Pré-Publicações do Departamento de Matemática
Universidade de Coimbra
Preprint Number 19–20

DRUG RELEASE FROM VISCOELASTIC POLYMERIC MATRICES - A STABLE AND SUPRACONVERGENT FDM

J.S. BORGES, J.A. FERREIRA, G. ROMANAZZI AND E. ABREU

Abstract: Drug release from viscoelastic polymeric matrices is a complex phenomenon where the main actors are the fluid, the polymeric structure and the drug. As the fluid enters into the polymer, the polymeric chains relax inducing a resistance to the fluid entrance. In contact with the fluid, a dissolution processes takes place and the dissolved drug diffuses through the medium. Our main goal in this paper is to propose a stable finite difference method that leads to a supraconvergent approximations for the fluid, solid and dissolved drug concentrations. The analysis proposed is non-standard in the sense that the error estimates have an important role in the stability analysis.

Keywords: Drug release, viscoelastic polymeric matrix, fluid entrance, dissolution, dissolved drug transport, stability, convergence.

1. Introduction

Controlled drug delivery systems (CDDS) belong to the second generation of drug delivery devices that were proposed to avoid the drawbacks of the fist generation of DDS: oscillatory behaviour of the drug concentration in the target tissue that can exceeds the bounds that define the therapeutic window - the drug can be toxic (exceeds the highest therapeutic window threshold) or it may have no therapeutic effect (the drug concentration is lower than the lowest therapeutic window threshold) ([18]). While in the first generation of DDS the drug release mechanisms are: dissolution and diffusion, the properties of the reservoir used to transport drug enter in the game in the second generation of DDS. The need of drug delivery devices characterized by a sustained drug release and a constant concentration profile in the target tissues was the main motivation for the dialogue between material engineers, chemical engineers, pharmaceutics and medical doctors which led to the design of intelligent drug delivery systems with prescribed properties.

Viscoelastic polymers are today an important component of several smart drug delivery devices. For instance, in tablets that are orally administered, intelligent polymers are used to transport the drug trough the gastrointestinal

Received June 03, 2019.

system. The polymeric cross-links and the drug properties (dissolution and diffusion) are the main responsible by the drug release control ([1]). In these systems, a solid drug is initially dispersed. When the device is in contact with a solvent, the fluid enters in the polymer and it swells. The fluid entrance due to the difference of concentrations induces a polymeric response that was mathematically translated in [10] by an anti-convective transport defined by the polymeric stress σ that depends on the polymeric characteristics

$$v_{ac}(t) = D_v \nabla \sigma(t).$$

In contact with the solvent, the solid drug initially homogeneously distributed in the polymeric reservoir, dissolves and diffuses through the relaxed polymeric structure. In what follows we assume that the polymeric chains do not induce an opposition to the transport of drug particles being this transport defined only by diffusion. In [10], [11] and [12] the authors assume that σ is given by the Boltzmann integral

$$\sigma(t) = -\int_0^t E(t-s)\frac{\partial \varepsilon}{\partial s}(s)\, ds \tag{1}$$

where ϵ denotes the strain, $E(s)$ is given by the Maxwell-Wiechert model ([3])

$$E(s) = E_0 + \sum_{j=1}^{m} E_j \exp\left(-\frac{s}{\tau_j}\right) \tag{2}$$

where E_j denotes the Young's modulus, $\tau_j = \frac{\mu_j}{E_j}$ with μ_j that represent the polymeric viscosity. Non-Fickian diffusion in polymeric coating and arterial vessel wall tissue in the context of drug eluting stents applications were recently considered in [9] and [17].

The mathematical description of diffusion processes in polymers that do not follow Fick's law has been prosed in the literature. Without being exhaustive, we mention [4], the work of Cohen and his coauthors [5], [6], [7] and [8] and the reference therein, and finally, [16] and [19]. We remark that in the last papers, the relation

$$\frac{\partial \sigma}{\partial t} + \beta\sigma = \phi\epsilon + \gamma\frac{\partial \epsilon}{\partial t} \tag{3}$$

between the stress σ and strain ϵ was considered. In (3), ϕ and γ are positive constants whose physical meaning is associated to the mechanistic description of the behaviour of polymers, the inverse of the relaxation parameter β was taken constant in [19] and depending on the concentration in [5] and [19].

In what follows we do not take into account the polymeric swelling. In this work we consider that the polymeric device is an homogeneous and isotropic sphere and these properties allow us to replace the 3D system by an one dimensional problem defined in the radial direction.

Let $\Omega = (0, R)$ be the spatial domain and let c_ℓ, c_d and c_s be the solvent, dissolved drug and solid drug concentrations. The behaviour of the these variables is described by the following system of partial differential equations

$$\begin{cases} \dfrac{\partial c_\ell}{\partial t} = \dfrac{\partial}{\partial x}(D_\ell \dfrac{\partial c_\ell}{\partial x}) + \dfrac{\partial}{\partial x}(D_v \dfrac{\partial \sigma}{\partial x}) \\ \dfrac{\partial c_d}{\partial t} = \dfrac{\partial}{\partial x}(D_d \dfrac{\partial c_d}{\partial x}) + f(c_s,\, c_d,\, c_\ell) \\ \dfrac{\partial c_s}{\partial t} = -f(c_s,\, c_d,\, c_\ell), \end{cases} \tag{4}$$

defined in $\Omega \times (0, T]$, where T is a final time, and the reaction term f defining the dissolution process is given by

$$f(c_s,\, c_d,\, c_\ell) = H(c_s)\, k_d \frac{c_{sol} - c_d}{c_{sol}} c_\ell. \tag{5}$$

In this definition, k_d denotes the dissolution rate, c_{sol} is the solubility limit and $H(c_s)$ is the Heaviside function.
In (4), the diffusion coefficients are of Fujita type ([15])

$$D_\ell = D_{eq} \exp\left(-\beta_\ell \left(1 - \frac{c_\ell}{c_{ext}}\right)\right), \tag{6}$$

$$D_d = D_{de} \exp\left(-\beta_d \left(1 - \frac{c_\ell}{c_{ext}}\right)\right). \tag{7}$$

D_{eq} and D_{de} denote the diffusion coefficients of the solvent and of the dissolved drug in the fully swollen sample, respectively, and β_ℓ, β_d denote dimensionless positive constants. In [10] the following expression for D_v was deduced

$$D_v = \frac{r^2}{8\hat{\mu}} c_\ell. \tag{8}$$

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

In (1), the strain ϵ is given by

$$g(c_\ell) = \Big(\frac{\rho_\ell}{\rho_\ell - c_\ell}\Big)^{1/3} - 1, \tag{9}$$

where ρ_ℓ is the solvent density (see [12]). In [11] a different g expression was proposed for polymeric cylinders. From (1), we obtain

$$\sigma(t) = -g(c_\ell(t))\hat{E} + g(c_\ell(0))\Big(E_0 + \sum_{j=1}^{m} E_j e^{-\frac{t}{\tau_j}}\Big) + \int_0^t \sum_{j=1}^{m} \frac{E_j}{\tau_j} e^{-\frac{t-s}{\tau_j}} g(c_\ell(s))ds.$$

As $c_\ell(0) = 0$, then, from (9), we conclude that $g(c_\ell(0)) = 0$ and consequently

$$\sigma(t) = -g(c_\ell(t))\hat{E} + \int_0^t k_{er}(t-s)g(c_\ell(s))ds, \tag{10}$$

with $k_{er}(s) = \sum_{j=1}^{m} \frac{E_j}{\tau_j} e^{-\frac{s}{\tau_j}}$ and $\hat{E} = \sum_{j=0}^{m} E_j$.

Combining now the first equation of (4) with (10), we conclude for c_ℓ the following differential equation

$$\begin{aligned} \frac{\partial c_\ell}{\partial t} &= \frac{\partial}{\partial x}\Big(\big(D_\ell(c_\ell) - D_v(c_\ell)\hat{E}g'(c_\ell)\big)\frac{\partial c_\ell}{\partial x}\Big) \\ &+ \frac{\partial}{\partial x}\Big(D_v(c_\ell)\int_0^t k_{er}(t-s)g'(c_\ell(s))\frac{\partial c_\ell}{\partial x}(s)ds\Big). \end{aligned} \tag{11}$$

We observe that this equation can be rewritten in the following equivalent form

$$\frac{\partial c_\ell}{\partial t} + \frac{\partial J_\ell}{\partial x} = 0,$$

where J_ℓ denotes the solvent mass flux which is given by

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

The drug release from the polymeric sphere is then described by (11) coupled with

$$\frac{\partial c_d}{\partial t} = \frac{\partial}{\partial x}(D_d\frac{\partial c_d}{\partial x}) + f(c_s,\, c_d,\, c_\ell) \tag{12}$$

and

$$\frac{\partial c_s}{\partial t} = -f(c_s,\, c_d,\, c_\ell). \tag{13}$$

The differential system (11), (12) and (13) is completed by the following boundary conditions

$$\frac{\partial c_\ell}{\partial x}(0,t) = 0, \qquad c_\ell(R,t) = c_{ext}, \tag{14}$$

$$\frac{\partial c_d}{\partial x}(0,t) = 0, \qquad c_d(R,t) = 0. \tag{15}$$

The first condition for c_ℓ and c_d are consequence of the symmetry of the polymeric sphere at the origin, the second condition for c_ℓ means that at the boundary of the surface the concentration is equal to the solvent concentration c_{ext} at the medium where the sphere is imbedded. This last condition is considered as a simplification of

$$J_\ell(R,t) = \alpha(c_\ell(R,t) - c_{ext}), \tag{16}$$

considered before in [12], where α represents a permeability constant. We remark that the simplified boundary conditions (14), (15) will be considered in what follows.

The differential problem is coupled with the general initial conditions

$$c_\ell(x,\,0) = c_{\ell,0}(x), x \in \Omega, \tag{17}$$

$$c_s(x,\,0) = c_{s,0}(x),\, c_d(x,\,0) = c_{d,0}(x), x \in \Omega. \tag{18}$$

In this paper our main goal is to propose a finite difference method to solve the system of partial differential equations (11), (12) and (13), complemented with the boundary conditions (14), (15), and the initial conditions (17), (18), defined on nonuniform grids that presents second convergence order. We observe that a finite difference method for a simplified version of the integro-differential equation (11) was studied in [13]. In [2] the coupling between a quasi-linear elliptic equation with an quasi-linear integro-differential equation was studied from numerical point of view considering only Dirichlet boundary conditions. In the present work, the symmetric conditions (14), (15) introduce additional difficulties in the stability and convergence analysis that need to be carefully treated. The method that we propose can be seen simultaneously as a finite difference method and a fully discrete piecewise linear finite element method (see for instance [2], [13] and [14]). The nonlinearity of the IBVP under analysis in this work, introduces another difficulty in the stability analysis. In fact, as we will see, to conclude the stability we need to impose the boundness of the sequence of the numerical approximations for the variables of the model. However, to avoid such anomalous restriction, we start by proving the second convergence order being the boundness of the numerical approximations consequence of such result. Although the truncation error of the method that we propose hast first order, with respect to the norm $\|.\|_\infty$, we will prove that the global error presents second convergence order. The finite difference methods is said supraconvergent.

The paper is organized as follows. In Section 2 we present the notations, auxiliary results and the the new numerical method that is based on MOL approach (method of lines approach). We start by analysing the solvent concentration showing the convergence properties and its stability in Section 3. We remark that in the convergence analysis we do not use the stability but we conclude such property analysing the error equation. The stability result is consequence of the error estimates established in this section. The solvent concentration properties are crucial in the study of the dissolved and solid drug concentrations. In fact, as we will show in Section 4 where the convergence and stability of the dissolved and solid drugs are studied, we need to use the boundness of the solvent semi-discrete approximation with respect to the norm $\|.\|_\infty$. In Section 5 we include some numerical experiments illustrating the theoretical results proved in the previous sections and, finally, in Section 6 we present some conclusions.

2. Preliminary results

Let Λ be a sequence of vector $h = (h_1, \dots, h_N)$ such that $h_i > 0, i = 1, \dots, N$, $R = \sum_{i=1}^{N} h_i$, $h_{max} = \max_{i=1,\dots,N} h_i \to 0$. Let $h \in \Lambda$ and $\overline{\Omega}_h$ be the grid defined by h

$$\overline{\Omega}_h = \{x_i, i = 0, \dots, N, x_i = x_{i-1} + h_i, i = 1, \dots, N, x_0 = 0, x_N = R\}.$$

To discretize the Neumann boundary condition for c_ℓ and c_d at $x = 0$, we define the fictitious point $x_{-1} = -x_1$, and then $x_0 - x_{-1} = h_0 = h_1$. We introduce the following sets

$$\overline{\Omega}_h^* = \overline{\Omega}_h \cup \{x_{-1}\}, \Omega_h = \overline{\Omega}_h \cap \Omega.$$

Let $V_{h,0}^*$, W_h and U_h be the following sets of grid functions

$$V_{h,0}^* = \{v_h : \overline{\Omega}_h^* \to \mathbb{R},\ v_h(x_N) = 0\},$$

$$W_h = \{w_h : \overline{\Omega}_h \to \mathbb{R}\}$$

and

$$U_h = \{u_h : \Omega_h \to \mathrm{I\!R}\},$$

respectively. By D_{-x} we denote the backward finite difference operator and let D_x^* be defined by

$$D_x^* v_h(x_i) = \frac{v_h(x_{i+1}) - v_h(x_i)}{h_{i+1/2}}, i = 0, \ldots, N-1,$$

where $h_{i+1/2} = \dfrac{h_i + h_{i+1}}{2}$.

