E} &+ \int_0^{t_{n-1}} E'(t_n-s)g(c_\ell(r_i(s),s)) \\ &+ \int_{t_{n-1}}^{t_n} E'(t_n-s)g(c_\ell(r_i(s),s))\,ds.\end{aligned}$$

So, we consider the composed trapezoidal rule

$$\sigma_i^n = -g(c_{\ell,i}^n)\hat{E} + S_i^{n-1} + \frac{\Delta t}{2}\Big(\Big(\sum_{j=1}^m \frac{E_j}{\tau_j}\Big)g(c_{\ell,i}^n) + \eta_{n-1}g(c_{\ell,i}^{n-1})\Big), \tag{46}$$

where

$$S_i^{n-1} = \Delta t\Big(\frac{1}{2}\eta_0 g(c_{\ell,i}^0) + \sum_{k=1}^{n-2}\eta_k g(c_{\ell,i}^k) + \frac{1}{2}\eta_{n-1}g(c_{\ell,i}^{n-1})\Big),$$

with

$$\eta_0 = \sum_{j=1}^{m} \frac{E_j}{\tau_j} e^{-\frac{n\Delta t}{\tau_j}},\ \eta_k = \sum_{j=1}^{m} \frac{E_j}{\tau_j} e^{-\frac{(n-k)\Delta t}{\tau_j}},\ \eta_{n-1} = \sum_{j=1}^{m} \frac{E_j}{\tau_j} e^{-\frac{\Delta t}{\tau_j}}.$$

We specify in what follows the discretization of the interface conditions (22) and boundary conditions (23) and (24).

At the interface grid boundary point $r_{N(t_{n+1})}$ we assume the following:

$$\begin{aligned}
&D^n_{\ell,i} D_{-h} c^{n+1}_{\ell,N(t_{n+1})} + D^n_{v,i} D_{-h} \sigma^{n+1}_{N(t_{n+1})} = \alpha(c^{n+1}_{\ell,N(t_{n+1})} - c_{\ell e}),\\
&D^n_{d,i} D_{-h} c^{n+1}_{d,N(t_{n+1})} = D_{de} D_{-h} c^{n+1}_{de,N(t_{n+1})+1},\\
&c^{n+1}_{d,N(t_{n+1})} = c^{n+1}_{de,N(t_{n+1})},\\
&c^{n+1}_{ud,N(t_{n+1})} = 0,
\end{aligned} \tag{47}$$

where $D_{-h}$ denotes the backward finite difference operator with respect to the variable $r$. The first finite difference equation in (47) is established assuming that $\sigma^{n+1}_{N(t_{n+1})} = 0$.

By $D_c$ we denote the usual first order centered finite difference operator. Then the boundary conditions at $r = 0$ are replaced by

$$D_c c^{n+1}_{\ell,0} = 0,\ D_c c^{n+1}_{d,0} = 0. \tag{48}$$

At $r = \bar{R}$ we consider

$$D_{-h} c^{n+1}_{de,\bar{N}} = 0. \tag{49}$$

To define the new front position we remark that from (22) and (26) we obtain

$$\begin{aligned}
r'(t) = &\frac{1}{1 - \left(\frac{c_\ell(r(t),t)}{\rho_\ell} + \frac{c_d(r(t),t)}{\rho_d}\right)}\\
&\Big(\frac{1}{\rho_\ell}\Big(D_\ell(c_\ell(r(t),t))\frac{\partial c_\ell}{\partial r}(r(t),t) + D_v(c_\ell(r(t),t))\frac{\partial \sigma_\ell}{\partial r}(r(t),t)\Big)\\
&+ \frac{1}{\rho_d} D_d(c_\ell(r(t),t))\frac{\partial c_d}{\partial r}(r(t),t)\Big).
\end{aligned}$$

Then we consider for the front position at time level $t_{n+2}$ the following finite difference equation:

$$\begin{aligned}
\frac{r_{N(t_{n+2})} - r_{N(t_{n+1})}}{\Delta t} = &\frac{1}{1 - \left(\frac{c^{n+1}_{\ell,N(t_{n+1})}}{\rho_\ell} + \frac{c^{n+1}_{d,N(t_{n+1})}}{\rho_d}\right)}\\
&\Big(\frac{1}{\rho_\ell}\big(D^{n+1}_{\ell,N(t_{n+1})} D_c c^{n+1}_{\ell,N(t_{n+1})} + D^{n+1}_{v,N(t_{n+1})} D_{-h} \sigma^{n+1}_{\ell,N(t_{n+1})}\big)\\
&+ \frac{1}{\rho_d} D^{n+1}_{d,N(t_{n+1})} D_c c^{n+1}_{d,N(t_{n+1})}\Big).
\end{aligned} \tag{50}$$

The finite difference scheme (43)–(50) is completed with the initial conditions

$$\begin{aligned}
&c^0_{\ell,i} = 0,\ c^0_{ud,i} = c_0,\ c^0_{d,i} = 0, \quad i = 0, \ldots, N(0) - 1,\\
&c^0_{de,i} = 0, \quad i = N(0) + 1, \ldots, \bar{N} - 1.
\end{aligned} \tag{51}$$

**5.2. Numerical results.** In this section we present some numerical simulations that illustrate our results. We consider a polymeric sphere with initial radius $R_0 = 10^{-3}m$, where a solid drug is dispersed with an initial concentration $c_0 = 1\text{kg/m}^3$ and solubility $c_{sol} = 1\text{kg/m}^3$. This sphere is inside a closed system represented by a second sphere with radius $\bar{R} = 3 \times 10^{-3}\text{m}$. In $\Omega_e - \overline{\Omega}(t)$ the solvent concentration $c_{\ell e}$ is constant $c_{\ell e} = 755.74\text{kg/m}^3$.

