Drug release from polymeric platforms for non smooth solutions

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Abstract

This paper aims to conclude a sequence of works focused in the numerical study of a system of partial differential equations in a nonuniform grid that can be used to describe the drug release from polymeric platforms. The drug release is a consequence of the non-Fickian fluid uptake, the dissolution process and the Fickian drug transport. The development of a computational tool and its theoretical convergence support was the common driven force. In a previous work from the authors, second order error estimates were established for the numerical approximations for the solvent, solid drug and dissolved drug considering severe smoothness assumption on the solutions: the solvent and the dissolve drug were C^4-functions. In the present work, our aim is to establish second order estimates for the same variables reducing the smoothness assumption, namely, we assume that the solvent and the dissolved drug are H^3- functions. Numerical experiments illustrating the obtained theoretical results are also included.

1 Introduction

In this paper we consider the numerical analysis of a semi-discrete approximation and an implicit-explicit (IMEX) approximation for the quasilinear initial boundary value problem (IBVP)

$$\begin{cases} \dfrac{\partial c_\ell}{\partial t} = \dfrac{\partial}{\partial x}\Big(a_\ell(c_\ell)\dfrac{\partial c_\ell}{\partial x}\Big) + \dfrac{\partial}{\partial x}\Big(\displaystyle\int_0^t q(t,s,c_\ell(s),c_\ell(t))\dfrac{\partial c_\ell}{\partial x}(s)ds\Big), \\ \dfrac{\partial c_d}{\partial t} = \dfrac{\partial}{\partial x}(a_d(c_\ell)\dfrac{\partial c_d}{\partial x}) + f(c_s,\, c_d,\, c_\ell), \\ \dfrac{\partial c_s}{\partial t} = -f(c_s,\, c_d,\, c_\ell) \end{cases} \quad (1)$$

for $x \in (0,R)$, $t \in (0,T]$, where T is a final time, and q is a function that depends on $t, s, c_\ell(s)$ and $c_\ell(t)$, f is a nonlinear function depending on $c_s(t), c_d(t)$ and $c_\ell(t)$. System (1) is coupled with initial condition

$$\begin{aligned} c_\ell(x,0) &= c_{\ell,0}(x), \\ c_d(x,0) &= 0, \\ c_s(x,0) &= c_{s,0}(x), \end{aligned} \quad (2)$$

for $x \in (0, R)$, and boundary conditions

$$\begin{aligned}
&\frac{\partial c_\ell}{\partial x}(0,t) = \frac{\partial c_d}{\partial x}(0,t) = 0,\\
&c_\ell(R,t) = c_{ext},\\
&c_d(R,t) = 0,
\end{aligned} \tag{3}$$

for $t \in (0, T]$. The IBVP (1)-(3) was proposed in [11] to describe the drug release from a polymeric sphere. We specify the coefficient functions a_ℓ, a_d as well as the functions q and f in this scenario. In the last paper, the numerical simulation was obtained considering a numerical method constructed using the so called MOL approach (Method of Lines): spatial discretization followed by the time integration. It should be pointed out that the method used belongs to the family of finite difference method and it is obtained coupling the piecewise linear finite element method with spatial quadrature rules. The numerical analysis of the method used in [11] was presented in [4] assuming restrictive smoothness assumptions for the solution than those considered in the present paper because it was based on the behavior of the spatial truncation error associated with the spatial discretization. The main objective of the present paper is to generalize the results obtained in [4] for low smooth solutions where the error estimates are obtained using the so called Bramble-Hilbert Lemma (Theorem 2 of [5]). We observe that the use of Bramble-Hilbert lemma on the study of numerical methods with solutions with low smoothness was introduced in [2], [12] for elliptic equations, and largely followed for other classes of equations. Without being exhaustive we mention [13] for integro-differential equations, [3] for integro-differential equation coupled with an elliptic equation, [10] for a quasi-linear integro-differential equation.

The main problem in the stability and convergence analysis of numerical methods for certain system of time dependent nonlinear equations is the dependence of the nonlinear reaction term on the dependent variables. This problem has being studied in the literature and without being exhaustive we mention [1], [18], [19], [8], [9] and their references. The paper [1] is concerned with an implicit second order method for linear and nonlinear parabolic equations. To avoid the difficulties coming from the nonlinear reaction term, the authors assume a Lipschitz condition. Implicit-explicit Crank-Nicolson Galerkin piecewise linear finite element methods were studied in [18] for ar thermistor systems. The authors propose a uncoupled splitting method and the error estimates are established considering error estimates for the spatial discretization and time integration errors. In [19] general quasilinear parabolic equations are considered and a linearized piecewise linear Crank-Nicolson method is proposed. The authors establish unconditionally optimal error estimates. The study of a Crank-Nicolson method for a system of nonlinear parabolic equations that can be used to describe light-controlled drug delivery systems was presented in [8] and [9]. In the nonlinear system (1), the reaction term has no bounded partial derivatives nor it satisfies a Lipschitz condition. As we will see, these facts require a careful treatment of the nonlinear reaction term being essential uniform bounds for the numerical approximations for the solvent and dissolved drug concentrations.

As mentioned before, the method studied here can be seen simultaneously as a finite difference scheme and as fully discrete scheme. We establish second convergence order in space with respect to a discrete version of the usual H^1- norm, that means that the L^2-norm of the spatial error and of its discrete spatial derivative are both second order convergent. Consequently, our results can be seen relevant contributions in two different directions:

1. As finite difference scheme, and taking into account that the spatial truncation error is of

first-order accurate with respect to the norm $\|.\|_\infty$, the method is said supraconvergent. This phenomenon was largely studied in the 1980s and without being exhaustive we mention [14, 15, 16, 17, 20, 22, 7] where different techniques were proposed to deal with the low order of the truncation error. While in [14, 16, 17, 20, 22] the properties of the error equation were the main tools used to obtain second order for the global error, in [15, 7] the error analysis is based in the refinement of stability inequalities that allow us to obtain the desired error estimates.

2. As finite element method, we will establish an unexpected convergence rate. In fact, for linear problems at least, it is known that the L^2-norm of the error is second order accurate while with respect to the usual H^1-norm, the error is first-order accurate. So, as we will show second-order accurate with respect to a discrete H^1-norm, the method can be said superconvergent. This phenomenon was largely studied in the literature and we recommend [23] and the references contained there.

The paper is organized as follows. In Section 2 we present a drug release process that can be considered in the drug delivery to stomach [6] and that can be mathematically described by the IBVP (1)-(3). The basic definitions and results needed in the numerical analysis presented in the paper are introduced in Section 3. Section 4 is devoted to the convergence analysis of a semi-discrete approximation that can be simultaneously as a finite difference approximation and as fully discrete in space piecewise linear approximation. The main results of this section are Theorems 1 and 2 that establishes second convergence order for the semi-discrete approximations for the solvent, solid and dissolved drugs concentrations requiring lower smoothness for these concentrations respect that used in [4]. An IMEX method is proposed and studied in Section 5. In Theorem 3 and 4 we establish errors estimates that allow us to conclude that the IMEX method leads to second order approximations in space and first order in time approximations. In Section 6 we present some numerical experiments that illustrate the theoretical results proved in the previous sections. Finally, some conclusions are presented in Section 7.