In W_h we introduce the following inner product

$$(w_h, q_h)_h = \frac{h_1}{2} w_h(x_0) q_h(x_0) + \sum_{i=1}^{N-1} h_{i+1/2} w_h(x_i) q_h(x_i) + \frac{h_N}{2} w_h(x_N) q_h(x_N),$$

for $w_h, q_h \in W_h$, and by $\|.\|_h$ we denote the correspondent induced norm. We use the following notation

$$(u_h, v_h)_+ = \sum_{j=1}^{N} h_j u_h(x_j) v_h(x_j), \ u_h, v_h \in U_h,$$

and $\|u_h\|_+ = \Big(\sum_{j=1}^{N} h_j u_h(x_j)^2 \Big)^{1/2}$.

Let D_c be the first order centered operator defined by

$$D_c v_h(x_i) = \frac{v_h(x_{i+1}) - v_h(x_{i-1})}{h_i + h_{i+1}}, i = 0, \ldots, N-1.$$

By M_h we denote the average operator $M_h v_h(x_i) = \dfrac{1}{2}(v_h(x_i) + v_h(x_{i-1}))$.

Proposition 1. *For all $v_h, w_h \in V_{h,0}^*$ we have*

$$(-D_x^* D_{-x} v_h, w_h)_h = D_c v_h(x_0) w_h(x_0) + (D_{-x} v_h, D_{-x} w_h)_+. \tag{19}$$

As we are dealing with homogeneous Neumann boundary conditions at $x = 0$, a new boundary finite difference operator needs to be introduced

$$\tilde{D}_{c,a} v_h(x_0) = \frac{1}{2}\Big(a\left(M_h v_h(x_1)\right) D_{-x} v_h(x_1) + a\left(M_h v_h(x_0)\right) D_{-x} v_h(x_0) \Big), \tag{20}$$

where $v_h \in V_{h,0}^*$ and $a : \mathrm{I\!R} \to \mathrm{I\!R}$. Using summation by parts, it is easy to show the following proposition.

Proposition 2. *For all* $v_h, w_h \in V_{h,0}^*$ *and* $a : \mathbb{R} \to \mathbb{R}$, *we have*

$$(-D_x^*(a(M_h v_h)D_{-x}v_h), w_h)_h = \tilde{D}_{c,a}(v_h(x_0))w_h(x_0) + (a(M_h v_h)D_{-x}v_h, D_{-x}w_h)_+. \tag{21}$$

As for $u_h \in V_{h,0}^*$, $u_h(x_0) = -\sum_{i=1}^{N} h_i D_{-x}u_h(x_i)$, we conclude the next result.

Proposition 3. *For all* $u_h \in V_{h,0}^*$ *we have*

$$|u_h(x_0)| \leq \sqrt{R}\|D_{-x}u_h\|_+ \tag{22}$$

Proposition 4. *For all* $u_h \in W_h$ *we have*

$$\|u_h\|_\infty \leq \sqrt{R}\|D_{-x}u_h\|_+ + |u_h(x_N)| \tag{23}$$

where $\|u_h\|_\infty = \max_{\overline{\Omega}_h} |u_h|$.

We consider the solvent equation (11) rewritten in the following abstract form

$$\frac{\partial c_\ell}{\partial t} = \frac{\partial}{\partial x}\Big(a(c_\ell)\frac{\partial c_\ell}{\partial x}\Big) + \frac{\partial}{\partial x}\Big(\int_0^t q(t,s,c_\ell(s),c_\ell(t))\frac{\partial c_\ell}{\partial x}(s)ds\Big), \tag{24}$$

where $a(z) = D_\ell(z) - \hat{E}D_v(z)g'(z)$ and $q(t,s,z,y) = D_v(y)k_{er}(t-s)g'(z)$.

As g is a discontinuous function at equilibrium state when $c_\ell(t) = \rho_\ell$, from theoretical point of view we need to replace g by its regularization g_ϵ, where ϵ is positive and arbitrarily small. Such regularization can be defined for instance considering the Hermite interpolator at $(\rho_\ell \pm \epsilon, g(\rho_\ell \pm \epsilon))$. We assume that

H$_1$: $M \geq a(x) \geq a_0 > 0, |a'(x)| \leq M,\ x \in \mathbb{R}$,
H$_2$: $|q(t,s,z,y)| \leq M,\ \left|\frac{\partial q}{\partial z}(t,s,z,y)\right| \leq M, \left|\frac{\partial q}{\partial y}(t,s,z,y)\right| \leq M, \quad (t,s,z,y) \in [0,T] \times \mathbb{R} \times \mathbb{R}$.

By $c_{\ell,h}(t)$ we represent the semi-discrete approximation for $c_\ell(t)$ defined by the following initial boundary value problem

$$\begin{cases} \dfrac{dc_{\ell,h}}{dt}(t) = D_x^*\Big(a(M_h c_{\ell,h}(t))D_{-x}c_{\ell,h}(t)\Big) \\ + D_x^*\Big(\displaystyle\int_0^t q(t,s,M_h c_{\ell,h}(s), M_h c_{\ell,h}(t))D_{-x}c_{\ell,h}(s)ds\Big) \\ \qquad\qquad \text{in}\, \overline{\Omega}_h - \{x_N\} \times (0,T], \\ D_c c_{\ell,h}(x_0,t) = 0,\; c_{\ell,h}(x_N,t) = c_{ext},\; t \in (0,T], \\ c_{\ell,h}(0) \text{ given} \end{cases} \tag{25}$$

The semi-discrete approximations $c_{d,h}, c_{s,h}$ for the dissolved and undissolved drugs c_d and c_s are solutions of the following differential problems

$$\begin{cases} \dfrac{dc_{d,h}}{dt} = D_x^*(D_d(M_h c_{\ell,h}(t))D_{-x}c_{d,h}(t)) + f(c_{s,h}(t), c_{d,h}(t), c_{\ell,h}(t)) \\ \qquad\qquad\qquad\qquad\qquad\qquad \text{in } \overline{\Omega}_h - \{x_N\} \times (0,T], \\ D_c c_{d,h}(x_0,t) = 0,\; c_{d,h}(x_N,t) = 0,\; t \in (0,T] \\ c_{d,h}(0) \text{ given,} \end{cases} \tag{26}$$

and

$$\begin{cases} \dfrac{dc_{s,h}}{dt} = -f(c_{s,h}(t), c_{d,h}(t), c_{\ell,h}(t)) \text{ in } \overline{\Omega}_h - \{x_N\} \times (0,T], \\ c_{s,h}(0) \text{ given.} \end{cases} \tag{27}$$

3. Solvent concentration: convergence analysis and stability

Let $c_{\ell,h}(t), \tilde{c}_{\ell,h}(t)$ be two solutions of the IBVP (25) with different initial conditions. The nonlinear stability analysis with respect to the discrete L^2-norm $\|.\|_h$ requires the boundness of $\|D_{-x}c_{\ell,h}(t)\|_\infty$ or $\|D_{-x}\tilde{c}_{\ell,h}(t)\|_\infty$, as it will be shown in this section (see (33)). We note that this boundness does not follow from the application of the energy method to the IBVP (25) to obtain upper bounds for $c_{\ell,h}(t)$ or for $\tilde{c}_{\ell,h}(t)$ and it is crucial to get stability. In fact, let $w_h(t) = c_{\ell,h}(t) - \tilde{c}_{\ell,h}(t) \in V_{h,0}^*$ and, to simplify, we consider

(25) without the integral term. Using Proposition 2, it can be shown that $\|w_h(t)\|_h^2$ is solution of the initial value problem

$$\left\{\begin{array}{rl} \dfrac{1}{2}\dfrac{d}{dt}\|w_h(t)\|_h^2 & +(a(M_h\tilde{c}_{\ell,h}(t))D_{-x}w_h(t), D_{-x}w_h(t))_+ \\ = & -(\big(a(M_hc_{\ell,h}(t)) - a(M_h\tilde{c}_{\ell,h}(t))\big)D_{-x}c_{\ell,h}(t), D_{-x}w_h(t))_+ \\ & -\tilde{D}_{c,a}c_{\ell,h}(x_0,t)w_h(x_0,t) + \tilde{D}_{c,a}\tilde{c}_{\ell,h}(x_0,t)w_h(x_0,t),\ t \in (0,T], \\ w_{\ell,h}(0) & = c_{\ell,h}(0) - \tilde{c}_{\ell,h}(0), \end{array}\right. \tag{28}$$

where the finite difference operator $\tilde{D}_{c,a}$ is defined in (20).

As

$$\tilde{D}_{c,a}c_{\ell,h}(x_0,t) = \tfrac{1}{2}a'(\eta)h_1 D_c c_{\ell,h}(x_0,t)D_{-x}c_{\ell,h}(x_1,t) + a(M_hc_{\ell,h}(x_0,t))D_c c_{\ell,h}(x_0,t),$$

where η is in the interval defined by $M_hc_{\ell,h}(x_0,t)$ and $M_hc_{\ell,h}(x_1,t)$, and since $D_c c_{\ell,h}(x_0,t) = 0$, we obtain

$$\tilde{D}_{c,a}c_{\ell,h}(x_0,t) = 0. \tag{29}$$

Analogously, we also have

$$\tilde{D}_{c,a}\tilde{c}_{\ell,h}(x_0,t) = 0. \tag{30}$$

Using assumption H_1, it can be shown the next estimates

$$\begin{aligned} &\Big(\big(a(M_hc_{\ell,h}(t)) - a(M_h\tilde{c}_{\ell,h}(t))\big)D_{-x}c_{\ell,h}(t), D_{-x}w_h(t)\Big)_+ \\ &\quad \le M\sqrt{2}\|w_h(t)\|_h\|D_{-x}c_{\ell,h}(t)\|_\infty\|D_{-x}w_h(t)\|_+ \\ &\quad \le \frac{1}{2\epsilon^2}M^2\|w_h(t)\|_h^2\|D_{-x}c_{\ell,h}(t)\|_\infty^2 + \epsilon^2\|D_{-x}w_h(t)\|_+^2, \end{aligned} \tag{31}$$

where $\epsilon \neq 0$. In (31), the following notation is used

$$\|D_{-x}c_{\ell,h}(t)\|_\infty = \max_{i=1,\ldots,N}|D_{-x}c_{\ell,h}(x_i,t)|.$$

Then, considering (29), (30) and (31) in (28) and the assumption H_1, we obtain

$$\frac{d}{dt}\Big(\|w_h(t)\|_h^2 e^{-\frac{1}{\epsilon^2}M^2\int_0^t \|D_{-x}c_{\ell,h}(s)\|_\infty^2 ds} + 2(a_0-\epsilon^2)\int_0^t e^{-\frac{1}{\epsilon^2}M^2\int_0^s \|D_{-x}c_{\ell,h}(\mu)\|_\infty^2 d\mu} \|D_{-x}w_h(s)\|_+^2 ds\Big) \le 0, \tag{32}$$

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

$$\|w_{\ell,h}(t)\|_h^2 + 2(a_0-\epsilon^2)\int_0^t e^{\frac{1}{\epsilon^2}M^2\int_s^t \|D_{-x}c_{\ell,h}(\mu)\|_\infty^2 d\mu} \|D_{-x}w_h(s)\|_+^2 ds \le e^{\frac{1}{\epsilon^2}M^2\int_0^t \|D_{-x}c_{\ell,h}(s)\|_\infty^2 ds} \|w_h(0)\|_h^2, t \in [0,T], \tag{33}$$

provided that $c_{\ell,h}, \tilde{c}_{\ell,h} \in C^1[([0,T], V_{h,0}^*)$.

To conclude the stability we need to impose that $\int_0^t \|D_{-x}c_{\ell,h}(s)\|_\infty^2 ds$ is uniformly bounded in $h \in \Lambda$ and $t \in [0,T]$. Such assumption should be avoided and, as we will see in what follows, it is consequence of the convergence properties of the finite difference scheme (25).