The viscoelastic behavior of the polymeric sphere is described by the Maxwell–Wiechert model (11) with one Maxwell arm ($m = 1$) with Young modulus $E_1 = 10^3 Pa$ and relaxation time $\tau_1 = 250s$. The Young modulus of the free spring is $E_0 = 10^3 Pa$. We also take $\hat{\mu} = 10^6 Pa\, s$ for the viscosity of the polymer-solvent solution.

The following parameters are used: $k_d = 10^{-2}\text{s}^{-1}$ in the dissolution reaction, $\beta_\ell = 0.8$, $\beta_d = 0.5$ in the diffusion coefficients $D_\ell, D_d$, respectively, $D_{eql} = 3.74 \times 10^{-9}\text{m}^2/\text{s}$ and $D_{de} = 2.72 \times 10^{-10}\text{m}^2/\text{s}$, the densities $\rho_\ell = 10^3\text{kg/m}^3$, $\rho_d = 1400\text{kg/m}^3$, and $\rho_p = 1175\text{kg/m}^3$.

In the numerical calculations, constant stepsizes were used: in the radius $h_i(t_n) = 10^{-5}$ and in time $\Delta_t = 10^{-4}$.

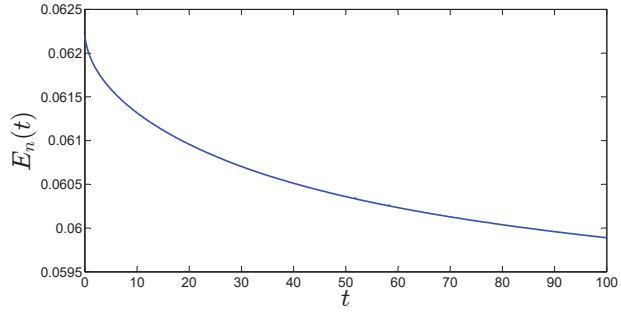


FIG. 2. *Behavior of the energy* $E_n(t)$.

In Figure 2 we present the behavior of the energy $E_n(t)$ for the dissolution reaction defined by (8). We observe that $E_n(t)$ decreases in time. We remark that for $f$ defined by (7) we proved in Proposition 2 that $\sum_{i\in\{ud,d\}} \|c_i(t)\|^2_{L^2(\Omega)}$ decreases and for the dissolution reaction $f$ given by (8) only the boundedness of this term was shown. We exhibit in what follows plots of the different concentrations that illustrate the physical soundness of the model. In Figure 3 we plot the solvent concentration $c_\ell$. As the swelling front advances, the solvent concentration increases inside the polymeric sphere. For large times an interior-exterior solvent concentration equilibrium is observed.

The behavior of the dissolved drug is illustrated in Figure 4. As the swelling front advances, a dissolution front inside of the polymeric sphere recedes. Moreover, higher dissolved concentration values are observed near the transition point and outside of the polymer.

In Figure 5 we present an illustration of the behavior of the dissolved drug in the external medium. As time increases, the swelling front advances and the dissolved drug outside polymeric sphere increases.

The behavior of the solid drug concentration is illustrated in Figure 6. As $t$ increases, a decreasing of the solid drug inside the interior sphere is observed. For large values of $t$ the solid drug is dissolved completely.

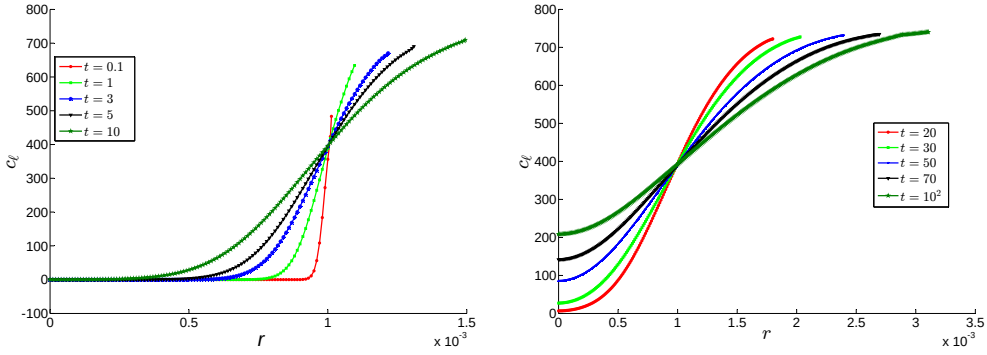


FIG. 3. *Behavior of the solvent concentration $c_\ell$ in the polymeric sphere.*