2 Drug release from polymeric platforms

The IBVP (1)-(3) in its abstract form deserves to be object of study and the theoretical analysis will be presented for general case. Nevertheless to increase its importance, we observe that it can be considered to describe mathematically the drug release from a polymeric platform to combat gastrointestinal diseases (see [6]). In this context, we motivate our study presenting the scenario previously described in [11] that leads to a system of partial differential equations as the one defined by (1)-(3). We consider a viscoelastic spherical polymeric structure of radius R containing a drug. This sphere is immersed in a spherical environment Ω_e, of fixed radius $\bar{R}$, with $\bar{R} > R$. The drug release is consequence of a set of phenomena that are regulated by the dissolution process and the polymeric solvent uptake:

1. The solvent molecules are absorbed by the polymeric structure due to the solvent gradient concentration (solvent absorption);
2. The polymeric chains relax, the structure swells and a pressure gradient arises (swelling);
3. The dissolution process occurs due to the contact of the solid drug with the absorbed solvent molecules (dissolution);

4. The molecules of the dissolved drug diffuse through the platform and continue to diffuse in the external surrounding (diffusion).

We assume that the polymeric sphere presents radial symmetry and consequently we consider the the radius as the spatial variable. We observe that the polymeric chains induce an opposition to the uptake of the solvent molecules being the solvent transport described by a non-Fickian law that takes into account the Fickian transport and the stress developed by the polymeric chains

$$J_\ell(x,t) = -D_\ell \frac{\partial c_\ell}{\partial x}(x,t) - D_v \frac{\partial \sigma}{\partial x}(x,t), \tag{4}$$

where $J_\ell(x,t)$ denotes the solvent flux, $c_\ell(x,t)$ and $\sigma(x,t)$ are the solvent concentration and the polymeric chains stress, respectively, at point x at time t. In (4), D_ℓ and D_v represent the solvent diffusion and the viscoelastic diffusion coefficients. For the drug transport, we assume that the relaxed polymer do not offer any opposition to the movement of drug particles being the drug transport described by Fick's law

$$J_d(x,t) = -a_d \frac{\partial c_d}{\partial x}(x,t) \tag{5}$$

where $J_d(x,t)$ denotes the dissolved drug flux, $c_d(x,t)$ is the dissolved drug concentration and a_d denotes the dissolved drug diffusion coefficient at point x at time t.

Then, assuming that we have an instantaneously swelling, the behaviour of c_ℓ, c_d and solid drug concentration c_s is described by the following system of partial differential equations

$$\begin{cases} \dfrac{\partial c_\ell}{\partial t} = \dfrac{\partial}{\partial x}(D_\ell \dfrac{\partial c_\ell}{\partial x}) + \dfrac{\partial}{\partial x}(D_v \dfrac{\partial \sigma}{\partial x}) \\ \dfrac{\partial c_d}{\partial t} = \dfrac{\partial}{\partial x}(a_d \dfrac{\partial c_d}{\partial x}) + f(c_s,\, c_d,\, c_\ell) \\ \dfrac{\partial c_s}{\partial t} = -f(c_s,\, c_d,\, c_\ell), \end{cases} \tag{6}$$

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

As in [11], we consider that the drug dissolution is described by reaction term

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

In (7)-(6), k_d denotes the dissolution rate, c_{sol} is the solubility limit and $H(c_s)$ is the Heaviside function.

In (6), the diffusion coefficients are of Fujita type

$$D_\ell = D_{\ell e}\; e^{-\beta_\ell \left(1 - \frac{c_\ell}{c_{ext}}\right)}, \tag{8}$$

$$a_d = D_{de}\; e^{-\beta_d \left(1 - \frac{c_\ell}{c_{ext}}\right)} \tag{9}$$

where $D_{\ell e}$ 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 (4), D_v is given by

$$D_v = \frac{r^2}{8\hat{\mu}} c_\ell, \tag{10}$$

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. Moreover, σ is given by the Boltzmann integral

$$\sigma(t) = -\int_0^t E(t-s)\frac{\partial \varepsilon}{\partial s}(s)\,ds \tag{11}$$

where $\varepsilon(t)$ denotes the strain defined by

$$\varepsilon(t) = g(c_\ell(t)) = \left(\frac{\rho_\ell}{\rho_\ell - c_\ell(t)}\right)^{\frac{1}{3}} - 1$$

and $E(s)$ is given by the Maxwell-Wiechert model

$$E(s) = E_0 + \sum_{j=1}^{m} E_j e^{-\frac{s}{\tau_j}} \tag{12}$$

where E_j denotes the Young's modulus, $\tau_j = \frac{\mu_j}{E_j}$ with μ_j that represents the polymeric viscosity.

Considering the last definitions in (6) we obtain (1) with

$$a_\ell = D_\ell(c_\ell) - \hat{E}D_v(c_\ell)g'(c_\ell), \tag{13}$$

$$q(t,\, s,\, c_\ell(s),\, c_\ell(t)) = D_v(c_\ell(t))ker(t-s)g'(c_\ell(s)), \tag{14}$$

and $\hat{E} = \displaystyle\sum_{j=0}^{m} E_j$, $g'(c_\ell) = \dfrac{1}{3}\rho_\ell^{\frac{1}{3}}(\rho_\ell - c_\ell)^{-\frac{4}{3}}$ and $ker(t) = \displaystyle\sum_{j=1}^{m} \frac{E_j}{\tau_j} e^{-\frac{t}{\tau_j}}$. Note that in (14) for each $t \in [0,T]$, $c_\ell(t)$ defines the function $c_\ell(t)(x) = c_\ell(x,t)$ for $x \in (0,R)$.

3 Preliminaries

This section aims to introduce the functional context needed in the convergence analysis presented later. Let $\Omega = (0,R)$ and Λ be a sequence of vectors $h = (h_1,\ldots,h_N)$ be such that $h_i > 0, i = 1,\ldots,N$, $\displaystyle\sum_{i=1}^{N} h_i = R$ and $h_{max} = \displaystyle\max_{i=1,\ldots,N} h_i$.

For $h \in \Lambda$ we introduce in $\overline{\Omega}$ the spatial grid

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

To discretize the Neumann boundary conditions at $x = 0$, we introduce the fictitious point $x_{-1} = -x_1$ and $h_0 = h_1$. We use the notation $\overline{\Omega}_h^\star = \overline{\Omega}_h \cup \{x_{-1}\}$. We introduce now the following vector spaces

$$V_h = \{v_h : \overline{\Omega}_h \to \mathbb{R}\},$$

$$V_{h,0} = \{v_h \in V_h : v_h(x_N) = 0\}.$$

$$V_h^\star = \{v_h : \overline{\Omega}_h^\star \to \mathbb{R}\},$$

and

$$V_{h,0}^{\star} = \{v_h \in V_h^{*} : v_h(x_N) = 0\},$$

In $V_{h,0}$ we introduce the inner product

$$(u_h, v_h)_h = \frac{h_1}{2} u_h(x_0) v_h(x_0) + \sum_{i=1}^{N-1} h_{i+1/2} u_h(x_i) v_h(x_i), \tag{15}$$

for $u_h, v_h \in V_{h,0}$, and $\|.\|_h$ denotes the corresponding norm. In (15), $h_{i+\frac{1}{2}} = \frac{h_i + h_{i+1}}{2}$ for $i = 1, \ldots, N-1$. We also use the notation

$$(u_h, v_h)_+ = \sum_{i=1}^{N} h_i u_h(x_i) v_h(x_i), \; \|u_h\|_+ = \sqrt{(u_h, u_h)_+},$$

for each $u_h, v_v \in V_h$. For $v_h \in V_h^*$ we introduce the finite difference operators D_{-x} and $D_x^{\star}$ defined by

$$D_{-x} v_h(x_i) = \frac{v_h(x_i) - v_h(x_{i-1})}{h_i}, \quad i = 0, \ldots, N, \tag{16}$$

$$D_x^{\star} v_h(x_i) = \frac{v_h(x_{i+1}) - v_h(x_i)}{h_{i+1/2}}, \quad i = 0, \ldots, N-1, \tag{17}$$

respectively, and the first order centered operator

$$D_c v_h(x_i) = \frac{v_h(x_{i+1}) - v_h(x_{i-1})}{h_i + h_{i+1}}, \quad i = 0, \cdots, N-1. \tag{18}$$

By M_h we denote the average operator

$$M_h v_h(x_i) = \frac{v_h(x_i) + v_h(x_{i-1})}{2}, \; i = 0, \ldots, N-1, \tag{19}$$

for $v_h \in V_h^*$.