Let $e_{\ell,h}(t) = R_h c_\ell(t) - c_{\ell,h}(t)$ be the semi-discrete error where R_h denotes the restriction operator. Let us suppose that the following estimate holds

$$\int_0^t \|D_{-x}e_{\ell,h}(s)\|_+^2 ds \le C\Big(h_{max}^4 + \|e_{\ell,h}(0)\|_h^2\Big), \tag{34}$$

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

If we assume that the sequence Λ of vectors $h = (h_1, h_2, \dots, h_N)$ is such that

$$\frac{h_{max}}{h_{min}} \le C \tag{35}$$

then

$$\begin{aligned}\int_0^t \|D_{-x}c_{\ell,h}(s)\|_\infty^2 ds &\leq 2\int_0^t \|D_{-x}e_{\ell,h}(s)\|_\infty^2 ds + 2\int_0^t \|D_{-x}R_hc_\ell(s)\|_\infty^2 \\ &\leq 2\frac{1}{h_{min}}\int_0^t \|D_{-x}e_{\ell,h}(s)\|_+^2 ds + 2\int_0^t \|D_{-x}R_hc_\ell(s)\|_\infty^2 ds \\ &\leq 2C\Big(h_{max}^3 + \frac{1}{h_{min}}\|e_{\ell,h}(0)\|_h^2\Big) + 2\|c_\ell\|^2_{L^2(0,T,C^1[0,R])}. \end{aligned} \tag{36}$$

If $\|e_{\ell,h}(0)\|_h = O(\sqrt{h_{max}})$, then, using (35),(36), we conclude

$$\int_0^t \|D_{-x}c_{\ell,h}(s)\|_\infty^2 ds \leq M_{\ell,d} \tag{37}$$

for some positive constant $M_{\ell,d}$, h and t independent, and provided that $c_\ell \in L^2(0,T,C^1[0,R])$.

The previous remarks show the importance of the estimate (34) in the stability analysis. In what follow we analyse the behaviour of the error $e_{\ell,h}(t)$. Let $T_h(t)$ be the truncation error induced by the spatial discretization that leads to the semi-discrete IBVP (25). These two errors are related by the equation

$$\begin{cases} \dfrac{de_{\ell,h}}{dt}(t) = D_x^*\Big(a(M_hc_\ell(t))D_{-x}R_hc_\ell(t)\Big) - D_x^*\Big(a(M_hc_{\ell,h}(t))D_{-x}c_{\ell,h}(t)\Big) \\ \quad +D_x^*\displaystyle\int_0^t q(t,s,M_hc_\ell(s),M_hc_\ell(t))D_{-x}R_hc_\ell(s)ds \\ \quad -D_x^*\displaystyle\int_0^t q(t,s,M_hc_{\ell,h}(s),M_hc_{\ell,h}(t))D_{-x}c_{\ell,h}(s)ds \\ \quad +T_h(t) \quad \text{in } \overline{\Omega}_h - \{x_N\}\times(0,T], \\ D_ce_{\ell,h}(x_0,t) = T_{h_0}(t),\ e_{\ell,h}(x_N,t) = 0,\ t\in(0,T], \\ e_{\ell,h}(0) \text{ given }, \end{cases} \tag{38}$$

where, to simplify, $M_hc_\ell(t) \equiv M_hR_hc_\ell(t)$. Such simplification will be also used in what follows.

Theorem 1. *Under the assumption H_1, H_2, and assuming that*

$$c_\ell \in C^1([0,T],C^0[0,R]) \cap C^0([0,T],C^3[0,R]) \cap L^2(0,T,C^4[0,R])$$

and

$$c_{\ell,h} \in C^1([0,T], V^*_{h,0}),$$

then for the semi-discretization error $e_{\ell,h}(t) = R_h c_\ell(t) - c_{\ell,h}(t)$*, where* $c_\ell(t)$ *and* $c_{\ell,h}(t)$ *are defined respectively by the IBVPs (24), (14), (17) and (25), there exist positive constants* $C_i(c_\ell)$*,* $i = 1, 2$*, that are* h *and* t *independent, such that holds the following*

$$\|e_{\ell,h}(t)\|_h^2 + \int_0^t \|D_{-x} e_{\ell,h}(s)\|_+^2 ds \le C_1(c_\ell) e^{C_2(c_\ell)t} \left(h_{max}^4 + \|e_{\ell,h}(0)\|_h^2\right), t \in [0,T], \tag{39}$$

Proof: From (38) we easily obtain

$$\begin{aligned}
\frac{1}{2}\frac{d}{dt}\|e_{\ell,h}(t)\|_h^2 &+ (a(M_h c_{\ell,h}(t)) D_{-x} e_{\ell,h}(t), D_{-x} e_{\ell,h}(t))_+ \\
&= -(\big(a(M_h c_{\ell,h}(t)) - a(M_h c_{\ell,h}(t))\big) D_{-x} R_h c_\ell(t), D_{-x} e_{\ell,h}(t))_+ \\
&- \int_0^t \big((q(t,s,M_h c_\ell(s), M_h c_\ell(t)) \\
&\qquad -q(t,s,M_h c_{\ell,h}(s), M_h c_\ell(t))) D_{-x} R_h c_\ell(s) ds, D_{-x} e_{\ell,h}(t)\big)_+ \\
&- \int_0^t \big((q(t,s,M_h c_{\ell,h}(s), M_h c_\ell(t)) \\
&\qquad -q(t,s,M_h c_{\ell,h}(s), M_h c_{\ell,h}(t))) D_{-x} R_h c_\ell(s) ds, D_{-x} e_{\ell,h}(t)\big)_+ \\
&- \int_0^t \big(q(t,s,M_h c_{\ell,h}(s), M_h c_{\ell,h}(t)) D_{-x} e_{\ell,h}(s) ds, D_{-x} e_{\ell,h}(t)\big)_+ \\
&+ \tilde{D}_{c,a} c_{\ell,h}(x_0,t) e_{\ell,h}(x_0,t) - \tilde{D}_{c,a} R_h c_\ell(x_0,t) e_{\ell,h}(x_0,t) \\
&- \int_0^t \tilde{D}_{c,q,t} R_h c_\ell(x_0,s) ds\, e_{\ell,h}(x_0,t) + \int_0^t \tilde{D}_{c,q,t} c_{\ell,h}(x_0,s) ds\, e_{\ell,h}(x_0,t) \\
&\qquad +(T_h(t), e_{\ell,h})_h,\ t \in (0,T],
\end{aligned} \tag{40}$$

where $\tilde{D}_{c,a}$ is defined by (20) and

$$\begin{aligned}
\tilde{D}_{c,q,t} v_h(x_0,s) = \tfrac{1}{2}\Big(&q(t,s,M_h v_h(x_1,s), M_h v_h(x_1,t)) D_{-x} v_h(x_1,s) \\
&+q(t,s,M_h v_h(x_0,s), M_h v_h(x_0,t)) D_{-x} v_h(x_0,s)\Big).
\end{aligned}$$

Let $\hat{T}_h(t)$ be given by the terms involving the boundary point x_0

$$\begin{aligned}
\hat{T}_h(t) = \ &\tilde{D}_{c,a} c_{\ell,h}(x_0,t) - \tilde{D}_{c,a} R_h c_\ell(x_0,t) \\
&- \int_0^t \tilde{D}_{c,q,t} R_h c_\ell(x_0,s) ds \ + \int_0^t \tilde{D}_{c,q,t} c_{\ell,h}(x_0,s) ds.
\end{aligned}$$

In what follow we obtain an upper bound for $\hat{T}_h(t)$. As in (30) we have

$$\tilde{D}_{c,a} c_{\ell,h}(x_0, t) = 0.$$

Analogously, as $\dfrac{\partial c_\ell}{\partial x}(0,t) = 0$, for $\tilde{D}_{c,a} R_h c_\ell(x_0, t)$ we obtain

$$|\tilde{D}_{c,a} R_h c_\ell(x_0, t)| \leq M h_1^2 \Big(\frac{1}{2} \|c_\ell(t)\|_{C^2[0,R]} + \frac{1}{6} \|c_\ell(t)\|_{C^3[0,R]} \Big).$$

As $D_c c_{\ell,h}(x_0, s) = 0$, for the integral term we conclude

$$\begin{aligned} \int_0^t \tilde{D}_{c,q,t} c_{\ell,h}(x_0, s) ds &= \frac{1}{2} \int_0^t \Big(q(t, s, M_h c_{\ell,h}(x_1, s), M_h c_{\ell,h}(x_1, t)) \\ &\qquad - q(t, s, M_h c_{\ell,h}(x_0, s), M_h c_{\ell,h}(x_0, t)) \Big) D_{-x} c_{\ell,h}(x_1, s) ds \\ &\quad + \int_0^t q(t, s, M_h c_{\ell,h}(x_0, s), M_h c_{\ell,h}(x_0, t)) D_c c_{\ell,h}(x_0, s) ds \\ &= 0. \end{aligned}$$

Moreover, it can be shown that

$$\begin{aligned} \Big| \int_0^t \tilde{D}_{c,q,t} R_h c_\ell(x_0, s) ds \Big| &\leq M \Big(\int_0^t h_1^2 \frac{1}{2} \Big(\| \frac{\partial^2 c_\ell}{\partial x^2}(s) \|_\infty + \| \frac{\partial^2 c_\ell}{\partial x^2}(t) \|_\infty \Big) |D_{-x} R_h c_\ell(x_1, s)| \\ &\qquad + |D_c R_h c_\ell(x_0, s)| \Big) ds \\ &\leq h_1^2 M \Big(\tfrac{1}{2} \|c_\ell\|^2_{L^2(0,t,C^2[0,R])} + \tfrac{1}{2} \sqrt{T} \|c_\ell(t)\|_{C^2[0,R]} \|c_\ell\|_{L^2(0,t,C^1[0,R])} \\ &\qquad + \frac{1}{6} \sqrt{T} \|c_\ell\|_{L^2(0,t,C^3[0,R])} \Big) \\ &\leq h_1^2 \frac{1}{2} M \|c_\ell\|_{L^2(0,t,C^3[0,R])} \Big(\|c_\ell\|_{L^2(0,t,C^2[0,R])} + \sqrt{T} \big(\frac{1}{3} + \|c_\ell(t)\|_{C^2[0,R]} \big) \Big). \end{aligned}$$

Consequently, for $\hat{T}_h()$ we obtain

$$\begin{aligned} |\hat{T}_h(t)| &\leq h_1^2 \tfrac{1}{2} M \Big(\|c_\ell\|_{L^2(0,t,C^3[0,R])} \Big(\|c_\ell\|_{L^2(0,t,C^2[0,R])} + \sqrt{T} \big(\tfrac{1}{3} + \|c_\ell(t)\|_{C^2[0,R]} \big) \Big) \\ &\qquad + \|c_\ell(t)\|_{C^3[0,R]} \Big(\|c_\ell(t)\|_{C^2[0,R]} + \frac{1}{3} \Big) \Big) := h_1^2 \hat{T}_b(t). \end{aligned} \tag{41}$$

Considering now the assumptions H_1 and H_2 in (40) we get

$$
\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\|e_{\ell,h}(t)\|_h^2 + a_0\|D_{-x}e_{\ell,h}(t)\|_+^2 \\
&\quad\leq \sqrt{2}M\|D_{-x}R_hc_\ell(t)\|_\infty\|e_{\ell,h}(t)\|_h\|D_{-x}e_{\ell,h}(t)\|_+ \\
&\quad+\sqrt{2}M\int_0^t(\|e_{\ell,h}(s)\|_h + \|e_{\ell,h}(t)\|_h)\|D_{-x}R_hc_\ell(s)\|_\infty ds\|D_{-x}e_{\ell,h}(t)\| \\
&\quad+M\int_0^t\|D_{-x}e_{\ell,h}(s)\|_+ds\|D_{-x}e_{\ell,h}(t)\|_+ \\
&\quad+|\hat{T}_h(t)||e_{\ell,h}(x_0,t)| + (T_h(t), e_{\ell,h})_h,\ t\in(0,T],
\end{aligned}
\tag{42}
$$

We estimate now the first three terms of right hand side of (42). We have successively

$$
\begin{aligned}
&\sqrt{2}M\|D_{-x}R_hc_\ell(t)\|_\infty\|e_{\ell,h}(t)\|_h\|D_{-x}e_{\ell,h}(t)\|_+ \\
&\qquad\leq \tfrac{1}{2\epsilon^2}M^2\|c_\ell(t)\|^2_{C^1[0,R]}\|e_{\ell,h}(t)\|_h^2 + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2,
\end{aligned}
$$

$$
\begin{aligned}
&\sqrt{2}M\int_0^t(\|e_{\ell,h}(s)\|_h + \|e_{\ell,h}(t)\|_h)\|D_{-x}R_hc_\ell(s)\|_\infty ds\|D_{-x}e_{\ell,h}(t)\|_+ \\
&\leq \frac{1}{\epsilon^2}(MT)^2\Big(\|c_\ell\|^2_{C^0([0,T],C^1[0,R])}\int_0^t\|e_{\ell,h}(s)\|_h^2ds + \|c_\ell\|^2_{L^2(0,T,C^1[0,R])}\|e_{\ell,h}(t)\|_h^2\Big) \\
&\qquad +2\epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2 \\
&\leq \frac{1}{\epsilon^2}(MT)^2\Big(R^2\|c_\ell\|^2_{C^0([0,T],C^1[0,R])}\int_0^t\|D_{-x}e_{\ell,h}(s)\|_+^2ds + \|c\|^2_{L^2(0,T,C^1[0,R])}\|e_{\ell,h}(t)\|_h^2\Big) \\
&\qquad +2\epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2
\end{aligned}
$$

and

$$
\begin{aligned}
&M\int_0^t\|D_{-x}R_he_{\ell,h}(s)\|_+ds\|D_{-x}e_{\ell,h}(t)\|_+ \\
&\leq \frac{1}{4\epsilon^2}(MT)^2\int_0^t\|D_{-x}R_he_{\ell,h}(s)\|_+^2ds + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2.
\end{aligned}
$$