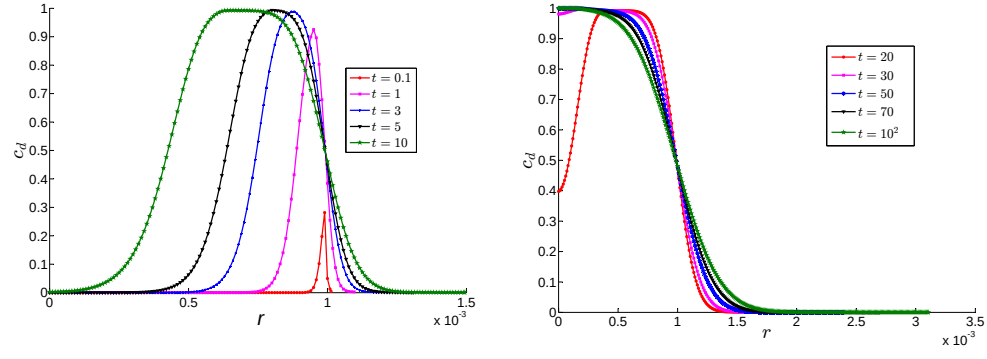


FIG. 4. *Behavior of dissolved drug concentration $c_d$ in the interior polymeric sphere.*

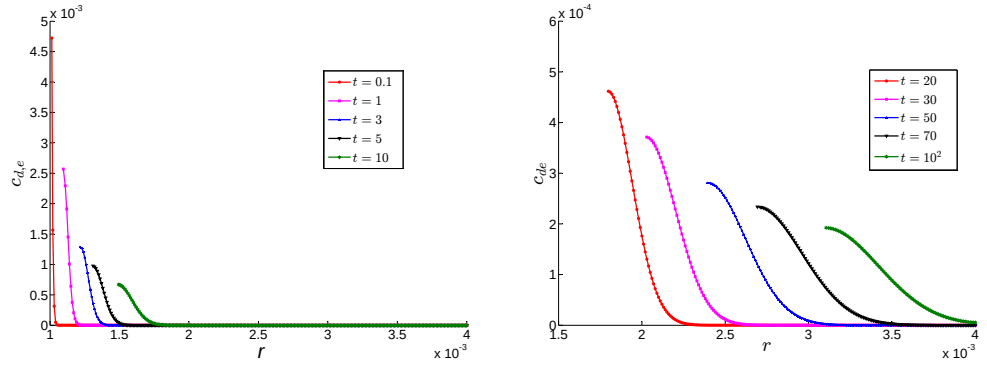


FIG. 5. *Concentration of the dissolved drug $c_{de}$ in the external medium $\Omega_e - \Omega(t)$.*

As the solvent permeates the polymeric sphere, the opposite force, represented by $|\sigma|$, is larger in the region where the polymer is not relaxed, that is, behind the swelling front. This fact induces an increase in the stress on the left side of the swollen front and a decrease on the right side, as illustrated in Figure 7.

There are two important factors that influence the swelling of polymers: the

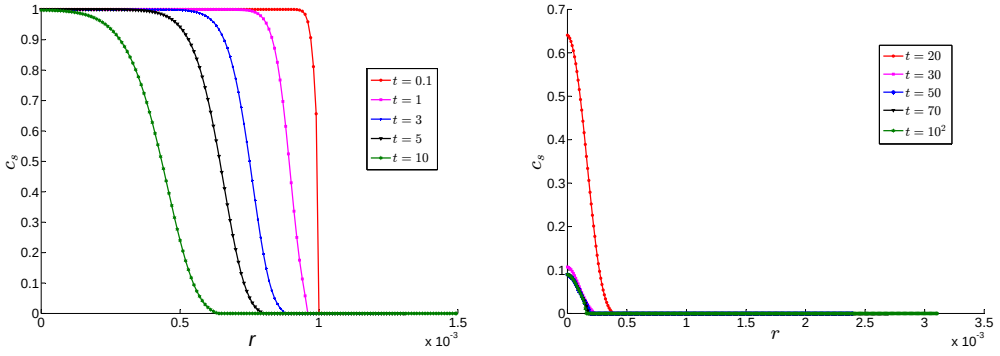


FIG. 6. *Behavior of the solid drug concentration $c_{ud}$ in the interior polymeric sphere.*