Proposition 1 *Let $A : \mathbb{R} \to \mathbb{R}$ and $u_h, w_h \in V_h^*, v_h \in V_{h,0}$. Then*

$$(D_x^*(A(M_h w_h) D_{-x} u_h), v_h)_h = -(A(M_h w_h) D_{-x} u_h, D_{-x} v_h)_+ - M_h(A(M_h w_h(x_1)) D_{-x} u_h(x_1)) v_h(x_0). \tag{20}$$

Proof: By assumption, $u_h \in V_h^*$ then $D_x^*(A(M_h u_h) D_{-x} u_h)$ is well defined in $\overline{\Omega}_h - \{x_N\}$. As $v_h \in V_{h,0}$, using summation by parts, it can be easily shown that

$$\begin{aligned}(D_x^*(A(M_h u_h) D_{-x} u_h), v_h)_h = \; & -\frac{1}{2}\left(A(M_h u_h(x_0)) D_{-x} u_h(x_0) + A(M_h u_h(x_1)) D_{-x} u_h(x_1)) v_h(x_0)\right) \\ & + \sum_{i=1}^{N-1} A(M_h u_h(x_i)) D_{-x} u_h(x_i) v_h(x_{i-1}) \\ & - \sum_{i=1}^{N-1} A(M_h u_h(x_i)) D_{-x} u_h(x_i) v_h(x_i),\end{aligned}$$

that leads to (20).

■

We remark that if A is constant then $M_h(A D_{-x} u_h(x_1)) = A D_c u_h(x_0)$.

Proposition 2 *There exists a positive constant C_P such that holds the following Friedrichs-Poincaré inequality*

$$\|v_h\|_h \leq C_P \|D_{-x} v_h\|_+, \text{for all } v_h \in V_{h,0}. \tag{21}$$

Proof: For $v_h \in V_{h,0}$ we have the following representation

$$v_h(x_i) = -\sum_{j=i+1}^{N} h_j D_{-x} v_h(x_j),$$

and, consequently, we also have

$$v_h(x_i)^2 \leq R \sum_{j=i+1}^{N} h_j (D_{-x} v_h(x_j))^2,$$

that leads to (21).

■

We introduce now the finite difference method used in [4]. Let $c_{\ell,h}(.,t)$ be a grid function defined in V_h^*. To simplify the presentation, we use the notations: $c_{\ell,h}(t)(x_i) = c_{\ell,h}(x_i,t)$, $c'_{\ell,h}(t)(x_i) = \dfrac{\partial c_{\ell,h}}{\partial t}(x_i,t)$. The grid functions $c_{d,h}(t), c'_{d,h}(t)$ and $c_{s,h}(t), c'_{s,h}(t)$ are defined analogously. Then the finite difference semi-discrete approximations $c_{\ell,h}(t) \in V_h^*$, $c_{d,h}(t) \in V_{h,0}^*$, $c_{s,h}(t) \in V_{h,0}$ for the solution of the IBVP (1), (2) and (3) are defined by the initial value problem

$$\begin{cases} c'_{\ell,h}(t) = D_x^*\big(a_\ell(M_h c_{\ell,h}(t)) D_{-x} c_{\ell,h}(t)\big) + D_x^*\Big(\displaystyle\int_0^t q(t,s,M_h c_{\ell,h}(s), M_h c_{\ell,h}(t)) D_{-x} c_{\ell,h}(s) ds\Big), \\ c'_{d,h}(t) = D_x^*\big(a_d(M_h c_{\ell,h}(t)) D_{-x} c_{d,h}(t)\big) + f(c_{s,h}(t), c_{d,h}(t), c_{\ell,h}(t)) \\ c'_{s,h}(t) = -f(c_{s,h}(t), c_{d,h}(t), c_{\ell,h}(t)), \end{cases} \tag{22}$$

in $(\overline{\Omega}_h - \{x_N\}) \times (0,T]$, with

$$\begin{array}{l} c_{\ell,h}(x_i,0) = c_{\ell,0}(x_i), \\ c_{d,h}(x_i,0) = 0, \\ c_{s,h}(x_i,0) = c_{s,0}(x_i), \end{array} \tag{23}$$

for $i = 0,\ldots,N-1$, and

$$\begin{array}{l} M_h(a_\ell(M_h c_{\ell,h}(x_1,t)) D_{-x} c_{\ell,h}(x_1,t)) = M_h(a_d(M_h c_{\ell,h}(x_1,t)) D_{-x} c_{d,h}(x_1,t)) = 0, \\ c_{\ell,h}(x_N,t) = c_{ext}, \\ c_{d,h}(x_N,t) = 0, \end{array} \tag{24}$$

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

We remark that considering Proposition 1, it can be shown that the solution of the IBVP (22), (23), (24) satisfies

$$\begin{cases} (c'_{\ell,h}(t), v_h)_h &= -(a_\ell(M_h c_{\ell,h}(t)) D_{-x} c_{\ell,h}(t), D_{-x} v_h)_+ \\ & \quad - \displaystyle\int_0^t (q(t,s,M_h c_{\ell,h}(s), M_h c_{\ell,h}(t)) D_{-x} c_{\ell,h}(s), D_{-x} v_h)_+ ds, \forall v_h \in V_{h,0}, \\ (c'_{d,h}(t), w_h)_h &= -(a_d(M_h c_{\ell,h}(t)) D_{-x} c_{d,h}(t), D_{-x} w_h)_+ + (f(c_{s,h}(t), c_{d,h}(t), c_{\ell,h}(t)), w_h)_h, \forall w_h \in V_{h,0}, \\ (c'_{s,h}(t), p_h)_h &= -(f(c_{s,h}(t), c_{d,h}(t), c_{\ell,h}(t)), p_h)_h, \ \forall p_h \in V_{h,0}, \end{cases} \tag{25}$$

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

$$\begin{array}{l} (c_{\ell,h}(0), v_h)_h = (c_{\ell,0}, v_h)_h, \forall v_h \in V_{h,0}, \\ (c_{d,h}(0), w_h)_h = 0, \forall w_h \in V_{h,0}, \\ (c_{s,h}(0), p_h)_h = (c_{s,0}, p_h), \forall p_h \in V_{h,0}. \end{array} \tag{26}$$

We prove in the following that the previous finite difference method (25)- (26) can be seen as a space discrete piecewise finite element method - piecewise linear for the solvent c_ℓ and dissolved drug c_d and piecewise constant for the solid drug c_s, applied to (22), (23), (24). This fact allow us to see our convergence results simultaneously for the finite difference method (25) and for the corresponding finite element method.