Taking the last upper bounds in (42) we conclude

$$\begin{cases} \frac{1}{2}\frac{d}{dt}\|e_{\ell,h}(t)\|_h^2 + (a_0 - 4\epsilon^2)\|D_{-x}e_{\ell,h}(t)\|_+^2 \\ \qquad \le \frac{1}{2\epsilon^2}M^2\Big(\|c_\ell(t)\|^2_{C^1[0,R]} + 2T^2\|c_\ell\|^2_{L^2(0,T,C^1[0,R])}\Big)\|e_{\ell,h}(t)\|_h^2 \\ \qquad +\frac{1}{4\epsilon^2}(MT)^2\Big(1+4R^2\|c_\ell\|^2_{C^0([0,T],C^1[0,R])}\Big)\int_0^t \|D_{-x}e_{\ell,h}(s)\|_+^2 ds \\ \qquad +|\hat{T}_h(t)||e_{\ell,h}(x_0,t)| + (T_h(t), e_{\ell,h})_h,\ t\in(0,T], \\ \\ e_{\ell,h}(0) = R_h c_\ell(0) - c_{\ell,h}(0). \end{cases} \tag{43}$$

We establish in what follows an an estimate for $|\hat{T}_h(t)||e_{\ell,h}(x_0,t)|$ and $(T_h(t), e_{\ell,h})_h$. We recall that, from Proposition 3 and (41), we deduce

$$\begin{aligned} |\hat{T}_h(t)||e_{\ell,h}(x_0,t)| &\le \sqrt{R}|\hat{T}_h(t)|\|D_{-x}e_{\ell,h}(t)\|_+ \\ &\le \frac{1}{4\epsilon^2}R|\hat{T}_h(t)|^2 + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2 \\ &\le \frac{1}{4\epsilon^2}Rh_1^4\hat{T}_b(t)^2 + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2. \end{aligned} \tag{44}$$

We establish in what follows an estimate for $(T_h(t), e_{\ell,h})_h$ considering, to simplify, the coefficient function a constant (for non constant a the differences are minor). To obtain such an estimate we observe that $T_h(t)$ has the representation

$$T_h(x_i,t) = T_h^{(1)}(x_i,t) + T_h^{(2)}(x_i,t),\ i = 0,\dots,N-1,$$

where

$$T_h^{(1)}(x_i,t) = \frac{1}{3}(h_{i+1}-h_i)\frac{\partial^3 c_\ell}{\partial x^3}(x_i,t),$$

and

$$|T_h^{(2)}(x_i,t)| \le \frac{1}{12}h_{max}^2\|c_\ell(t)\|_{C^4[0,R]}.$$

For the term $(T_h^{(2)}(t), e_{\ell,h})_h$ we easily get

$$\begin{aligned} (T_h^{(2)}(t), e_{\ell,h})_h &\le \frac{1}{4\epsilon^2}\|T_h^{(2)}(t)\|_h^2 + \epsilon^2\|e_{\ell,h}(t)\|_h^2 \\ &\le \frac{1}{4\epsilon^2}\frac{1}{144}R\|c_\ell(t)\|^2_{C^4[0,R]}h_{max}^4 + \epsilon^2\|e_{\ell,h}(t)\|_h^2. \end{aligned} \tag{45}$$

To obtain an estimate for $(T_h^{(1)}(t), e_{\ell,h})_h$, we remark that using summation by parts, it can be shown the following

$$\begin{aligned}
(T_h^{(1)}(t), e_{\ell,h})_h &= \frac{h_1}{2} T_h^{(1)}(x_0,t)e_{\ell,h}(x_0,t) + \frac{1}{6}\sum_{i=1}^{N-1}\big(h_{i+1}^2 - h_i^2\big)\frac{\partial^3 c_\ell}{\partial x^3}(x_i,t)e_{\ell,h}(x_i,t) \\
&= \frac{h_1}{2} T_h^{(1)}(x_0,t)e_{\ell,h}(x_0,t) - \frac{1}{6}h_1^2\frac{\partial^3 c_\ell}{\partial x^3}(x_0,t)e_{\ell,h}(x_0,t) \\
&-\frac{1}{6}\sum_{i=1}^{N} h_i^2\Big(\frac{\partial^3 c_\ell}{\partial x^3}(x_i,t)e_{\ell,h}(x_i,t) - \frac{\partial^3 c_\ell}{\partial x^3}(x_{i-1},t)e_{\ell,h}(x_{i-1},t)\Big) \\
&= \frac{h_1}{2} T_h^{(1)}(x_0,t)e_{\ell,h}(x_0,t) - \frac{1}{6}h_1^2\frac{\partial^3 c_\ell}{\partial x^3}(x_0,t)e_{\ell,h}(x_0,t) \\
&-\frac{1}{6}\sum_{i=1}^{N} h_i^2 \int_{x_{i-1}}^{x_i}\frac{\partial^4 c_\ell}{\partial x^4}(x,t)dx e_{\ell,h}(x_{i-1},t) \\
&-\frac{1}{6}\sum_{i=1}^{N} h_i^3 \frac{\partial^3 c_\ell}{\partial x^3}(x_i,t)D_{-x}e_{\ell,h}(x_i,t) \\
&= \sum_{j=1}^{3} T_h^{(1,j)}(t),
\end{aligned} \tag{46}$$

where

$$\begin{aligned}
T_h^{(1,1)}(t) &= \Big(\frac{h_1}{2}T_h^{(1)}(x_0,t) - \frac{1}{6}h_1^2\frac{\partial^3 c_\ell}{\partial x^3}(x_0,t)\Big)e_{\ell,h}(x_0,t) \\
&= h_1^2\Big(\frac{1}{12}\big(\frac{\partial^3 c_\ell}{\partial x^3}(\xi_1,t) - \frac{\partial^3 c_\ell}{\partial x^3}(\xi_2,t)\big) - \frac{1}{6}\frac{\partial^3 c_\ell}{\partial x^3}(x_0,t)\Big)e_{\ell,h}(x_0,t),
\end{aligned}$$

and $\xi_1 \in [0, x_1]$, $\xi_2 \in [x_{-1}, 0]$,

$$T_h^{(1,2)}(t) = -\frac{1}{6}\sum_{i=1}^{N} h_i^2 \int_{x_{i-1}}^{x_i}\frac{\partial^4 c_\ell}{\partial x^4}(x,t)dx e_{\ell,h}(x_{i-1},t)$$

and

$$T_h^{(1,3)}(t) = -\frac{1}{6}\sum_{i=1}^{N} h_i^3 \frac{\partial^3 c_\ell}{\partial x^3}(x_i,t)D_{-x}e_{\ell,h}(x_i,t).$$

For $T_h^{(1,2)}(t)$ and $T_h^{(1,3)}(t)$ we have, respectively,

$$|T_h^{(1,2)}(t)| \le \frac{1}{4\epsilon^2}\frac{1}{36}R\|c_\ell(t)\|^2_{C^4[0,R]}h_{max}^4 + 2\epsilon^2\|e_{\ell,h}(t)\|_h^2, \tag{47}$$

and

$$|T_h^{(1,3)}(t)| \leq \frac{1}{4\epsilon^2}\frac{1}{36}R\|c_\ell(t)\|^2_{C^3[0,R]}h^4_{max} + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|^2_+. \tag{48}$$

For $T_h^{(1,1)}(t)$, applying Proposition 3, we obtain

$$\begin{aligned} |T_h^{(1,1)}(t)| &\leq \frac{1}{3}h_1^2\|c_\ell(t)\|_{C^3[0,R]}|e_{\ell,h}(x_0,t)| \\ &\leq \frac{1}{36\epsilon^2}Rh_1^4\|c_\ell(t)\|^2_{C^3[0,R]} + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|^2_+. \end{aligned} \tag{49}$$

Finally, considering in (46) the upper bounds (47)-(49) we get for $(T_h^{(1)}(t), e_{\ell,h})_h$ the following upper bound

$$\begin{aligned} (T_h^{(1)}(t), e_{\ell,h})_h &\leq \frac{3}{4\epsilon^2}\frac{1}{36}Rh^4_{max}\|c_\ell(t)\|^2_{C^4[0,R]} \\ &\quad +3\epsilon^2\|e_{\ell,h}(t)\|^2_h + 2\epsilon^2\|D_{-x}e_{\ell,h}(t)\|^2_+. \end{aligned} \tag{50}$$

To obtain an upper bound for $(T_h(t), e_{\ell,h}(t))_h$ we observe that the error bounds (45) and (50) lead to

$$\begin{aligned} (T_h(t), e_{\ell,h}(t))_h &\leq \frac{13}{4\epsilon^2 144}Rh^4_{max}\|c_\ell(t)\|^2_{C^4[0,R]} \\ &\quad +4\epsilon^2\|e_{\ell,h}(t)\|^2_h + 2\epsilon^2\|D_{-x}e_{\ell,h}(t)\|^2_+. \end{aligned} \tag{51}$$

Taking into account in (43) the upper bounds (44) and (51), we get

$$\begin{aligned} &\frac{d}{dt}\|e_{\ell,h}(t)\|^2_h + 2(a_0 - 7\epsilon^2)\|D_{-x}e_{\ell,h}(t)\|^2 \\ &\quad \leq \Big(\frac{1}{\epsilon^2}M^2\Big(\|c_\ell(t)\|^2_{C^1[0,R]} + 2T^2\|c_\ell\|^2_{L^2(0,T,C^1[0,R])}\Big) + 8\epsilon^2\Big)\|e_{\ell,h}(t)\|^2_h \\ &\quad +\frac{1}{2\epsilon^2}(MT)^2\Big(1 + 4R^2\|c_\ell\|^2_{[0,T],C^1[0,R])}\Big)\int_0^t \|D_{-x}e_{\ell,h}(s)\|^2_+ ds \\ &\quad +\frac{1}{\epsilon^2}Rh^4_{max}\Big(\frac{13}{288}\|c_\ell(t)\|^2_{C^4[0,R]} + \frac{1}{2}\hat{T}_b(t)^2\Big),\ t \in (0,T], \end{aligned} \tag{52}$$

with $e_{\ell,h}(0)$ given. Consequently,

$$\begin{aligned}
&\|e_{\ell,h}(t)\|_h^2 + 2(a_0 - 7\epsilon^2)\int_0^t \|D_{-x}e_{\ell,h}(s)\|^2 ds\\
&\quad\le \Big(\frac{1}{\epsilon^2}M^2\Big(\|c_\ell\|^2_{C^0([0,T],C^1[0,R])} + 2T^2\|c_\ell\|^2_{L^2(0,T,C^1[0,R])}\Big) + 8\epsilon^2\Big)\int_0^t \|e_{\ell,h}(s)\|_h^2 ds\\
&\quad+\frac{1}{2\epsilon^2}(MT)^2\Big(1+4R^2\|c_\ell\|^2_{C^0([0,T],C^1[0,R])}\Big)\int_0^t\int_0^s \|D_{-x}e_{\ell,h}(\mu)\|^2 d\mu\, ds\\
&\quad+\frac{1}{\epsilon^2}Rh_{max}^4\Big(\|c_\ell\|^2_{L^2(0,T,C^4[0,R])} + \frac{1}{2}\hat{T}_b(t)^2\Big) + \|e_{\ell,h}(0)\|_h^2,\ t\in(0,T].
\end{aligned} \tag{53}$$

Fixing ϵ^2 by

$$a_0 - 7\epsilon^2 > 0 \tag{54}$$

and applying Gronwall lemma we conclude the existence of positive constants $C_i(c_\ell)$ depending on c_ℓ and h and t independent such that (39) holds.