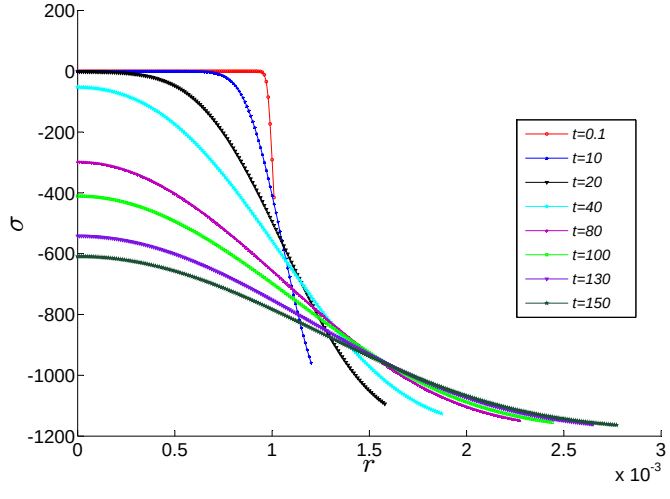


FIG. 7. *Behavior of the stress $\sigma$ in the interior polymeric sphere.*

amount $c_\ell$ of available release medium and the cross-link density $E$ of the polymer. Concerning the first factor, the polymeric sphere needs solvent to swell. When the solvent is not enough, it will be completely absorbed and there will remain no fluid to act as a diffusion medium. In Figure 8 we exhibit the time evolution of $r(t)$ for different values of the exterior solvent concentration $c_{\ell e}$ and for $E_0 = E_1 = 10^3$. We observe that the swelling properties are enhanced with higher concentrations of the swelling agent [1].

The second factor is the cross-link density. For high Young modulus, the polymer behaves like a solid and its swelling is minimal. As the Young modulus decreases, that is, as the cross-link density decreases, the forces between the polymeric chains decrease and a larger swell can be observed. In Figure 9 the behavior of $r(t)$ with Young modulus is plotted. As the Young modulus increases, a decrease in the polymeric swelling is observed. In Figure 10 we plot the absorbed solvent mass for different Young moduli. An increase in the cross-link density induces a decrease in the solvent absorbed mass. In fact, a higher Young modulus induces a decrease in the relaxation

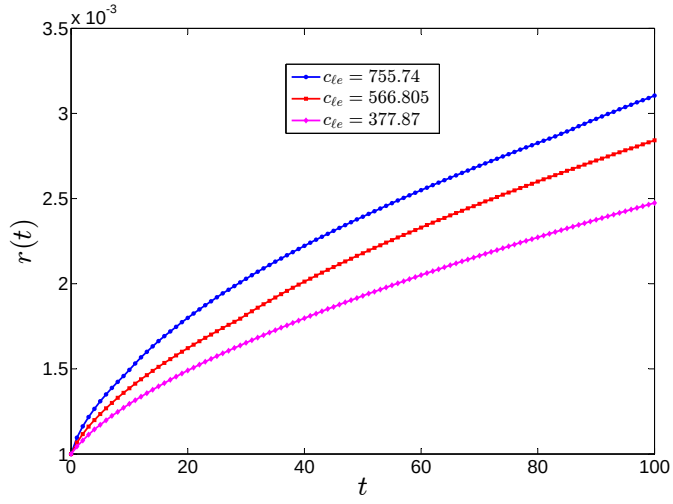


FIG. 8. *Behavior of the swelling front for different values of the exterior solvent concentration* $c_{\ell e}$.

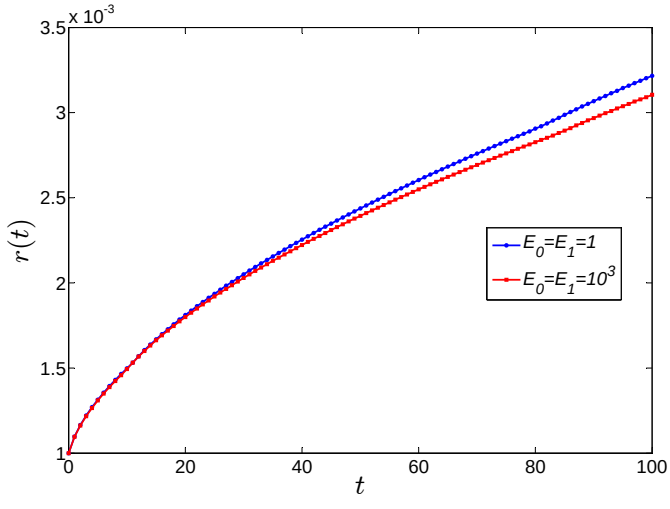


FIG. 9. *Behavior of swelling front for different Young moduli.*

of the polymeric chains and consequently a decrease in the amount of solvent that can be accommodated in the relaxed polymeric matrix.

The behavior of the mass $M_\ell$ of released drug for different Young moduli is illustrated in Figure 11. We observe that an increase in the Young modulus is accomplished by an increase in the released mass. This behavior is due to the maintenance of an organized internal polymeric structure that allows the entrance of a lower quantity of solvent but enough to have drug dissolution and drug diffusion. The behavior of the mass $M_r$ of released drug on the solubility limit is illustrated in Figure 12. An increase in the solubility limit induces an increase in the drug released mass.