We use the following notation: if $g(x,t)$ is a function depending on the time and space, by $g(t)$ we denote the function $g(t)(x) = g(x,t)$, where x and t belong to the corresponding space and time domains. Let $H^1(0,R)$ and $L^2(0,R)$ be the usual Sobolev spaces where we consider the usual inner products $(.,.)_1$ and $(.,.)$, respectively. By $\|.\|_1$ and $\|.\|$ we denote the usual corresponding norms. The space of function in $H^1(0,R)$ that are null at $x = R$ is denoted by $H^1_{0,R}(0,R)$. We define analogously $L^2_{0,R}(0,R)$.

A weak solution for the IBVP (1), (2) and (3) is defined by the following variational problem: find $c_\ell(t) \in H^1(0,R)$, $c_d(t) \in H^1_{0,R}(0,R)$, $c_s(t) \in L^2_{0,R}(0,R)$ such that $c'_\ell(t), c'_d(t), c'_s(t) \in L^2(0,R)$, $c_\ell(t) = c_{ext}$ at $x = R$, and

$$\begin{cases} (c'_\ell(t), v) = -(a_\ell(c_\ell(t))\dfrac{\partial c_\ell}{\partial x}(t), v') + \displaystyle\int_0^t (q(t,s,c_\ell(s),c_\ell(t))\dfrac{\partial c_\ell}{\partial x}(s), v')ds, \ \forall v \in H^1_{0,R}(0,R), \\ (c'_d(t), w) = -(a_d(c_\ell(t))\dfrac{\partial c_d}{\partial x}(t), w') + (f(c_s(t),\, c_d(t),\, c_\ell(t)), w), \forall w \in H^1_{0,R}(0,R), \\ (c'_s(t), p) = -(f(c_s(t),\, c_d(t),\, c_\ell(t)), p), \ \forall p \in L^2_{0,R}(0,R), \end{cases} \tag{27}$$

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

$$\begin{array}{l} (c_\ell(0), v) = (c_{\ell,0}, v), \forall v \in L^2(0,R), \\ (c_d(0), w) = 0, \forall w \in L^2(0,R), \\ (c_s(0), p) = (c_{s,0}, p), \forall p \in L^2(0,R). \end{array} \tag{28}$$

Let P_h and Q_h be respectively the piecewise linear and constant interpolator operators associated with the partition $\overline{\Omega}_h$. We use the notations $\widehat{u_h} = P_h u_h$, for $u_h \in V_h$, and $\overline{u_h} = Q_h u_h$, for $u_h \in V_{h,0}$, that is defined by

$$\overline{u_h}(x) = \begin{cases} u_h(x_0), & x \in [x_0, x_{1/2}], \\ u_h(x_i), & x \in (x_{i-\frac{1}{2}}, x_{i+\frac{1}{2}}), i = 1, \dots, N-1, \\ u_h(x_N), & x \in [x_{N-\frac{1}{2}}, x_N] \end{cases}$$

where $x_{i\pm\frac{1}{2}} = \frac{x_i + x_{i\pm 1}}{2}$. Then the piecewise linear approximation for the solution of (27), (28) is obtained considering the following finite dimensional weak problem: find $c_{\ell,h}(t) \in V_h$,

$c_{d,h}(t), c_{s,h}(t) \in V_{h,0}$ such that $c_{\ell,h}(x_N,t) = c_{ext}$ and

$$\begin{cases} (\widehat{c_{\ell,h}}'(t), \widehat{v_h}) = -(a_\ell(\widehat{c_{\ell,h}}(t))\dfrac{\partial \widehat{c_{\ell,h}}}{\partial x}(t), \widehat{v_h}') + \displaystyle\int_0^t (q(t,s,\widehat{c_{\ell,h}}(s),\widehat{c_{\ell,h}}(t))\dfrac{\partial \widehat{c_{\ell,h}}}{\partial x}(s)), \widehat{v_h}')ds, \, \forall v_h \in V_{h,0}, \\ (\widehat{c_{d,h}}'(t), \widehat{w_h}) = -(a_d(\widehat{c_{\ell,h}}(t))\dfrac{\partial \widehat{c_{d,h}}}{\partial x}(t), \widehat{w_h}') + (f(\overline{c_{s,h}}(t), \, \widehat{c_{d,h}}(t), \, \widehat{c_{\ell,h}}(t)), \widehat{w_h}), \forall w_h \in V_{h,0}, \\ (\overline{c_{s,h}}'(t), \overline{p_h}) = -(f(\overline{c_{s,h}}(t), \, \widehat{c_{d,h}}(t), \, \widehat{c_{\ell,h}}(t)), \overline{p_h}), \, \forall p_h \in V_{h,0}, \end{cases} \tag{29}$$

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

$$\begin{array}{l} (\widehat{c_{\ell,h}}(0), \widehat{v_h}) = (P_h(R_h c_{\ell,0}), \widehat{v_h}), \forall v_h \in V_{h,0}, \\ (\widehat{c_{d,h}}(0), \widehat{w_h}) = 0, \forall w_h \in V_{h,0}, \\ (\overline{c_{s,h}}(0), \overline{p_h}) = (P_h(R_h c_{s,0}), \overline{p_h}), \forall p_h \in V_{h,0}, \end{array} \tag{30}$$

where $R_h : C[0,R] \to V_h$ denotes the restriction operators.

Finally, we consider the following quadrature rules for all $u, v \in H^1(0,R)$

$$\int_{x_i}^{x_{i+1}} A(u)u'v'dx \simeq A(u(M_h(x_{i+1}))) \int_{x_i}^{x_{i+1}} u'v'dx, i = 0, \dots, N-1, \tag{31}$$

$$\begin{aligned} \int_{x_0}^{x_{1/2}} uvdx \quad & \simeq \frac{h_1}{2} u(x_0)v(x_0), \\ \int_{x_{i-1/2}}^{x_{i+1/2}} uvdx \quad & \simeq h_{i+1/2} u(x_i)v(x_i), i = 1, \dots, N-1, \\ \int_{x_{N-1/2}}^{x_N} uvdx \quad & \simeq \frac{h_N}{2} u(x_N)v(x_N). \end{aligned} \tag{32}$$

To obtain a fully discrete piecewise linear method, we apply the last quadrature rules in (29), (30). For instance, for $(\widehat{c_{\ell,h}}'(t), \widehat{v_h})$ we get

$$\begin{aligned} (\widehat{c_{\ell,h}}'(t), \widehat{v_h}) \quad &= \int_{x_0}^{x_{1/2}} \widehat{c_{\ell,h}}'(t)\widehat{v_h}dx + \sum_{i=1}^{N-1} \int_{x_{i-1/2}}^{x_{i+1/2}} \widehat{c_{\ell,h}}'(t)\widehat{v_h}dx + \int_{x_{N-1/2}}^{x_N} \widehat{c_{\ell,h}}'(t)\widehat{v_h}dx \\ &\simeq \frac{h_1}{2} c'_{\ell,h}(x_0,t)v_h(x_0) + \sum_{i=0}^{N-1} h_{i+1/2} c'_{\ell,h}(x_i,t)v_h(x_i) + \frac{h_N}{2} c'_{\ell,h}(x_N,t)v_h(x_N) \\ &= (c'_{\ell,h}(t), v_h)_h. \end{aligned}$$