■

Theorem 1 allows us to conclude that there exists a positive constant C, h and t independent, such that

$$\|e_{\ell,h}(t)\|_h^2 + \int_0^t \|D_{-x}e_{\ell,h}(s)\|_+^2 ds \le C\Big(h_{max}^4\|c_\ell\|^2_{L^2(0,T,C^4[0,R])} + \|e_{\ell,h}(0)\|_h^2\Big), t\in[0,T],$$

for $h\in\Lambda$. This fact implies that there exists a positive constant C, h and t independent, such that

$$\begin{aligned}
&\|e_{\ell,h}(t)\|_h^2 \le C\Big(h_{max}^4 + \|e_{\ell,h}(0)\|_h^2\Big),\\
&\int_0^t \|D_{-x}e_{\ell,h}(s)\|_+^2 ds \le C\Big(h_{max}^4 + \|e_{\ell,h}(0)\|_h^2\Big),
\end{aligned} \tag{55}$$

for $t\in[0,T], h\in\Lambda$. If $c_{\ell,h}(0) = R_h c_\ell(0)$, then Proposition 4 leads to the following upper bounds

$$\int_0^t \|e_{\ell,h}(s)\|_\infty^2 ds \le Ch_{max}^4\|c\|^2_{L^2(0,T,C^4[0,R])}, t\in[0,T], \tag{56}$$

and

$$\int_0^t \|c_{\ell,h}(t)\|_\infty^2 ds \le C, t\in[0,T], h\in\Lambda, \tag{57}$$

We have the following corollaries:

Corollary 1. *Under the assumptions of Theorem 1, if* $c_{\ell,h}(0) = R_h c_\ell(0)$ *and the sequence of vectors* Λ *is such that (35) holds, then there exist positive constants* C*,* h *and* t *independent, such that*

$$\int_0^t \|D_{-x}c_{\ell,h}(s)\|_\infty^2 ds \le C,\ t \in [0,T], h \in \Lambda. \tag{58}$$

■

Corollary 2. *Let* $c_{\ell,h}, \tilde{c}_{\ell,h} \in C^1([0,T], V_{h,0}^*)$ *be solutions of the IBVP (25) with initial conditions* $c_{\ell,h}(0)$ *and* $\tilde{c}_{\ell,h}(0)$*, respectively, such that* $|R_h c_\ell(0) - c_{\ell,h}(0)| \le C\sqrt{h_{max}}$ *and* $|R_h c_\ell(0) - \tilde{c}_{\ell,h}(0)| \le C\sqrt{h_{max}}$*. Then for* $w_h(t) = c_{\ell,h}(t) - \tilde{c}_{\ell,h}(t)$ *we conclude*

$$\|w_h(t)\|_h^2 + \int_0^t \|D_{-x}w_h(s)\|_+^2 ds \le C\|w_h(0)\|_h^2,\ t \in [0,T]. \tag{59}$$

■

The last result means that we have stability provided that the initial conditions are in $B_\rho(R_h c_\ell(0))$, for $\rho \le C\sqrt{h_{max}}$.

4. Dissolved and solid drug concentrations: stability and convergence

In what follows we establish an upper bound for the semi-discrete approximations $c_{d,h}(t)$ and $c_{s,h}(t)$ for the dissolved and solid drug concentrations $c_d(t)$ and $c_s(t)$, respectively, as well as we analyse their convergence properties. In order to do that, we need to assume that the partial derivatives of f are bounded. To guarantee this requirement we assume that f defined in (5) is replaced by f_{ap} that is obtained replacing H by some of its regularization H_k as for instance

$$H(z) \simeq \frac{1}{1+e^{-2Kz}} := H_k(z).$$

Other regularization possibilities for $H(z)$ can be considered. We will impose that such regularization satisfies the following assumptions

R$_1$: $|H_k| \le M_r$ in $\mathbb{R}$,
R$_2$: $|H_k'| \le M_r$ in $\mathbb{R}$,

where M_r is a positive constant.

In the stability analysis for the dissolved and solid drug concentrations, the estimate (57) has an important role as we can see in what follows.

4.1. Stability. We start by establishing the uniform boundness of

$$\|c_{d,h}(t)\|_h^2 + \|c_{s,h}(t)\|_h^2 + \int_0^t \|D_{-x}c_{d,h}(s)\|_+^2 ds,$$

in $t \in [0,T]$ and $h \in \Lambda$, provided that $c_{d,h}(0), c_{s,h}(0)$ are uniformly bounded in $h \in \Lambda$, where $c_{d,h}(t)$ and $c_{s,h}(t)$ are solutions of the following initial value problems

$$\begin{cases} \dfrac{dc_{d,h}}{dt} = D_x^*(d(M_h c_{\ell,h}(t))D_{-x}c_{d,h}(t)) + f_{ap}(c_{s,h}(t), c_{d,h}(t), c_{\ell,h}(t)) \\ \hfill \text{in } \overline{\Omega}_h - \{x_N\} \times (0,T], \\ D_c c_{d,h}(x_0,t) = 0,\ c_{d,h}(x_N,t) = 0,\ t \in (0,T], \\ c_{d,h}(0) \ \text{given}, \end{cases} \tag{60}$$

and

$$\begin{cases} \dfrac{dc_{s,h}}{dt} = -f_{ap}(c_{s,h}(t), c_{d,h}(t), c_{\ell,h}(t)) \text{ in } \overline{\Omega}_h - \{x_N\} \times (0,T], \\ c_{s,h}(0) \text{ given.} \end{cases} \tag{61}$$

In the IBVP (60), the generic function $d : \mathbb{R} \to \mathbb{R}$ replaces the diffusion coefficient D_d and satisfies the following assumptions

D_1: $0 < d_0 \le d \le M_d$ in $\mathbb{R}$,
D_2: $|d'| \le M_d$ in $\mathbb{R}$,

where d_0 and M_d are positive constants. Since, from Proposition 3, we have

$$\int_0^t \|c_{d,h}(s)\|_\infty^2 ds \le R \int_0^t \|D_{-x}c_{d,h}(s)\|_+^2 ds,$$

thus establishing the uniform boundness of $\int_0^t \|D_{-x}c_{d,h}(s)\|_+^2 ds$, in $h \in \Lambda$ and $t \in [0,T]$, we can conclude, as done in Corollary 3, the uniform boundness of $\int_0^t \|c_{d,h}(s)\|_\infty^2 ds$. This result will be used in the proof of the stability of the initial value problems (60) and (61).

Theorem 2. *Let $c_{d,h} \in C^1([0,T], V_{h,0}^*)$ and $c_{s,h}$ in $C^1([0,T], W_h)$ be solutions of the IBVPs (60) and (61), respectively. If d satisfies D_1 and H_k satisfies*

R_1, then, under the assumptions of Theorem 1, we have

$$\|c_{d,h}(t)\|_h^2+\|c_{s,h}(t)\|_h^2+2d_0\int_0^t e^{\left(2+\frac{3}{c_{sol}}\right)M_rk_d\int_s^t\|c_{\ell,h}(\mu)\|_\infty d\mu}\|D_{-x}c_{d,h}(s)\|_+^2ds$$
$$\leq \Big(\|c_{d,h}(0)\|_h^2+\|c_{s,h}(0)\|_h^2\Big)e^{\left(2\frac{3}{c_{sol}}\right)M_rk_d\int_s^t\|c_{\ell,h}(\mu)\|_\infty d\mu}$$
$$+M_rk_d\int_0^t e^{\left(2+\frac{3}{c_{sol}}\right)M_rk_d\int_s^t\|c_{\ell,h}(\mu)\|_\infty d\mu}\|c_{\ell,h}(s)\|_h^2ds, \tag{62}$$

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

Proof: From (60) (61), using the assumption D_1, and Proposition 2, we obtain

$$\frac{1}{2}\frac{d}{dt}\Big(\|c_{d,h}(t)\|_h^2+\|c_{s,h}(t)\|_h^2\Big)+d_0\|D_{-x}c_{d,h}(t)\|_+^2$$
$$\leq (f_{ap}(c_{s,h}(t),c_{d,h}(t),c_{\ell,h}(t)),c_{d,h}(t)-c_{s,h}(t))_h \tag{63}$$
$$+\hat{D}_{c,d}c_{d,h}(x_0,t)c_{d,h}(x_0,t), t\in(0,T],$$

where the finite difference operator $\hat{D}_{c,d}$ is defined by

$$\hat{D}_{c,d}v_h(x_0)=\frac{1}{2}\Big(d(M_hc_{\ell,h}(x_1,t))D_{-x}v_h(x_1)+d(M_hc_{\ell,h}(x_0,t))D_{-x}v_h(x_0)\Big),$$

for $v_h\in V_{h,0}^*$. As $D_cc_{d,h}(x_0,t)=0$, it can be shown that

$$\hat{D}_{c,d}c_{d,h}(x_0,t)=0. \tag{64}$$

Considering the assumption R_1 in the first term of the right hand side of (63) we obtain successively that

$$|(f_{ap}(c_{s,h}(t),c_{d,h}(t),c_{\ell,h}(t)),c_{d,h}(t)-c_{s,h}(t))_h|$$
$$\leq M_rk_d\Big(\|c_{\ell,h}(t)\|_h+\frac{1}{c_{sol}}\|c_{\ell,h}(t)\|_\infty\|c_{d,h}(t)\|_h\Big)\Big(\|c_{d,h}(t)\|_h+\|c_{s,h}(t)\|_h\Big)$$
$$\leq\frac{M_rk_d}{2}\left(2+3\frac{\|c_{\ell,h}(t)\|_\infty}{c_{sol}}\right)\left(\|c_{d,h}(t)\|_h^2+\|c_{s,h}(t)\|_h^2\right)+\frac{1}{2}M_rk_d\|c_{\ell,h}(t)\|_h^2. \tag{65}$$

Taking (64), (65) in (63) we get

$$\frac{d}{dt}\Big(\|c_{d,h}(t)\|_h^2 + \|c_{s,h}(t)\|_h^2\Big) + 2d_0\|D_{-x}c_{d,h}(t)\|_+^2$$
$$\leq M_r k_d \left(2 + 3\frac{\|c_{\ell,h}(t)\|_\infty}{c_{sol}}\right)\left(\|c_{d,h}(t)\|_h^2 + \|c_{s,h}(t)\|_h^2\right) + M_r k_d \|c_{\ell,h}(t)\|_h^2,\ t \in (0,T], \tag{66}$$

and consequently

$$\frac{d}{dt}\Big(e^{-\left(2+\frac{3}{c_{sol}}\right)M_r k_d \int_0^t \|c_{\ell,h}(s)\|_\infty ds}\Big(\|c_{d,h}(t)\|_h^2 + \|c_{s,h}(t)\|_h^2\Big)$$
$$+ 2d_0\int_0^t e^{-\left(2+\frac{3}{c_{sol}}\right)M_r k_d \int_0^s \|c_{\ell,h}(\mu)\|_\infty d\mu}\|D_{-x}c_{d,h}(s)\|_+^2 ds$$
$$- M_r k_d \int_0^t e^{-\left(2+\frac{3}{c_{sol}}\right)M_r k_d \int_0^s \|c_{\ell,h}(\mu)\|_\infty d\mu}\|c_{\ell,h}(s)\|_h^2 ds\Big) \leq 0, \tag{67}$$

for $t \in (0,T]$, that leads to (62).

■

Corollary 3. *Under the assumptions of Theorems 1 and 2, if* $\|c_{d,h}(0)\|_h^2 + \|c_{s,h}(0)\|_h^2, h \in \Lambda$, *is bounded, and* $|R_h c_\ell(0) - c_{\ell,h}(0)| \leq C\sqrt{h_{max}}$, *then there exists a positive constant* C, h *and* t *independent, such that*

$$\|c_{d,h}(t)\|_h^2 + \|c_{s,h}(t)\|_h^2 + \int_0^t \|D_{-x}c_{d,h}(s)\|_+^2 ds \leq C, t \in [0,T], h \in \Lambda, \tag{68}$$

and

$$\int_0^t \|c_{d,h}(s)\|_\infty^2 ds \leq C, t \in [0,T], h \in \Lambda, \tag{69}$$

$$\|c_{s,h}(t)\|_h^2 \leq C, t \in [0,T], h \in \Lambda. \tag{70}$$

■

Let $c_{\ell,h}, \tilde{c}_{\ell,h} \in C^1([0,T], V_{h,0}^*)$ be solutions of the IBVP (25) with initial conditions $c_{\ell,h}(0), \tilde{c}_{\ell,h}(0)$, respectively. Let $c_{d,h}, \tilde{c}_{d,h} \in C^1([0,T], V_{h,0}^*)$ and $c_{s,h}, \tilde{c}_{s,h} \in C^1([0,T], W_h)$ be solutions of the IBVP (60) and (61) with initial conditions $c_{d,h}(0), \tilde{c}_{d,h}(0)$ and $c_{s,h}(0), \tilde{c}_{s,h}(0)$ respectively.