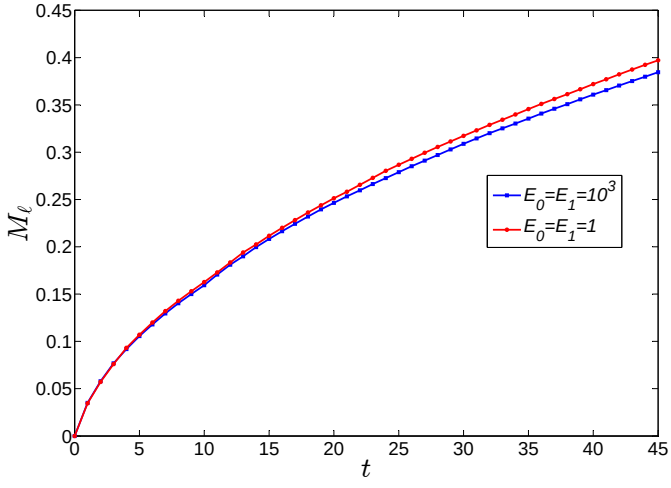


FIG. 10. *Absorbed solvent mass for different Young moduli.*

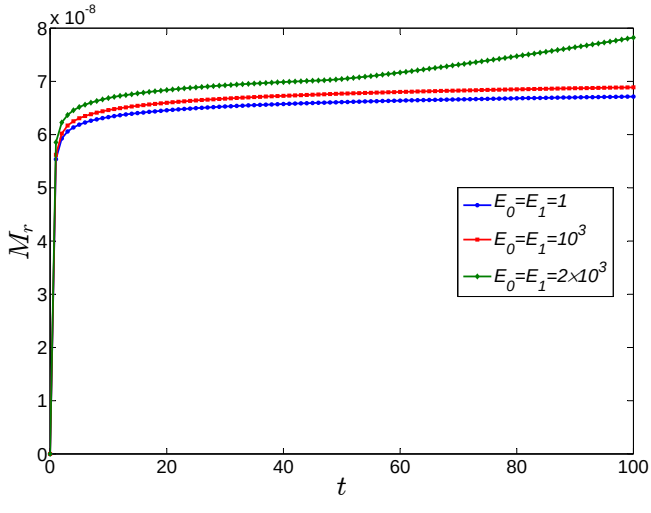


FIG. 11. *Drug mass released for different Young moduli.*

In Figure 13 we plot the drug released mass for different exterior solvent concentrations. An increase in $c_{\ell e}$ induces a decrease in the drug released mass.

**6. Conclusions.** A model of drug delivery into a closed release medium, from a swellable platform, is presented in this paper. The model is represented by two coupled systems of PDEs, defined in two adjacent moving boundary domains. Two major types of outputs are achieved: theoretical results concerning the behavior of the PDEs systems that describe the phenomena involved; and practical results related to predictions of the in vitro behavior of swelling devices.

Concerning the theoretical outputs, we mention

(i) the establishment of the moving front rate (section 3);

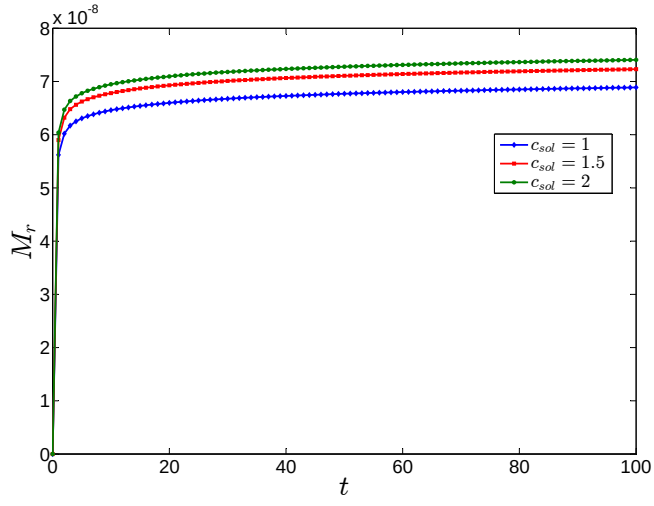


FIG. 12. *Drug mass released for different solubilities* $c_{sol}$.

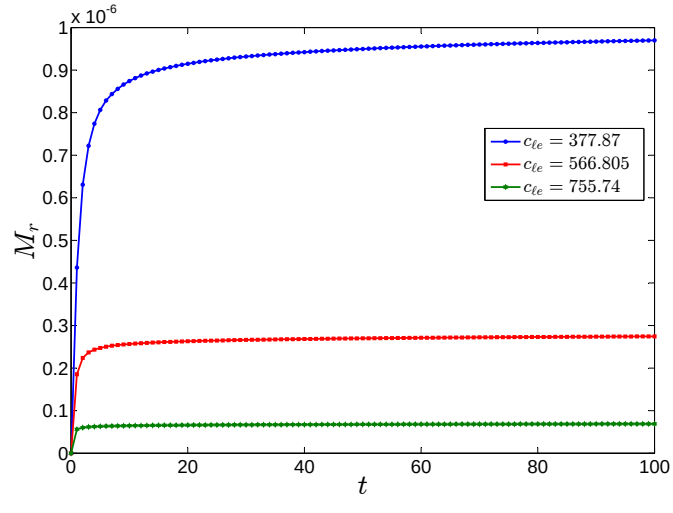


FIG. 13. *Drug mass released for different exterior concentrations* $c_{\ell e}$.