For the term $(a_\ell(\widehat{c_{\ell,h}}(t))\dfrac{\partial \widehat{c_{\ell,h}}}{\partial x}(t), \widehat{v_h}')$, we have, successively,

$$\begin{aligned} (a_\ell(\widehat{c_{\ell,h}}(t))\frac{\partial \widehat{c_{\ell,h}}}{\partial x}(t), \widehat{v_h}') \quad &= \sum_{i=0}^{N-1} \int_{x_i}^{x_{i+1}} a_\ell(\widehat{c_{\ell,h}}(t))\frac{\partial \widehat{c_{\ell,h}}}{\partial x}(t)\widehat{v_h}'dx \\ &\simeq \sum_{i=0}^{N-1} a_\ell(M_h(c_{\ell,h}(x_{i+1},t))) \int_{x_i}^{x_{i+1}} \frac{\partial \widehat{c_{\ell,h}}}{\partial x}(t)\widehat{v_h}'dx \\ &= \sum_{i=0}^{N-1} a_\ell(M_h(c_{\ell,h}(x_{i+1},t)))h_{i+1}D_{-x}c_{\ell,h}(x_{i+1},t)D_{-x}v_h(x_{i+1}) \\ &= (a_\ell(M_h(c_{\ell,h}(t)))D_{-x}c_{\ell,h}(t), D_{-x}v_h)_+. \end{aligned}$$

Using the same approach on the term $\int_0^t (q(t,s,\widehat{c_{\ell,h}}(s),\widehat{c_{\ell,h}}(t))\frac{\partial \widehat{c_{\ell,h}}}{\partial x}(s),\hat{v_h}')ds$ we get

$$\int_0^t (q(t,s,\widehat{c_{\ell,h}}(s),\widehat{c_{\ell,h}}(t))\frac{\partial \widehat{c_{\ell,h}}}{\partial x}(s),\hat{v_h}')ds \simeq \int_0^t (q(t,s,c_{\ell,h}(s),c_{\ell,h}(t))D_{-x}c_{\ell,h}(s),D_{-x}v_h)_+ds.$$

Analogously, from the second and the third equations of (29) we establish the second and the third equations of (25), respectively.

As in [4] we assume the following hypotheses:

- H_{dif} For $\mu = \ell, d$, there exist the positive constants $a_{0,\mu}$ and M_μ such that $0 < a_{0,\mu} \le a_\mu \le M_\mu$, $|a'_\mu| \le M_\mu$;
- H_q There exists a positive constant M_q such that $|q(t,s,y,z)| \le M_q$, $|\frac{\partial q}{\partial y}(t,s,y,z)| \le M_q$, $|\frac{\partial q}{\partial z}(t,s,y,z)| \le M_q$, $|\frac{\partial q}{\partial s}(t,s,y,z)| \le M_q$, for $(t,s,y,z) \in [0,T]^2 \times \mathbb{R}^2$.
- H_f There exists a positive constant $C_F > 0$ such that

  $$|(f(x,y,z) - f(\tilde{x},\tilde{y},\tilde{z})| \le C_F((1+|y|)(|z||x-\tilde{x}| + |z-\tilde{z}|) + |\tilde{z}||y-\tilde{y}|), x,y,z,\tilde{x},\tilde{y},\tilde{z} \in \mathbb{R}.$$

The assumption H_f for the reaction term f is motivated by the expression (7).

4 Convergence analysis

The stability and the convergence analysis of the scheme (22), (23), (24) was proved in [4]. In what concerns the convergence, the analysis was based on the use of Taylor expansion that requires smoothness of the solutions $c_\ell(t), c_d(t) \in C^4[0,R]$. In this section we present the convergence analysis reducing the smoothness required before. We follow [10] for the solvent concentration approximation $c_{\ell,h}(t)$. We observe that the semi-discrete approximation for the solid drug concentration $c_{s,h}(t)$ can be assumed in $V_{h,0}$. If $g \in C[0,R]$, we use the following notation

$$(g)_h(x_i) = \begin{cases} \frac{2}{h_1}\int_{x_0}^{x_{1/2}} g(x)dx & i = 0, \\ \frac{1}{h_{i+1/2}}\int_{x_{i-1/2}}^{x_{i+1/2}} g(x)dx & i = 1,\dots,N-1, \\ \frac{2}{h_N}\int_{x_{N-1/2}}^{x_N} g(x)dx & i = N. \end{cases} \tag{33}$$

The proof of the convergence result is based on the introduction of convenient linear functional whose dual norms are estimated by using the Bramble-Hilbert Lemma (see [5]). In Proposition 3 we summarize such results that are used in the proof of Theorem 1 and 2. The proof of this result can be seen in Theorem 3.1 of [2].

Proposition 3 *1. There exists a positive constant C such that*

$$\sum_{i=1}^N h_i\left(D_{-x}u(x_i) - u'(x_{i-1/2})\right)D_{-x}v_h(x_i) \le C\Big(\sum_{i=1}^N h_i^4\|u\|^2_{H^3(x_{i-1},x_i)}\Big)^{1/2}\|D_{-x}v_h\|_+, \tag{34}$$

for all $u \in H^3(0,R)$, $v_h \in V_{h,0}$, *2. There exists a positive constant C such that*

$$\sum_{i=0}^{N-1}\left(\int_{x_{i-1/2}}^{x_{i+1/2}} u(x)dx - h_{i+1/2}u(x_i)\right) v_h(x_i) \leq C\Big(\sum_{i=1}^{N} h_i^4 \|u\|^2_{H^2(x_{i-1},x_i)}\Big)^{1/2} \|D_{-x}v_h\|_+, \quad (35)$$

where the $x_{0-1/2} = x_0, h_{0+1/2} = \frac{1}{2}h_1$, and

$$\sum_{i=1}^{N} h_i \left(u(x_{i-1/2}) - M_h R_h u(x_i)\right) D_{-x}v_h(x_i) \leq C\Big(\sum_{i=1}^{N} h_i^4 \|u\|^2_{H^2(x_{i-1},x_i)}\Big)^{1/2} \|D_{-x}v_h\|_+, \quad (36)$$

for all $u \in H^2(0, R)$, $v_h \in V_{h,0}$.

Proof: We prove (34). The proof of (35) and (36) can be seen in [2] (Theorem 1). We have, successively,

$$\begin{aligned}\sum_{i=1}^{N} h_i \left(D_{-x}u(x_i) - u'(x_{i-1/2})\right) D_{-x}v_h(x_i) &= \sum_{i=1}^{N} \left(u(x_i) - u(x_{i-1}) - h_i u'(x_{i-1/2})\right) D_{-x}v_h(x_i)\\ &= \sum_{i=1}^{N} \left(v(1) - v(0) - v'(1/2)\right) D_{-x}v_h(x_i),\end{aligned} \quad (37)$$

where $v(s) = u(x_{i-1} + sh_i), s \in [0, 1]$. Let $F : W^{3,1}(0, 1) \to \mathbb{R}$ be the defined by $F(w) = w(1) - w(0) - w'(1/2), w \in W^{3,1}(0, 1)$. As $i_d : W^{3,1}(0, 1) \to C^2[0, 1]$ is continuous, F is a well defined, linear and bounded functional. Moreover, $F(w) = 0$ for $w = 1, s, s^2$. From Bramble-Hilbert Lemma (see [5]), there exists a positive constant C independent of w such that

$$|F(w)| \leq C|w|_{W^{3,1}(0,1)}, \forall w \in W^{3,1}(0, 1),$$

where $|.|_{W^{3,1}(0,1)}$ denotes the usual semi-norm is $W^{3,1}(0, 1)$. Then

$$\begin{aligned}|F(v)| &\leq C\int_0^1 |v'''(s)|ds\\ &= Ch_i^2\int_{x_{i-1}}^{x_i} |u'''(x)|dx\\ &\leq Ch_i^{5/2}\|u'''\|_{L^2(x_{i-1},x_i)}.\end{aligned} \quad (38)$$