If $|R_h c_\ell(0) - c_{\ell,h}(0)| \leq C\sqrt{h_{max}}$ and $|R_h c_\ell(0) - \tilde{c}_{\ell,h}(0)| \leq C\sqrt{h_{max}}$, from Corollary 2 concluded (59) and consequently, using Proposition 3 for $w_{\ell,h} = c_{\ell,h} - \tilde{c}_{\ell,h}$, we have

$$\|w_{\ell,h}(t)\|_h^2 \leq C\|w_{\ell,h}(0)\|_h^2, \int_0^t \|w_{\ell,h}(s)\|_\infty^2 ds \leq C\|w_{\ell,h}(0)\|_h^2,\ t \in [0,T]. \quad (71)$$

Let $w_{d,h} = c_{d,h} - \tilde{c}_{d,h}$ and $w_{s,h} = c_{s,h} - \tilde{c}_{s,h}$. From (60) and (61) we get

$$\begin{aligned}
&\frac{1}{2}\frac{d}{dt}\Big(\|w_{d,h}(t)\|_h^2 + \|w_{s,h}(t)\|_h^2\Big) + d_0\|D_{-x}w_{d,h}(t)\|_+^2 \\
&\leq M_d\|w_{\ell,h}(t)\|_\infty\|D_{-x}c_{d,h}(t)\|_+\|D_{-x}w_{d,h}(t)\|_+ \\
&+ (f_{ap}(c_{s,h}(t), c_{d,h}(t), c_{\ell,h}(t)) - f_{ap}(\tilde{c}_{s,h}(t), \tilde{c}_{d,h}(t), \tilde{c}_{\ell,h}(t)), w_{d,h}(t) - w_{s,h}(t))_h \\
&+ (\hat{D}_{c,d}c_{d,h}(x_0,t) - \hat{D}_{c,d}\tilde{c}_{d,h}(x_0,t))w_{d,h}(x_0,t).
\end{aligned} \quad (72)$$

As before, we have $\hat{D}_{c,d}c_{d,h}(x_0,t) = \hat{D}_{c,d}\tilde{c}_{d,h}(x_0,t) = 0$. Moreover, it can be shown using the assumption R_2 that

$$\begin{aligned}
&(f_{ap}(c_{s,h}(t), c_{d,h}(t), c_{\ell,h}(t)) - f_{ap}(\tilde{c}_{s,h}(t), \tilde{c}_{d,h}(t), \tilde{c}_{\ell,h}(t)), w_{d,h}(t) - w_{s,h}(t))_h \\
&\leq 2k_dM_r\Bigg(\big(1 + \frac{1}{c_{sol}}\|c_{d,h}(t)\|_\infty\big)\Big(\frac{1}{2}\big(1 + \frac{1}{c_{sol}}\|c_{d,h}(t)\|_\infty\big) + \|c_{\ell,h}(t)\|_\infty\Big) \\
&\qquad + \frac{1}{c_{sol}}\|\tilde{c}_{\ell,h}(t)\|_\infty\Bigg)\big(\|w_{d,h}(t)\|_h^2 + \|w_{s,h}(t)\|_h^2\big) + \frac{1}{2}k_dM_r\|w_{\ell,h}(t)\|_h^2 \\
&:= g(c_{d,h}(t), \tilde{c}_{d,h}(t), c_{\ell,h}(t))\big(\|w_{d,h}(t)\|_h^2 + \|w_{s,h}(t)\|_h^2\big) + \frac{1}{2}k_dM_r\|w_{\ell,h}(t)\|_h^2.
\end{aligned} \quad (73)$$

Then, considering the upper bound (73) in (72) we conclude

$$\begin{aligned}
&\frac{d}{dt}\left(\sum_{i=d,s}\|w_{i,h}(t)\|_h^2\right) + 2(d_0 - \epsilon^2)\|D_{-x}w_{d,h}(t)\|_+^2 \\
&\qquad -2g(c_{d,h}(t), \tilde{c}_{d,h}(t), c_{\ell,h}(t))\sum_{i=d,s}\|w_{i,h}(t)\|_h^2 \qquad (74)\\
&\leq \frac{1}{2\epsilon^2}M_d^2\|w_{\ell,h}(t)\|_\infty^2\|D_{-x}c_{d,h}(t)\|_+^2 + k_dM_r\|w_{\ell,h}(t)\|_h^2, t \in (0,T],
\end{aligned}$$

that leads to the next result:

Theorem 3. *Let* $c_{\ell,h}, \tilde{c}_{\ell,h} \in C^1([0,T], V_{h,0}^*)$, $c_{d,h}, \tilde{c}_{d,h} \in C^1([0,T], V_{h,0}^*)$ *and* $c_{s,h}, \tilde{c}_{s,h} \in C^1([0,T], W_h)$ *be solutions of the IBVP (25), (60) and (61) with initial conditions* $c_{\ell,h}(0), \tilde{c}_{\ell,h}(0)$, $c_{d,h}(0), \tilde{c}_{d,h}(0)$ *and* $c_{s,h}(0), \tilde{c}_{s,h}(0)$*, respectively. For* $w_{i,h} = c_{i,h} - \tilde{c}_{i,h}$ *for* $i = \ell, d, s$, *we have*

$$\begin{aligned}
&\sum_{i=d,s} \|w_{i,h}(t)\|_h^2 + 2(d_0 - \epsilon^2) \int_0^t e^{\displaystyle\int_s^t g(\mu)d\mu} \|D_{-x} w_{d,h}(s)\|_+^2 ds \\
&\leq \int_0^t e^{\displaystyle\int_s^t g(\mu)d\mu} \Big(\frac{1}{2\epsilon^2} M_d^2 \|w_{\ell,h}(s)\|_\infty^2 \|D_{-x} c_{d,h}(s)\|_+^2 + M_r \|w_{\ell,h}(s)\|_h^2 \Big) ds, \\
&+ e^{\displaystyle\int_0^t g(\mu)d\mu} \sum_{i=d,s} \|w_{i,h}(0)\|_h^2, \ t \in [0,T],
\end{aligned} \tag{75}$$

where $\epsilon \neq 0$ *and*

$$\begin{aligned}
g(t) = 4k_d M_r \Bigg(&\Big(1 + \tfrac{1}{c_{sol}} \|c_{d,h}(t)\|_\infty\Big) \Big(\tfrac{1}{2}\big(1 + \tfrac{1}{c_{sol}} \|c_{d,h}(t)\|_\infty\big) + \|c_{\ell,h}(t)\|_\infty \Big) \\
&+ \frac{1}{c_{sol}} \|\tilde{c}_{\ell,h}(t)\|_\infty \Bigg).
\end{aligned}$$

■

Let $\epsilon \neq 0$ be fixed such that $d_0 - \epsilon^2 > 0$. If the initial conditions $c_{\ell,h}(0)$, $\tilde{c}_{\ell,h}(0)$ are such that $|R_h c_\ell(0) - c_{\ell,h}(0)| \leq C\sqrt{h_{max}}$, $|R_h c_\ell(0) - \tilde{c}_{\ell,h}(0)| \leq C\sqrt{h_{max}}$, then

$$\begin{aligned}
&\int_0^t \|c_{\ell,h}(s)\|_\infty^2 ds \leq C, \\
&\int_0^t \|\tilde{c}_{\ell,h}(s)\|_\infty^2 ds \leq C, \\
&\int_0^t \|w_{\ell,h}(s)\|_\infty^2 ds \leq C,
\end{aligned} \tag{76}$$

for $t \in [0,T]$. In (76), C is h and t independent, and consequently, for $v_h = c_{\ell,h}, \tilde{c}_{\ell,h}, w_{\ell,h}$, $\|v_h\|_{C([0,T],L^\infty(W_h))}$ is bounded by a positive constant independent on h.

If $h \in \Lambda$, and $c_{d,h}(0), \tilde{c}_{d,h}(0)$ are uniformly bounded in h, then, from Corollary 3, we have

$$\begin{aligned} \int_0^t \|c_{d,h}(s)\|_\infty^2 ds \leq C, \\ \int_0^t \|\tilde{c}_{d,h}(s)\|_\infty^2 ds \leq C, \end{aligned} \tag{77}$$

for $t \in [0,T]$. In (77), C is h independent and consequently, for $v_h = c_{d,h}, \tilde{c}_{d,h}$, $\|v_h\|_{C([0,T],L^\infty(V_{h,0}))}$, $h \in \Lambda$, is bounded by a positive constant h independent.

From (76) and (77) we guarantee that there exists a positive constant C, h and t independent, such that

$$e^{\displaystyle\int_0^t g(\mu)d\mu} \leq C,\ t \in [0,T], h \in \Lambda,$$

and

$$\int_0^t e^{\displaystyle\int_s^t g(\mu)d\mu} \Big(\frac{1}{2\epsilon^2} M_d^2 \|w_{\ell,h}(s)\|_\infty^2 \|D_{-x} c_{d,h}(s)\|_+^2 + M_r \|w_{\ell,h}(s)\|_h^2\Big) ds \leq C,$$

for $t \in [0,T], h \in \Lambda$. These last conclusions allow us to finalize this section with the following stability result for the the dissolved and solid drugs.

Corollary 4. *Under the assumptions of Corollary 1 and Theorem 3, if the initial conditions $c_{\ell,h}(0)$, $\tilde{c}_{\ell,h}(0)$ are such that $|R_h c_\ell(0) - c_{\ell,h}(0)| \leq C\sqrt{h_{max}}$, $|R_h c_\ell(0) - \tilde{c}_{\ell,h}(0)| \leq C\sqrt{h_{max}}$, and $c_{d,h}(0), \tilde{c}_{d,h}(0)$ are uniformly bounded in h, $h \in \Lambda$, then there exists a positive constant C, h independent and t, such that*

$$\begin{aligned} &\sum_{i=d,s} \|w_{i,h}(t)\|_h^2 + \int_0^t \|D_{-x} w_{d,h}(s)\|_+^2 ds \\ &\leq C \sum_{i=d,s} \|w_{i,h}(0)\|_h^2,\ t \in [0,T]. \end{aligned} \tag{78}$$

4.2. Convergence analysis. In what follows we establish the convergence of the semi-discrete approximations $c_{d,h}(t), c_{s,h}(t)$ defined by (60) and (61) that depend on the approximation $c_{\ell,h}(t)$ for the approximation for the fluid concentration that is defined by (25). An estimate for the error $e_{\ell,h}(t) = R_h c_\ell(t) - c_{\ell,h}(t)$ was established in Theorem 1.

Theorem 4. *Let us suppose that the assumptions of Theorem 1 hold,*

$$c_d \in C^1([0,T], C^0[0,R]) \cap C^0([0,T], L^2([0,T], C^4[0,R])$$

and for the coefficient function d we assume also that $|d''| \leq M_d, |d'''| \leq M_d$ in $\mathbb{R}$. Let $e_{i,h}(t)$ be the semi-discretization error defined by $e_{i,h}(t) = R_h c_i(t) - c_{i,h}(t), i = d, s$, where $c_{d,h}(t), c_{s,h}(t)$ are defined by (60) and (61) that depend on the approximation $c_{\ell,h}(t)$ defined by (25). Then there exists a positive constant C, h independent, such that

$$\begin{aligned} &\sum_{i=s,d} \|e_{i,h}(t)\|_h^2 + 2(d_0 - \epsilon^2(R+3)) \int_0^t e^{\int_s^t g(\mu)d\mu} \|D_{-x} e_{d,h}(s)\|_+^2 ds \\ &\leq e^{\int_0^t g(\mu)d\mu} \sum_{i=s,d} \|e_{i,h}(0)\|_h^2 + M_r \int_0^t e^{\int_s^t g(\mu)d\mu} \|e_{\ell,h}(s)\|_h^2 ds \\ &+ C \cdot h_{max}^4 \int_0^t e^{\int_s^t g(\mu)d\mu} \Big(\|c_d(s)\|^2_{C^4[0,R]} + \|c_\ell(s)\|^2_{C^3[0,R]} \Big) ds, \end{aligned} \tag{79}$$

where $\epsilon \neq 0$, and

$$\begin{aligned} g(t) = 4k_d M_r \Bigg(&\Big(1 + \frac{1}{c_{sol}} \|c_d(t)\|_{C^0[0,R]}\Big) \Big(\frac{1}{2}\big(1 + \frac{1}{c_{sol}}\|c_d(t)\|_{C^0[0,R]}\big) + \|c_\ell(t)\|_{C^0[0,R]}\Big) \\ &+ \frac{1}{c_{sol}} \|c_{\ell,h}(t)\|_\infty \Bigg). \end{aligned}$$

Proof: It can be shown that for $e_{d,h}(t)$ and $e_{s,h}(t)$ we have

$$\begin{aligned} &\frac{1}{2}\frac{d}{dt} \sum_{i=s,d} \|e_{i,h}(t)\|_h^2 + d_0 \|D_{-x} e_{d,h}(t)\|_+^2 \\ &\leq -((d(M_h c_\ell(t)) - d(M_h c_{\ell,h}(t))) D_{-x} R_h c_d(t), D_{-x} e_{d,h}(t))_+ + (T_h(t), e_{d,h}(t))_h \\ &+ \Big(\tilde{D}^*_{c,d} c_d(t)(x_0, t) - \tilde{D}_{c,d} c_{d,h}(t)(x_0,t) \Big) e_{d,h}(x_0, t) \\ &+ (f_{ap}(c_s(t), c_d(t), c_\ell(t)) - f_{ap}(c_{h,s}(t), c_{d,h}(t), c_{\ell,h}(t)), e_{d,h}(t) - e_{s,h}(t))_h, \end{aligned} \tag{80}$$

where $T_h(t)$ denotes the spatial truncation error induced by the discretization defined by (60), and $\tilde{D}^*_{c,d}c_d(t)(x_0,t)$ is defined by

$$\tilde{D}^*_{c,d}c_d(t)(x_0,t) = \frac{1}{2}\Big(d(M_hc_\ell(x_1,t))D_{-x}c_d(x_1,t)+d(M_hc_\ell(x_0,t))D_{-x}c_d(x_0,t)\Big).$$

For the first term of right hand side of (80) we have

$$\begin{aligned}
&-((d(M_hc_\ell(t)) - d(M_hc_{\ell,h}(t)))D_{-x}c_d(t), D_{-x}e_{d,h}(t))_+\\
&\le M_d\sqrt{2}\|e_{\ell,h}(t)\|_h\|c_d(t)\|_{C^1[0,R]}\|D_{-x}e_{d,h}(t)\|_+\\
&\le \frac{1}{4\epsilon^2}\Big(M_d\sqrt{2}\|e_{\ell,h}(t)\|_h\|c_d(t)\|_{C^1[0,R]}\Big)^2 + \epsilon^2\|D_{-x}e_{d,h}(t)\|^2_+,
\end{aligned} \tag{81}$$

where $\epsilon \neq 0$.