(ii) the energy estimates in the case of instantaneous swelling (section 4).

From these estimates the stability of the continuous model and the uniqueness of the solution are concluded. Regarding the practical outputs, the model provides a tool for designing swellable delivery platforms. If new chemical compounds are the most important factor in drug development, it is also true that delivery technologies are nowadays considered crucial in the release process. The development of swellable polymeric systems is a major challenge as safe and efficient products need to be implemented. Our model includes two of the major factors that govern a swelling process of a polymeric spherical platform within a release medium:

(i) The concentration of the release medium. The dependence of the swelling

on the solvent concentration of the system is illustrated in Figure 8. As this concentration decreases, less swelling is observed.

(ii) The cross-link density of the polymer, which is directly related to the Young modulus. In Figure 9 we exhibit the behavior of the swelling radius as a function of the Young modulus $E(t)$ defined in (11). The result is physically sound and is in agreement with experimental work [19].

The cross-link density, the solvent contents of the system, and the solubility of the drug define the swelling behavior that in turn determines the evolution of the mass of drug released, $M_r(t)$.

(i) In Figure 11 we exhibit the dependence of $M_r(t)$ on the Young modulus.

(ii) In Figure 12 the dependence of $M_r(t)$ on the drug solubility is illustrated.

(iii) In Figure 13 the influence of the swelling fluid concentration on the mass $M_r(t)$ is illustrated.

The knowledge of the qualitative and quantitative dependence of the drug release behavior on these factors can be of great help in assisting manufacturers. The model can provide them with different tailoring means, such as, for example, the change of cross-link density, or the regulation of the amount of swelling medium.

Finally we note that one of the advantages of our model is that the rheological parameters can be experimentally measured.

**7. Appendix: Proof of Proposition 2.** We have

$$\frac{d}{dt}\|c_\ell(t)\|^2_{L^2(\Omega)} = 2\Big(\frac{\partial c_\ell}{\partial t}(t), c_\ell(t)\Big)_{L^2(\Omega)}. \tag{52}$$

From (13) for $(\frac{\partial c_\ell}{\partial t}(t), c_\ell(t))_{L^2(\Omega)}$ we obtain

$$\begin{aligned}\Big(\frac{\partial c_\ell}{\partial t}(t), c_\ell(t)\Big)_{L^2(\Omega)} &= (-J_\ell(t).\eta, c_\ell(t))_{L^2(\partial\Omega)} + (J_\ell(t), \nabla c_\ell(t))_{L^2(\Omega)\times L^2(\Omega)}\\ &\le \alpha\|c_\ell(t) - c_{\ell e}\|_{L^2(\partial\Omega)}\|c_\ell(t)\|_{L^2(\partial\Omega)}\\ &\quad + (J_\ell(t), \nabla c_\ell(t))_{L^2(\Omega)\times L^2(\Omega)}.\end{aligned} \tag{53}$$

Using the trace inequality, we get

$$\begin{aligned}\alpha\|c_\ell(t) - c_{\ell e}\|_{L^2(\partial\Omega)}\|c_\ell(t)\|_{L^2(\partial\Omega)} &\le \alpha\Big(\|c_\ell(t)\|_{L^2(\partial\Omega)} + c_{\ell e}|\partial\Omega|\Big)\|c_\ell(t)\|_{L^2(\partial\Omega)}\\ &\le (\alpha+\epsilon_1^2)C_{tr}^2\|c_\ell(t)\|_1^2 + \frac{1}{4\epsilon_1^2}(\alpha c_{\ell e}|\partial\Omega|)^2,\end{aligned} \tag{54}$$

where $\epsilon_1$ is an arbitrary nonzero constant and $|\partial\Omega|$ denotes the length of the surface $\partial\Omega$.

The term $(J_\ell(t), \nabla c_\ell(t))_{L^2(\Omega)\times L^2(\Omega)}$ can be split into

$$\begin{aligned}(J_\ell(t), \nabla c_\ell(t))_{L^2(\Omega)\times L^2(\Omega)} &= ((-D_d + \hat{E}D_v g'(c_\ell(t)))\nabla c_\ell(t), \nabla c_\ell(t))_{L^2(\Omega)\times L^2(\Omega)}\\ &\quad - \Big(D_v\int_0^t k_{er}(t-s)g'(c_\ell(s))\nabla c_\ell(s)\,ds, \nabla c_\ell(t)\Big)_{L^2(\Omega)\times L^2(\Omega)}\\ &= T_1 + T_2.\end{aligned} \tag{55}$$