Inserting the upper bound (38) in (37) we get

$$\begin{aligned}\sum_{i=1}^{N} h_i \left(D_{-x}u(x_i) - u'(x_{i-1/2})\right) D_{-x}v_h(x_i) &\leq C\sum_{i=1}^{N} h_i^{5/2}\|u'''\|_{L^2(x_{i-1},x_i)}|D_{-x}v_h(x_i)|\\ &\leq C\Big(\sum_{i=1}^{N} h_i^4\|u'''\|^2_{L^2(x_{i-1},x_i)}\Big)^{1/2}\|D_{-x}v_h\|_+.\end{aligned}$$

■

To simplify the presentation of our results we introduce the following spaces

$$V_\ell = C^1([0, T], C[0, R]) \cap L^2(0, T, H^3(0, R)) \cap H^1(0, T, H^2(0, R)),$$

$$V_d = C^1([0,T], C[0,R]) \cap L^2(0,T,H^3(0,R) \cap H^1_{0,R}(0,R)) \cap H^1(0,T,H^2(0,R)),$$

and

$$V_s = C^1([0,T], C[0,R]).$$

Taking into account that from our finite difference method (22), (23), (24) we get (25) with (23), following the proof of Theorem 1 of [10], it can be stated the following result

Theorem 1 *Under the assumption H_{dif} and H_q, if $c_\ell \in V_\ell$ and $c_{\ell,h} \in C^1([0,T], V_h) \cap C([0,T], V_h^*)$, for $h \in \Lambda$, then there exist positive constants $C_i, i = 1,2$, h and t independent, such that for $e_{\ell,h}(t) = R_h c_\ell(t) - c_{\ell,h}(t)$, we have*

$$\begin{array}{l} \|e_{\ell,h}(t)\|_h^2 + \displaystyle\int_0^t \|D_{-x} e_{\ell,h}(s)\|_+^2 ds \\ \leq C_1 e^{\int_0^t C_2(1+\|c_\ell\|^2_{L^\infty(0,s,C^1[0,R])})ds} \Big(\|e_{\ell,h}(0)\|_h^2 + h^4_{max} \displaystyle\int_0^t \sigma(s) ds\Big), \end{array} \tag{39}$$

for $t \in [0,T]$. In (39), $\sigma(t)$ is defined by

$$\begin{array}{rl} \sigma(t) = & \|c'_\ell(t)\|^2_{H^2(0,R)} + \|c_\ell(t)\|^2_{H^3(0,R)}\big(\|c_\ell(t)\|^2_{C^1[0,R]} + 1\big) \\ & +\big(\|c_\ell(t)\|^2_{H^2(0,R)} + \|c_\ell\|^2_{L^2(0,t,H^2(0,R))}\big)\|c_\ell\|^2_{L^2(0,t,C^1[0,R])}. \end{array} \tag{40}$$

Proof: From the first equation of (25), it can be shown that holds the following

$$\begin{array}{l} \dfrac{1}{2}\dfrac{d}{dt}\|e_{\ell,h}(t)\|_h^2 = -(a_\ell(M_h c_{\ell,h}(t)) D_{-x} e_{\ell,h}(t), D_{-x} e_{\ell,h}(t))_+ \\ \quad -((a_\ell(M_h R_h c_\ell(t)) - a_\ell(M_h c_{\ell,h}(t))) D_{-x} R_h c_\ell(t), D_{-x} e_{\ell,h}(t))_+ \\ \quad - \displaystyle\int_0^t (q(t,s,M_h c_{\ell,h}(s), M_h c_{\ell,h}(t)) D_{-x} e_{\ell,h}(s), D_{-x} e_{\ell,h}(t))_+ ds \\ \quad - \displaystyle\int_0^t ((q(t,s,M_h R_h c_\ell(s), M_h R_h c_\ell(t)) - q(t,s,M_h c_{\ell,h}(s), M_h c_{\ell,h}(t))) D_{-x} R_h c_\ell(s), D_{-x} e_{\ell,h}(t))_+ \, ds \\ \quad + \displaystyle\sum_{i=1}^5 T_{h,i}(t), \end{array} \tag{41}$$

with

$$T_{h,1}(t) = (R_h c'_\ell(t) - (c'_\ell(t))_h, e_{\ell,h}(t))_h,$$

$$T_{h,2}(t) = -((a_\ell(\widehat{c_\ell}(t)) - a_\ell(M_h R_h c_\ell(t)))\widehat{\frac{\partial c_\ell}{\partial x}}(t), D_{-x} e_{\ell,h}(t))_+,$$

$$T_{h,3}(t) = -(a_\ell(M_h R_h c_\ell(t))\big(\widehat{\frac{\partial c_\ell}{\partial x}}(t) - D_{-x} R_h c_\ell(t)\big), D_{-x} e_{\ell,h}(t))_+,$$

$$T_{h,4}(t) = -\int_0^t ((q(t,s,\widehat{c_\ell}(s),\widehat{c_\ell}(t)) - q(t,s,M_h R_h c_\ell(s), M_h R_h c_\ell(t)))\widehat{\frac{\partial c_\ell}{\partial x}}(s), D_{-x} e_{\ell,h}(t))_+ ds$$

and

$$T_{h,5}(t) = -\int_0^t (q(t,s,M_h R_h c_\ell(s), M_h R_h c_\ell(t))\big(\widehat{\frac{\partial c_\ell}{\partial x}}(s) - D_{-x} R_h c_\ell(s)\big), D_{-x} e_{\ell,h}(t))_+ ds.$$

We remark that in the previous $T_{h,i}$ definitions we have used the notations: $(c'_\ell(t))_h$ defined by (33) with g replaced by $c'_\ell(t)$, $\widehat{g}(x_i) = g(\frac{1}{2}(x_{i-1}+x_i))$ for $g = c_\ell, \dfrac{\partial c_\ell}{\partial x}$.

Considering the smoothness assumptions on the coefficient function a_ℓ and q_ℓ we can establish the following estimates

$$\begin{aligned}|((a_\ell(M_hR_hc_\ell(t)) - a_\ell(M_hc_{\ell,h}(t)))D_{-x}R_hc_\ell(t), D_{-x}e_{\ell,h}(t))_+| &\leq M_\ell\|c_\ell(t)\|_{C^1[0,R]}\|e_{\ell,h}(t)\|_h\|D_{-x}e_{\ell,h}(t)\|_+ \\ &\leq \frac{\|c_\ell(t)\|^2_{C^1[0,R]}}{4\epsilon^2}M_\ell^2\|e_{\ell,h}(t)\|_h^2 + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2,\end{aligned} \tag{42}$$

$$\begin{aligned}&\left|\int_0^t (q(t,s,M_hc_{\ell,h}(s), M_hc_{\ell,h}(t))D_{-x}e_{\ell,h}(s), D_{-x}e_{\ell,h}(t))_+ds\right| \\ &\qquad \leq \frac{1}{4\epsilon^2}M_q^2 t\int_0^t \|D_{-x}e_{\ell,h}(s)\|_+^2ds + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2,\end{aligned} \tag{43}$$

$$\begin{aligned}&\left|\int_0^t ((q(t,s,M_hR_hc_\ell(s), M_hR_hc_\ell(t)) - q(t,s,M_hc_{\ell,h}(s), M_hc_{\ell,h}(t)))D_{-x}R_hc_\ell(s), D_{-x}e_{\ell,h}(t))_+ds\right| \\ &\leq M_q\int_0^t \|c_\ell(s)\|_{C^1[0,R]}(\|e_{\ell,h}(s)\|_h + \|e_{\ell,h}(t)\|_h)\|D_{-x}e_{\ell,h}(t)\|_+ds \\ &\leq \frac{M_q^2}{2\epsilon^2}\|c_\ell\|^2_{L^2(0,t,C^1[0,R])}\Big(\int_0^t \|e_{\ell,h}(s)\|_h^2 + \|e_{\ell,h}(t)\|_h^2ds\Big) + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2 \\ &\leq \frac{M_q^2}{2\epsilon^2}\max\{C_P,t\}\|c_\ell\|^2_{L^2(0,t,C^1[0,R])}\Big(\int_0^t \|D_{-x}e_{\ell,h}(s)\|_+^2ds + \|e_{\ell,h}(t)\|_h^2\Big) + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2,\end{aligned} \tag{44}$$

where $\epsilon \neq 0$ is an arbitrary constant.