As

$$\begin{aligned}
T_h(x_i,t) &= (h_{i+1}-h_i)\Big(\frac{1}{2}d'(c_\ell)\frac{\partial^2 c_\ell}{\partial x^2}\frac{\partial c_d}{\partial x} + \frac{1}{4}d''(c_\ell)\Big(\frac{\partial c_\ell}{\partial x}\Big)^2\frac{\partial c_d}{\partial x}\\
&\quad +\frac{1}{2}d'(c_\ell)\frac{\partial^2 c_d}{\partial x^2}\frac{\partial c_\ell}{\partial x} + \frac{1}{3}d(c_\ell)\frac{\partial^3 c_d}{\partial x^3}\Big) + O(h^2_{max}),
\end{aligned}$$

where the partial derivatives are evaluated at (x_i,t) and $O(h^2_{max})$ is a error term that satisfies

$$|O(h^2_{max})| \le C\Big(\Big(1+\|c_\ell(t)\|_{C^3[0,R]}\Big)\|c_\ell(t)\|_{C^3[0,R]}\|c_d(t)\|_{C^3[0,R]}+\|c_d(t)\|_{C^4[0,R]}\Big)h^2_{max},$$

for a positive constant C h independent.

Following the procedure used to obtain the estimate (51), it can be shown that

$$\begin{aligned}
&(T_h(t), e_{d,h}(t)) \le Ch^4_{max}\Big(\|c_d(t)\|^2_{C^4[0,R]}+\\
&(1+\|c_\ell(t)\|^2_{C^1[0,R]})^2\|c_\ell(t)\|^2_{C^3[0,R]}\|c_d\|^2_{C^3[0,R]}\Big)\\
&+2\epsilon^2\|e_{d,h}(t)\|^2_h + 2\epsilon^2\|D_{-x}e_{d,h}(t)\|^2_+.
\end{aligned} \tag{82}$$

As $\dfrac{\partial c_i}{\partial x}(x_0,t) = 0, i = d, \ell$, we observe that

$$|\tilde{D}^*_{c,d}c_d(t)(x_0,t)| \le M_d\frac{1}{2}\Big(\frac{1}{2}\|c_\ell(t)\|_{C^2[0,R]}\|c_d(t)\|_{C^1[0,R]} + \frac{1}{3}\|c_d(t)\|_{C^3[0,R]}\Big)h_1^2. \tag{83}$$

Using the homogeneous Neumann boundary conditions for $c_{\ell,h}(t)$ and $c_{d,h}(t)$ at $x = x_0$ we deduce

$$\tilde{D}_{c,d} c_{d,h}(t)(x_0, t) = 0. \tag{84}$$

From (83) and Proposition 3 we get

$$\begin{aligned}
&\Big| \Big(\tilde{D}^*_{c,d} c_d(t)(x_0,t) - \tilde{D}_{c,d} c_{d,h}(t)(x_0,t) \Big) e_{d,h}(x_0,t) \Big| \\
&\le \frac{1}{4\epsilon^2} M_d^2 \frac{1}{4} \Big(\frac{1}{2} \|c_\ell(t)\|_{C^2[0,R]} \|c_d(t)\|_{C^1[0,R]} + \frac{1}{3} \|c_d(t)\|_{C^3[0,R]} \Big)^2 h_1^4 \\
&+ \epsilon^2 R \|D_{-x} e_{d,h}(t)\|_+^2.
\end{aligned} \tag{85}$$

Analogously to (73), we also have

$$\begin{aligned}
&(f_{ap}(c_s(t), c_d(t), c_\ell(t)) - f_{ap}(c_{s,h}(t), c_{d,h}(t), c_{\ell,h}(t)), e_{d,h}(t) - e_{s,h}(t))_h \\
&\le 2 k_d M_r \Big(\big(1 + \frac{1}{c_{sol}} \|c_d(t)\|_{C^0[0,R]}\big) \big(\frac{1}{2} \big(1 + \frac{1}{c_{sol}} \|c_d(t)\|_{C^0[0,R]}\big) + \|c_\ell(t)\|_{C^0[0,R]} \big) \\
&\qquad + \frac{1}{c_{sol}} \|c_{\ell,h}(t)\|_\infty \Big) \big(\|e_{d,h}(t)\|_h^2 + \|e_{s,h}(t)\|_h^2 \big) + \frac{1}{2} k_d M_r \|e_{\ell,h}(t)\|_h^2 \\
&= g(c_d(t), c_{d,h}(t), c_\ell(t)) \big(\|e_{d,h}(t)\|_h^2 + \|e_{s,h}(t)\|_h^2 \big) + \frac{1}{2} k_d M_r \|e_{\ell,h}(t)\|_h^2.
\end{aligned} \tag{86}$$

Finally, considering (81), (82), (85) and (86) in (80) we easily get (79). ■

If we assume that $c_{s,h}(0) = R_h c_0, c_{\ell,h}(0) = 0, c_{d,h}(0) = 0$, then, from Corollary 3, $\int_0^t \|c_{d,h}(s)\|_\infty^2 ds$ is uniformly bounded in h, as well as $\int_0^t \|c_d(s)\|_{C^0[0,R]}^2 ds$ and $\int_0^t \|c_\ell(s)\|_{C^0[0,R]}^2 ds$. Consequently, $e^{\int_0^t g(\mu) d\mu}$ is uniformly bounded in $h \in \Lambda$ and $t \in [0,T]$. Under the assumptions of Theorem 1, we have

$$\int_0^t \|e_{\ell,h}(s)\|_h^2 ds \le C h_{max}^4 \|c_\ell\|_{L^2(0,T,C^4[0,R])}^2.$$

Finally, under the assumptions of Theorem 4, for ϵ such that $d_0 - \epsilon^2(R+3) > 0$, we conclude the following result:

Corollary 5. *Under the assumptions of Theorems 1 and 4, there exists a positive constant C, h and t independent, such that*

$$\sum_{i=s,d} \|e_{i,h}(t)\|_h^2 + \int_0^t \|D_{-x}e_{d,h}(s)\|_+^2 ds \\ \leq C\Big(h_{max}^4\Big(\|c_d\|^2_{L^2(0,T,C^4[0,R])} + \|c_\ell\|^2_{L^2(0,T,C^4[0,R])}\Big) + \sum_{i=s,d}\|e_{i,h}(0)\|_h^2\Big), \tag{87}$$

for $t \in [0,T],\ h \in \Lambda$.

5. Numerical results

In what follows we illustrate the theoretical results established in this paper, namely, Theorems 1 and 4 (or Corollary 5). We take $c_{\ell,h}(0) = R_h c_\ell(0)$, $c_{d,h}(0) = R_h c_d(0)$ and $c_{s,h}(0) = R_h c_s(0)$ that implies that $e_{\ell,h}(0) = e_{d,h}(0) = e_{s,h}(0) = 0$. The time integration of the differential systems (25), (26), (27) is numerically performed in block using an explicit embedded Runge-Kutta (4,5) created by Dormand and Prince called variously RK5(4)7FM, DOPRI5, DP(4,5) and DP54 and included in the Matlab ode suite [22, 23] with the code `ode45`. Let $\{t_n, n =, 0\ldots, M\}$ be the time grid with variable step size less than Δt_{max}. By $c_{i,h}^n$, $i = \ell, d, s$, we denote the numerical approximation for $c_i(t_n)$, $i = \ell, d, s$, constructed using the described procedure.

We illustrate the behaviour of the errors

$$\|e_{i,h}\|_h = \max_{n=0,\ldots,M}\sqrt{\|e_{i,h}^n\|_h^2 + \sum_{j=0}^n \Delta t_j \|D_{-x}e_{i,h}^j\|_+^2}, \text{ for } i = \ell,\ d, \tag{88}$$

$$\|e_{s,h}\|_h = \max_{n=0,\ldots,M}\|e_{s,h}^n\|_h, \tag{89}$$

showing that the rates

$$Rate_i = \frac{\log\frac{\|e_{i,h}\|_h}{\|e_{i,\tilde h}\|_{\tilde h}}}{\log\frac{h_{max}}{\tilde h_{max}}}, \tag{90}$$

for $i = \ell, d, s$, are approximately 2. In (90), $\tilde h$ is obtained from h introducing the mean point in each subinterval $[x_{i-1}, x_i]$ defined by the vector h.

To consider differential problems with known solutions, we replace the system of partial differential equations (11), (12), and (13), complemented with the boundary conditions (14), (15), and the initial conditions (17), (18), by a corresponding new problem obtained by adding in each partial differential equation a reaction term $R_i(x,t), i = \ell, d, s$. These last terms will be such that the new problems have known solutions. As the present work deals with stability and convergence, the previous modifications do not disturb the established results, namely, Theorems 1 and 4 (or Corollary 5).

Example 1. *We start by considering a regular C^4 solution*

$$\begin{aligned} c_\ell(x,\,t) &= \begin{cases} (1-e^{-\frac{t}{\tau}})c_{ext} + e^{-\frac{t}{\tau}}\frac{c_{ext}}{(R-a)^5}(x-a)^5, & x > a, \\ (1-e^{-\frac{t}{\tau}})c_{ext} & x \le a, \end{cases} \\ c_d(x,\,t) &= te^{-t}\cos\left(\frac{\pi\, x}{2\,R}\right), \\ c_s(x,\,t) &= te^{-t}\cos\left(\frac{\pi\, x}{2\,R}\right) + 1, \end{aligned}$$

defined in $(0,R)\times(0,T]$, with $R=1$, $T=0.01$, $\tau=225$, and $a=0.75R$.

In Table 1 we present the norms of the measured errors and the corresponding

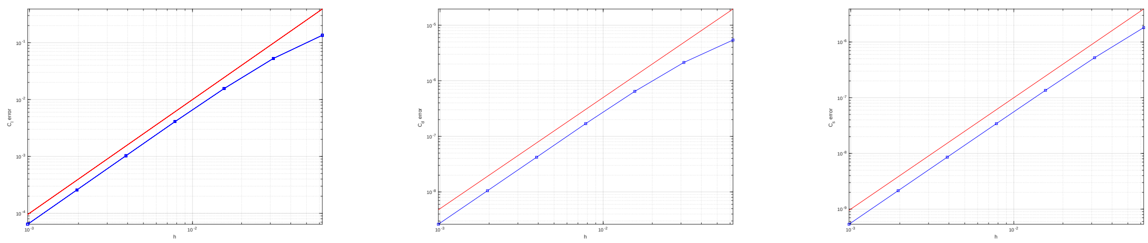
h_{max}	$\|e_{\ell,h}\|_h$	$Rate_\ell$	$\|e_{d,h}\|_h$	$Rate_d$	$\|e_{s,h}\|_h$	$Rate_s$
6.25×10^{-2}	1.3504×10^{-1}	–	5.4082×10^{-6}	–	1.8116×10^{-6}	–
3.125×10^{-2}	5.2621×10^{-2}	1.3597	2.1362×10^{-6}	1.3401	5.2196×10^{-7}	1.7953
1.563×10^{-2}	1.5601×10^{-2}	1.7536	6.4476×10^{-7}	1.7282	1.3568×10^{-7}	1.9437
7.813×10^{-3}	4.0923×10^{-3}	1.9310	1.6938×10^{-7}	1.9285	3.4223×10^{-8}	1.9872
3.906×10^{-3}	1.0275×10^{-3}	1.9937	4.2082×10^{-8}	2.0090	8.5739×10^{-9}	1.9970
1.953×10^{-3}	2.5705×10^{-4}	1.9991	1.050×10^{-8}	2.0027	2.1446×10^{-9}	1.9993
9.766×10^{-4}	6.4279×10^{-5}	1.9996	2.6239×10^{-9}	2.0007	5.3622×10^{-10}	1.9998

TABLE 1. Norm of the errors $\|e_{i,h}\|_h$ for $i=\ell, d$, $\|e_{s,h}\|_h$ and the corresponding convergence rates.

convergence rates for the concentration $c_{i,h}$ for $i=\ell,s,d$.