We establish in what follows an estimate for $T_2$. Let $\epsilon_2$ be a nonzero constant. It can

be shown that

$$|T_2| \leq \frac{D_v^2}{4\epsilon_2^2}\|g'(c_\ell)\|^2_{L^\infty(L^2)}\Big(\int_0^t k_{er}(t-s)\|\nabla c_\ell(s)\|_{L^2(\Omega)\times L^2(\Omega)}ds\Big)^2$$
$$+ \epsilon_2^2\|\nabla c_\ell(t)\|^2_{L^2(\Omega)\times L^2(\Omega)}$$

and, as

$$\Big(\int_0^t k_{er}(t-s)\|\nabla c_\ell(s)\|_{L^2(\Omega)\times L^2(\Omega)}ds\Big)^2 \leq \frac{E_1^2}{2\tau_1}\int_0^t \|\nabla c_\ell(s)\|^2_{L^2(\Omega)\times L^2(\Omega)}ds,$$

we obtain

$$|T_2| \leq \frac{D_v^2}{8\epsilon_2^2}\frac{E_1^2}{\tau_1}\|g'(c_\ell)\|^2_{L^\infty(L^2)}\int_0^t \|\nabla c_\ell(s)\|^2_{L^2(\Omega)\times L^2(\Omega)}ds \tag{56}$$
$$+ \epsilon_2^2\|\nabla c_\ell(t)\|^2_{L^2(\Omega)\times L^2(\Omega)}.$$

Combining (52)–(56), we get

$$\frac{d}{dt}\Big(\|c_\ell(t)\|^2_{L^2(\Omega)} + 2\gamma_1(c_\ell)\int_0^t \|\nabla c_\ell(s)\|^2_{L^2(\Omega)\times L^2(\Omega)}ds\Big)$$
$$\leq \frac{1}{2\epsilon_1^2}(\alpha c_{\ell e}|\partial\Omega|)^2 + 2(\alpha+\epsilon_1^2)C_{tr}^2\|c_\ell(t)\|^2_{L^2(\Omega)} \tag{57}$$
$$+ \frac{D_v^2E_1^2}{4\tau_1\epsilon_2^2}\|g'(c_\ell)\|^2_{L^\infty(L^2)}\int_0^t \|\nabla c_\ell(s)\|^2_{L^2(\Omega)\times L^2(\Omega)}ds.$$

Let $\epsilon_i, i=1,2$, such that $\gamma_1(c_\ell)$ as defined by (38) is positive. Inequality (57) leads to

$$\|c_\ell(t)\|^2_{L^2(\Omega)} + 2\gamma_1(c_\ell)\int_0^t \|\nabla c_\ell(s)\|^2_{L^2(\Omega)\times L^2(\Omega)}ds$$
$$\leq \frac{1}{2\epsilon_1^2}(\alpha c_{\ell e}|\partial\Omega|)^2 t + 2(\alpha+\epsilon_1^2)C_{tr}^2\int_0^t \|c_\ell(s)\|^2_{L^2(\Omega)}ds$$
$$+ \frac{D_v^2E_1^2}{4\tau_1\epsilon_2^2}\|g'(c_\ell)\|_{L^\infty(L^2)}\int_0^t\int_0^s \|\nabla c_\ell(u)\|^2_{L^2(\Omega)\times L^2(\Omega)}duds,$$

that is,

$$\|c_\ell(t)\|^2_{L^2(\Omega)} + \int_0^t \|\nabla c_\ell(s)\|^2_{L^2(\Omega)\times L^2(\Omega)}ds$$
$$\leq \frac{\max\{2(\alpha+\epsilon_1^2)C_{tr}^2, \frac{D_v^2E_1^2}{4\tau_1\epsilon_2^2}\|g'(c_\ell)\|_{L^\infty(L^2)}\}}{\min\{1, 2\gamma_1(c_\ell)\}} \tag{58}$$
$$\Big(\int_0^t \|c_\ell(s)\|^2_{L^2(\Omega)}ds + \int_0^t\int_0^s \|\nabla c_\ell(u)\|^2_{L^2(\Omega)\times L^2(\Omega)}duds\Big)$$
$$+ \frac{1}{2\epsilon_1^2\min\{1, 2\gamma_1(c_\ell)\}}(\alpha c_{\ell e}|\partial\Omega|)^2 t.$$

Finally, applying Gronwall's lemma, we conclude the existence of positive constants $C_i > 0, i=1,2$, such that

$$\|c_\ell(t)\|^2_{L^2(\Omega)} + \int_0^t \|\nabla c_\ell(s)\|^2_{L^2(\Omega)\times L^2(\Omega)}ds \leq C_1 e^{C_2 t}(\alpha c_{\ell e}|\partial\Omega|)^2 t,\ t\in[0,T]. \tag{59}$$

We obtain now an estimate for $E_n(t) = \sum_{i=d,ud} \|c_i(t)\|^2_{L^2(\Omega)} + \|c_{de}(t)\|^2_{L^2(\Omega_{c,e})}$. We have successively