Considering (35) and $I_i = (x_{i-1}, x_i)$, for $i = 1,\ldots,N$, we obtain for $T_{h,1}(t)$ the following estimate

$$\begin{aligned}|T_{h,1}(t)| &\leq C\Big(\sum_{i=1}^N h_i^4\|c'_\ell(t)\|^2_{H^2(I_i)}\Big)^{1/2}\|D_{-x}e_{\ell,h}(t)\|_+ \\ &\leq C\sum_{i=1}^N h_i^4\|c'_\ell(t)\|^2_{H^2(I_i)} + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2,\end{aligned} \tag{45}$$

where $\epsilon \neq 0$ and C denotes a new constant depending on $\frac{1}{\epsilon^2}$.

Taking into account now the assumption H_{dif} and the estimate (36) we get

$$\begin{aligned}|T_{h,2}(t)| &\leq CM_\ell\|c_\ell(t)\|_{C^1[0,R]}\Big(\sum_{i=1}^N h_i^4\|c_\ell(t)\|^2_{H^2(I_i)}\Big)^{1/2}\|D_{-x}e_{\ell,h}(t)\|_+ \\ &\leq C\|c_\ell(t)\|^2_{C^1[0,R]}\sum_{i=1}^N h_i^4\|c_\ell(t)\|^2_{H^2(I_i)} + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2.\end{aligned} \tag{46}$$

To obtain an estimate for $T_{h,3}(t)$ we apply (34) and we establish

$$\begin{aligned}|T_{h,3}(t)| &\leq CM_\ell\Big(\sum_{i=1}^N h_i^4\|c_\ell(t)\|^2_{H^3(I_i)}\Big)^{1/2}\|D_{-x}e_{\ell,h}(t)\|_+ \\ &\leq C\sum_{i=1}^N h_i^4\|c_\ell(t)\|^2_{H^3(I_i)} + \epsilon^2\|D_{-x}e_{\ell,h}(t)\|_+^2,\end{aligned} \tag{47}$$

where, as before, in the last inequality C denotes a positive constant, h and t independent, and depending on $\frac{1}{\epsilon^2}$.

Considering the assumption H_q and the estimate (36) we obtain

$$\begin{aligned}|T_{h,4}(t)| &\leq CM_q \int_0^t \Big(\big(\sum_{i=1}^N h_i^4 \|c_\ell(s)\|^2_{H^2(I_i)} \big)^{1/2} + \big(\sum_{i=1}^N h_i^4 \|c_\ell(t)\|^2_{H^2(I_i)} \big)^{1/2} \Big) \\ &\qquad \|c_\ell(s)\|_{C^1[0,R]} ds \|D_{-x} e_\ell(t)\|_+ \\ &\leq C \sum_{i=1}^N h_i^4 \big(\|c_\ell\|^2_{L^2(0,t,H^2(I_i))} + \|c_\ell(t)\|^2_{H^2(I_i)} \big) \|c_\ell\|^2_{L^2(0,t,C^1[0,R])} + \epsilon^2 \|D_{-x} e_{\ell,h}(t)\|^2_+ .\end{aligned} \tag{48}$$

Applying (34) for $T_{h,5}(t)$ holds the following

$$|T_{h,5}(t)| \leq C \sum_{i=1}^N h_i^4 \|c_\ell\|^2_{L^2(0,t,H^3(I_i))} + \epsilon^2 \|D_{-x} e_{\ell,h}(t)\|^2_+ . \tag{49}$$

Combining (41) with the upper bounds (42)-(49), we guarantee that there exists $m \in \mathbb{N}$, and a positive constant C, h and i independent, but depending on $\dfrac{1}{\epsilon^2}$ and T, such that

$$\begin{aligned}\frac{d}{dt} \|e_{\ell,h}(t)\|^2_h + 2(a_{0,\ell} - m\epsilon^2) \|D_{-x} e_{\ell,h}(t)\|^2_+ &\leq C(1 + \|c_\ell\|^2_{L^\infty(0,t,C^1(0,R))}) \Big(\|e_{\ell,h}(t)\|^2_h \\ &\quad + \int_0^t \|D_{-x} e_{\ell,h}(\tau)\|^2_+ d\tau \Big) + Ch^4_{max} \sigma(t),\end{aligned} \tag{50}$$

where $\sigma(t)$ is defined by (40). The last inequality leads to

$$\begin{aligned}&\|e_{\ell,h}(t)\|^2_h + 2(a_{0,\ell} - m\epsilon^2) \int_0^t \|D_{-x} e_{\ell,h}(s)\|^2_+ ds \\ &\quad \leq \|e_{\ell,h}(0)\|^2_h + \int_0^t C(1 + \|c_\ell\|^2_{L^\infty(0,s,C^1(0,R))}) \Big(\int_0^s \|D_{-x} e_{\ell,h}(\mu)\|^2_+ d\mu + \|e_{\ell,h}(s)\|^2_h \Big) ds \\ &\qquad + Ch^4_{max} \int_0^t \sigma(s) ds,\end{aligned} \tag{51}$$

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

From (51), considering Gronwall lemma and fixing ϵ such that $a_{0,\ell} - m\epsilon^2 > 0$, we conclude the existence of two positive constant C_1 and C_2, h and t independent, such that (39) holds.

■

As a corollary of the last result we can state that the numerical approximation for the solvent concentration is a second order approximation and it is uniformly bounded.

Corollary 1 *Under the assumptions of Theorem 1, if* $e_{\ell,h}(0) = 0$*, then there exists a positive constant* C*,* h *and* t *independent, such that*

$$\|e_{\ell,h}(t)\|^2_h + \int_0^t \|D_{-x} e_{\ell,h}(s)\|^2_+ ds \leq Ch^4_{max},$$

and

$$\int_0^t \|c_{\ell,h}(s)\|^2_\infty ds \leq C,$$

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

Proof: As we have for $s \in [0,T]$

$$\|c_{\ell,h}(s)\|_\infty \leq \|e_{\ell,h}(s)\|_\infty + \|R_h c_\ell(s)\|_\infty$$

and

$$\|e_{\ell,h}(s)\|_\infty \leq \sqrt{R}\|D_{-x}e_{\ell,h}(s)\|_+,$$

from (39) we conclude the proof.