In Figure 1 we plot the logarithmic of the errors of $c_{i,h}$, for $i=\ell,d,s$. The results in Table and the corresponding plots in Figure 1 show that we can reach the second order of convergence rate for all the concentrations when h_{max} smaller than 10^{-3}.

In the next example we reduce the smoothness of the solvent concentration c_ℓ and, to simplify, we take a t independent c_ℓ concentration. In this example our objective is to analyse the sharpness of the smoothness assumptions imposed in the convergence results.



(a) Solvent (b) Dissolved Drug (c) Undissolved Drug

FIGURE 1. Plot of the logarithmic of the errors and corresponding convergence rate: errors (in blue), line with slope equal to 2 (in red).

Example 2. *We consider the following solution*

$$c_\ell(x,\,t) = \begin{cases} \dfrac{c_{ext}}{(R-a)^4}\,(x-a)^4, & \text{if } x > a,\\ 0, & \text{if } x \le a, \end{cases}$$

$$c_d(x,\,t) = te^{-t}\cos\left(\frac{\pi\,x}{2\,R}\right),$$

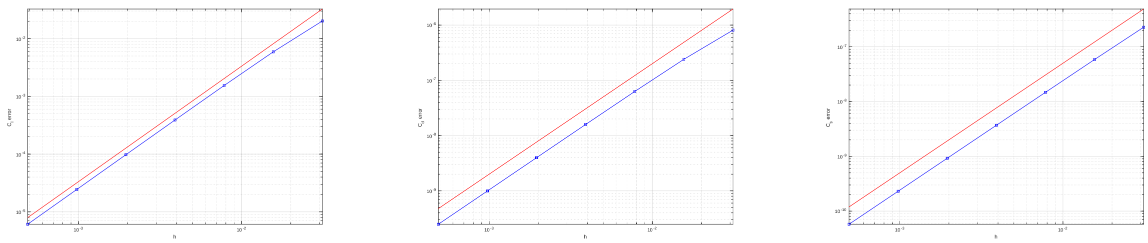
$$c_s(x,\,t) = te^{-t}\cos\left(\frac{\pi\,x}{2\,R}\right) + 1,$$

defined in $[0,R]\times[0,T]$ *with* $R=1$, $T=0.01$, *and* $a=0.75R$. *We observe that* $c_\ell(t)\notin C^4[0,R]$. *In fact this function belongs to* $C^3[0,R]$.

The resulting errors and the corresponding convergence rates are presented in Table 2. In Figure 2 we plot the logarithm of the error norms.

$h_{max}(approx.)$	$\|e_{\ell,h}\|_h$	$Rate_l$	$\|e_{d,h}\|_h$	$Rate_d$	$\|e_{s,h}\|_h$	$Rate_s$
3.125×10^{-2}	2.0197×10^{-2}	–	8.1087×10^{-7}	–	2.2732×10^{-7}	–
1.563×10^{-2}	5.8958×10^{-3}	1.7764	2.4043×10^{-7}	1.7539	5.8505×10^{-8}	1.9581
7.813×10^{-3}	1.5404×10^{-3}	1.9364	6.2919×10^{-8}	1.9340	1.4724×10^{-8}	1.9904
3.906×10^{-3}	3.8969×10^{-4}	1.9829	1.5907×10^{-8}	1.9838	3.6869×10^{-9}	1.9977
1.953×10^{-3}	9.7628×10^{-5}	1.9969	3.9804×10^{-9}	1.9987	9.2210×10^{-10}	1.9994
9.766×10^{-4}	2.4410×10^{-5}	1.9999	9.9459×10^{-10}	2.0007	2.3055×10^{-10}	1.9998
4.883×10^{-4}	6.1025×10^{-6}	2.0000	2.4862×10^{-10}	2.0002	5.7639×10^{-11}	2.0000

TABLE 2. Errors $\|e_{i,h}\|_h$ for $i=\ell,d,s$, and the corresponding convergence rates.



(a) Solvent (b) Dissolved Drug (c) Undissolved Drug

FIGURE 2. Logarithm of the errors (in blue) and line with a slope 2 (in red) for the second example.

The numerical results presented in Table 2 and plotted included in Figure 2 show that the convergence order remains equal to 2 when the smoothness of the solutions of the differential problem is reduced.

6. Conclusions

In this paper we propose a numerical tool to solve a coupled IBVP introduced in [12] to describe the drug release from a polymeric structure where a solid drug is initially dispersed. The polymer is in contact with a solvent that enters into the polymeric structure due to a solvent gradient concentration inducing a set of complex phenomena that take place within the polymeric chains. The solid drug in contact with the solvent dissolves and diffuses trough the polymer to the exterior. At microstructure level, the polymeric chains offer a resistance to the solvent entrance inducing a violation of Fick's law for the solvent transport.

The IBVP (11), (12), and (13), complemented with the boundary conditions (14), (15), is nonlinear and the boundary conditions for the solvent and drug concentrations at $x = 0$ are of Neumann type. These two factors requires a non-standard stability and convergence analysis. In the proof of the main convergence results - Theorems 1 and 4 - several assumptions were imposed on the coefficient function a (H_1), on q (H_2), on the function f (R_1 and R_2) and on d (D_1 and D_2). In the numerical experiments presented in Section 5, the following functions $a(x) = D_\ell(x) - D_v(x)\hat{E}g'(x)$, where D_ℓ and D_v are defined by (6) and (8), respectively, and g is given by (9), $q(t, s, z, y) = D_v(y)ker(t - s)g'(z)$ were used. It is clear that these functions do not satisfy all the assumptions mentioned before. Moreover, the function

f_{ap} that defines c_s and c_d was replaced by f defined by (5) that do not satisfies the assumptions imposed to f_{ap}.

The previous remark shows that the numerical tool proposed to solve the IBVP (11), (12), and (13), complemented with the boundary conditions (14), (15) lead to second order approximations for c_ℓ, c_d and c_s under weaker conditions on the the functions a, q and f_{ap} than those imposed in the proofs of Theorems 1 and 4.

The numerical results obtained in Example 2, in Section 5, shows that second order approximations for c_ℓ, c_d and c_s can be obtained under weaker smoothness assumptions in these solutions. This fact shows that the convergence results established in the present work may be true under weaker smoothness assumptions for the solutions of the differential problem. In the near future we intend to analyse the extension of the results established in this work considering the approach followed in [2], [13] and [14].

Finally, we comment the stability result Corollary 2. In this result is established that if $c_{\ell,h}(0), \tilde{c}_{\ell,h}(0) \in B_{r_h}(R_h c_\ell(0)) = \{v_h \in V_{h,0}^* : \|v_h - R_h c_\ell(0)\|_h \leq r_h\}$, where $r_h \leq C\sqrt{h_{max}}$ then (59) holds. This means that we have local stability at $R_h c_\ell$ and the domain for the initial conditions is threshold dependent [20].

7. Acknowledgements

J.A. Ferreira was partially supported by the project *NEXT.parts - Next-generation of advanced hybrid parts*, and by the Centre for Mathematics of the University of Coimbra – UID/MAT/00324/2019, funded by the Portuguese Government through FCT/MEC and co-funded by the European Regional Development Fund through the Partnership Agreement PT2020. G. Romanazzi was partially supported by the São Paulo Research Fundation (FAPESP) grant 2017/05519-5 and by the Unicamp grant FAEPEX-Pesquisa 519.292.

References

[1] G. Agarwal, S. Agarwal, P. Karar, S. Goyal, Oral sustained release tablets: an overview with a special emphasis on matrix tablet, American Journal of Advanced Drug Delivery, 5, 64–76, 2017.

[2] S. Barbeiro, S. Gh. Bardeji, J.A. Ferreira, L. Pinto, Non-Fickian convection-diffusion models in porous media, Numerische Mathematik, 138, 869–904, 2018.

[3] H.F. Brinson, L.C. Brinson, Polymer Engineering Science and Viscoelasticity: An Introduction, Springer, 2008.

[4] G. Camera-Roda, G.C. Sarti, Mass transport with relaxation in polymers, AIChE Journal, 36, 851–860, 1990.
[5] D.S. Cohen, A.B. White Jr., Sharp fronts due to diffusion and viscoelastic relaxation in polymers, SIAM Journal on Applied Mathematics, 51, 472–483, 1991.
[6] D. A. Edwards, Non-Fickian diffusion in thin polymer films, Journal of Polymer Science Part B: Polymer Physics, 34, 981–997, 1996.
[7] D.A. Edwards, D.S. Cohen, A mathematical model for a dissolving polymer, AIChE Journal, 41, 2345–2355, 1991.
[8] D. A. Edwards, D. S. Cohen, An unusual moving boundary condition arising in anomalous diffusion problems, SIAM Journal on Applied Mathematics, 55, 662–676, 1995.
[9] J.A. Ferreira, L. Gonçalves, J. Naghipoor, P. de Oliveira, T. Rabczuk, The effect of plaque eccentricity on blood hemodynamics and drug release in a stented artery, Medical Engineering and Physics, 60, 47-60, 2018.
[10] J.A. Ferreira, M. Grassi, E. Gudiño, P. de Oliveira, A 3D model for mechanistic control drug release, SIAM Journal on Applied Mathematics, 74, 620–633, 2014.
[11] J.A. Ferreira, M. Grassi, E. Gudiño, P. de Oliveira, A new look to non- Fickian diffusion, Applied Mathematical Modelling, 39, 194–204, 2015.
[12] J.A. Ferreira, M. Grassi, P. de Oliveira, G. Romanazzi, Drug release from viscoelastic swelling platforms, SIAM Journal on Applied Mathematics, 78, 1378–1401, 2018.
[13] J.A. Ferreira, E. Gudiño, P. de Oliveira, A second order approximation for quasilinear Non-Fickian models, Computational Methods in Applied Mathematics, 13, 471–493, 2013.
[14] J.A. Ferreira, L. Pinto, Supraconvergence and supercloseness in quasilinear coupled problems, Journal of Computational and Applied Mathematics 252, 120–131, 2013.
[15] H. Fujita, Diffusion in polymer-diluent systems, Fortschritte Der Hochpolymeren-Forschung, 3, pp. 1–47, 1961.
[16] M. Grassi, G. Grassi, Mathematical modeling and controlled drug delivery: matrix systems, Current Drug Delivery, 2, 97–116, 2005.
[17] E. Gudiño, C. M. Oishi, A. Sequeira, Modeling of non-Fickian diffusion and dissolution from a thin polymeric coating: An application to drug-eluting stents, 114, 292–320, 2018.
[18] Y. Yun, B. Lee, K. Park, Controlled drug delivery: historical perspective for the next generation, Journal of Controlled Release, 219, 2-7, 2015.
[19] Q. Liu, X. Wang, D. De Kee, Mass transport through swelling membranes, International Journal of Engineering Science, 43, 1464–1470, 2005.
[20] T. Ortega, J.M. Sanz-Sena, Nonlinear stability and convergence for finite difference methods for the "good" Boussinesque equation, Numerisch Mathematik, 58, 215–229, 1990.
[21] J. Dormand, P. Prince, A family of embedded Runge–Kutta formulae, Journal of Computational and Applied Mathematics, 6, 19–26, 1980.
[22] The MathWorks, Inc. , MATLAB, C 1984-2019
[23] Shampine, L. F. and M. W. Reichelt, "The MATLAB ODE Suite," SIAM Journal on Scientific Computing, Vol. 18, 1997, pp 1-22.

J.S. Borges
Institute of Mathematics, Statistics and Scientific Computing,, State University of Campinas UNICAMP, Campinas, Brazil, CCN, Federal University of São Carlos, Buri, Brazil

E-mail address: `juliaborges@ufscar.br`

J.A. Ferreira

CMUC, Department of Mathematics, University of Coimbra, Apartado 3008, EC Santa Cruz, 3001-501 Coimbra, Portugal

E-mail address: ferreira@mat.uc.pt
URL: http://www.mat.uc.pt/~ferreira

G. Romanazzi
Institute of Mathematics, Statistics and Scientific Computing, State University of Campinas UNICAMP, Campinas, Brazil

E-mail address: roman@ime.unicamp.br

E. Abreu
Institute of Mathematics, Statistics and Scientific Computing, State University of Campinas UNICAMP, Campinas, Brazil

E-mail address: eabreu@ime.unicamp.br