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\Big(\sum_{i=d,ud} \|c_i(t)\|^2_{L^2(\Omega)} + \|c_{de}(t)\|^2_{L^2(\Omega_{c,e})}\Big)\\
&= \sum_{i=d,ud} \Big(\frac{\partial c_i}{\partial t}(t), c_i(t)\Big)_{L^2(\Omega)} + \Big(\frac{\partial c_{de}}{\partial t}(t), c_{de}(t)\Big)_{L^2(\Omega_{c,e})}\\
&= -(\nabla.J_d(t), c_d(t))_{L^2(\Omega)} + (F(t), c_d(t) - c_{ud}(t))_{L^2(\Omega)} - (\nabla.J_{d,e}(t), c_{de}(t))_{L^2(\Omega_{c,e})}\\
&= -(J_d(t).\eta_\Omega, c_d(t))_{L^2(\partial\Omega)} + (J_d(t), \nabla c_d(t))_{L^2(\Omega)\times L^2(\Omega)} + (F(t), c_d(t) - c_{ud}(t))_{L^2(\Omega)}\\
&\quad - (J_{d,e}(t).\eta_{\Omega_{c,e}}, c_{de}(t))_{L^2(\partial(\Omega_{c,e}))} + (J_{d,e}(t), \nabla c_{de}(t))_{L^2(\Omega_{c,e})\times L^2(\Omega_{c,e})},
\end{aligned}$$

where $F(t) = f(c_{ud}(t), c_d(t), c_\ell(t))$, and $\eta_\Omega$ and $\eta_{\Omega_{c,e}}$ denote the exterior unitary normal to $\Omega$ and $\Omega_{c,e}$, respectively.

Taking into account the transition conditions (14) and the boundary condition (15), we conclude (39).

The desired upper bound is obtaining estimating $(F(t), c_d(t) - c_{ud}(t))_{L^2(\Omega)}$.

1. If $f$ is defined by (7), then

$$(F(t), c_d(t) - c_{ud}(t))_{L^2(\Omega)} \le 0. \tag{60}$$

Equation (39) enable us to establish that

(61)

$$\begin{aligned}
&\sum_{i=d,ud} \|c_i(t)\|^2_{L^2(\Omega)} + \|c_{de}(t)\|^2_{L^2(\Omega_{c,e})} + 2D_d \int_0^t \|\nabla c_d(s)\|^2_{L^2(\Omega)\times L^2(\Omega)} ds\\
&+ 2D_{d,e} \int_0^t \|\nabla c_{de}(s)\|^2_{L^2(\Omega_{c,e})\times L^2(\Omega_{c,e})} ds \le \|c_{ud}(0)\|^2_{L^2(\Omega)}, \quad t \in [0,T].
\end{aligned}$$

Finally, from (59), (61), (60), we conclude (40).

2. If $f$ is defined by (8), then we have

$$\begin{aligned}
&(F(t), c_d(t) - c_{ud}(t))_{L^2(\Omega)}\\
&\le k_d \|c_\ell(t)\|_{L^2(\Omega)} \Big(1 + \Big(1 + \frac{1}{c^2_{sol}}\Big)\big(\|c_d(t)\|^2_{L^2(\Omega)} + \|c_{ud}(t)\|^2_{L^2(\Omega)}\big)\Big),
\end{aligned} \tag{62}$$

and consequently, from (39), we deduce

$$\begin{aligned}
&\sum_{i=d,ud} \|c_i(t)\|^2_{L^2(\Omega)} + \|c_{de}(t)\|^2_{L^2(\Omega_{c,e})} + 2D_d \int_0^t \|\nabla c_d(s)\|^2_{L^2(\Omega)\times L^2(\Omega)} ds\\
&+ 2D_{d,e} \int_0^t \|\nabla c_{de}(s)\|^2_{L^2(\Omega_{c,e})\times L^2(\Omega_{c,e})} ds \le \|c_{ud}(0)\|^2_{L^2(\Omega)}\\
&+ \int_0^t k_d \|c_\ell(s)\|_{L^2(\Omega)} \Big(1 + \Big(1 + \frac{1}{c^2_{sol}}\Big)\big(\|c_d(s)\|^2_{L^2(\Omega)} + \|c_{ud}(s)\|^2_{L^2(\Omega)}\big)\Big) ds
\end{aligned}$$

for $t \in [0,T]$. Gronwall's lemma leads now to

$$\begin{aligned}
&\sum_{i=d,ud} \|c_i(t)\|^2_{L^2(\Omega)} + \|c_{de}(t)\|^2_{L^2(\Omega_{c,e})} + 2D_d \int_0^t \|\nabla c_d(s)\|^2_{L^2(\Omega)\times L^2(\Omega)} ds\\
&+ 2D_{d,e} \int_0^t \|\nabla c_{de}(s)\|^2_{L^2(\Omega_{c,e})\times L^2(\Omega_{c,e})} ds\\
&\le e^{k_d\left(1+\frac{1}{c^2_{sol}}\right)\int_0^t \|c_\ell(s)\|_{L^2(\Omega)} ds} \Big(\|c_{ud}(0)\|^2_{L^2(\Omega)} + \int_0^t k_d \|c_\ell(s)\|_{L^2(\Omega)} ds\Big)
\end{aligned} \tag{63}$$

for $t \in [0, T]$. Finally, using the upper bound (59) in (63), we conclude (41).

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