■

Theorem 2 *Under the assumption H_{dif} and H_f, if $c_\ell \in L^2(0,T,H^2(0,R))$, $c_d \in V_d$, $c_s \in V_s$, $f(c_s(t),c_d(t),c_\ell(t)) \in H^2(0,R)$, $c_{\ell,h} \in L^2(0,T,V_h)$, $c_{d,h} \in C^1([0,T],V_{h,0}) \cap C([0,T],V^*_{h,0})$, $c_{s,h} \in C^1([0,T],V_{h,0})$, for $h \in \Lambda$. Then there exist positive constants $C_i, i=1,2$, h and t independent, such that for $e_{i,h}(t) = R_h c_i(t) - c_{i,h}(t)$, $i = d,s,\ell$, we have*

$$\sum_{i=d,s}\|e_{i,h}(t)\|_h^2 + \int_0^t \|D_{-x}e_{d,h}(\tau)\|_+^2 d\tau \leq C_1 e^{C_2\int_0^t \big((1+\|c_d(\tau)\|_\infty)^2\|c_\ell(\tau)\|_\infty^2 + \|c_{\ell,h}(\tau)\|_\infty^2+1\big)d\tau}$$
$$\Big(\sum_{i=d,s}\|e_{i,h}(0)\|_h^2 + h_{max}^4\int_0^t \sigma(\tau)d\tau + \int_0^t (1+\|c_d(\tau)\|^2_{C^1[0,R]})\|e_{\ell,h}(\tau)\|_h^2 d\tau\Big), \tag{52}$$

for $t \in [0,T]$. In (52) $\sigma(t)$ is defined by

$$\begin{aligned}\sigma(t) = \;& \|c_d'(t)\|^2_{H^2(0,R)} + \|c_d(t)\|^2_{H^3(0,R)} + \|c_d(t)\|^2_{C^1[0,R]} + \|c_\ell(t)\|^2_{H^2(0,R)}\\ &+\|f(c_s(t),c_d(t),c_\ell(t))\|^2_{H^2(0,R)}.\end{aligned} \tag{53}$$

Proof: Following the proof of Theorem 1, it can be shown that

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\sum_{i=d,s}\|e_{i,h}(t)\|_h^2 = \;& -(a_d(M_h c_{\ell,h}(t))D_{-x}e_{d,h}(t), D_{-x}e_{d,h}(t))_+\\ &-((a_d(M_hR_hc_\ell(t)) - a_d(M_hc_{\ell,h}(t)))D_{-x}R_hc_d(t), D_{-x}e_{d,h}(t))_+\\ &+(f(t)-f_h(t), e_{d,h}(t)-e_{s,h}(t))_h\\ &+\sum_{i=1}^4 T_{h,i}(t),\end{aligned} \tag{54}$$

with

$$f(t) = f(R_hc_s(t), R_hc_d(t), R_hc_\ell(t)),\;\; f_h(t) = f(c_{s,h}(t), c_{d,h}(t), c_{\ell,h}(t)),$$
$$T_{h,1}(t) = (R_hc_d'(t) - (c_d'(t))_h, e_{d,h}(t))_h,$$

where $(c_d'(t))_h$ is defined by (33) with g replaced by $c_d'(t)$,

$$T_{h,2}(t) = -((a_d(\widehat{c_\ell}(t)) - a_d(M_hR_hc_\ell(t)))\widehat{\frac{\partial c_d}{\partial x}}(t), D_{-x}e_{d,h}(t))_+,$$

where $\widehat{g}(x_i) = g(\frac{x_{i-1}+x_i}{2})$ for $g = c_\ell, \frac{\partial c_d}{\partial x}$,

$$T_{h,3}(t) = -(a_d(M_hc_\ell(t))(\widehat{\frac{\partial c_d}{\partial x}}(t) - D_{-x}R_hc_d(t)), D_{-x}e_{d,h}(t))_+,$$

and

$$T_{h,4}(t) = ((f(t))_h - f(t), e_{d,h}(t))_h.$$

Considering (35) and $I_i = (x_{i-1}, x_i)$, for $i = 1, \dots, N$, we obtain for $T_{h,1}(t)$ the following estimate

$$\begin{aligned} |T_{h,1}(t)| &\le C\Big(\sum_{i=1}^{N} h_i^4 \|c_d'(t)\|^2_{H^2(I_i)}\Big)^{1/2} \|D_{-x} e_{d,h}(t)\|_+ \\ &\le C \sum_{i=1}^{N} h_i^4 \|c_d'(t)\|^2_{H^2(I_i)} + \epsilon^2 \|D_{-x} e_{d,h}(t)\|_+^2, \end{aligned} \tag{55}$$

where $\epsilon \neq 0$ and C denotes a new constant depending on $\frac{1}{\epsilon^2}$. In what follows we use the previous notation C and ϵ.

Analogously, for $T_{h,4}(t)$ we have

$$|T_{h,4}(t)| \le C \sum_{i=1}^{N} h_i^4 \|f(t)\|^2_{H^2(I_i)} + \epsilon^2 \|D_{-x} e_{d,h}(t)\|_+^2. \tag{56}$$

Taking into account now the assumption H_{dif} and the estimate (36) we get

$$\begin{aligned} |T_{h,2}(t)| &\le C M_d \|c_d(t)\|_{C^1[0,R]} \Big(\sum_{i=1}^{N} h_i^4 \|c_\ell(t)\|^2_{H^2(I_i)}\Big)^{1/2} \|D_{-x} e_{d,h}(t)\|_+ \\ &\le C \|c_d(t)\|^2_{C^1[0,R]} \sum_{i=1}^{N} h_i^4 \|c_\ell(t)\|^2_{H^2(I_i)} + \epsilon^2 \|D_{-x} e_{d,h}(t)\|_+^2. \end{aligned} \tag{57}$$

To obtain an estimate for $T_h^{(3)}(t)$ we apply (34) and we establish

$$\begin{aligned} |T_{h,3}(t)| &\le C M_d \Big(\sum_{i=1}^{N} h_i^4 \|c_d(t)\|^2_{H^3(I_i)}\Big)^{1/2} \|D_{-x} e_{d,h}(t)\|_+ \\ &\le C \sum_{i=1}^{N} h_i^4 \|c_d(t)\|^2_{H^3(I_i)} + \epsilon^2 \|D_{-x} e_{d,h}(t)\|_+^2. \end{aligned} \tag{58}$$

Considering the assumption H_{dif} for a_d, we deduce

$$\begin{aligned} &|((a_d(M_h R_h c_\ell(t)) - a_d(M_h c_{\ell,h}(t))) D_{-x} R_h c_d(t), D_{-x} e_{d,h}(t))_+| \\ &\qquad \le \|c_d(t)\|_{C^1[0,R]} M_d \|e_{\ell,h}(t)\|_h \|D_{-x} e_{d,h}(t)\|_+ \\ &\qquad \le \frac{M_d^2}{4\epsilon^2} \|c_d(t)\|^2_{C^1[0,R]} \|e_{\ell,h}(t)\|_h^2 + \epsilon^2 \|D_{-x} e_{d,h}(t)\|_+^2. \end{aligned} \tag{59}$$

From the assumption H_f we obtain

$$
\begin{aligned}
|(f(t)-f_h(t),e_{d,h}(t)-e_{s,h}(t))_h| &\leq \sqrt{2}C_F\Big(\sqrt{2}(1+\|c_d(t)\|_\infty)\big(\|c_\ell(t)\|_\infty\|e_{s,h}(t)\|_h+\|e_{\ell,h}(t)\|_h\big)\\
&\quad +\|c_{\ell,h}(t)\|_\infty\|e_{d,h}(t)\|_h\Big)\sum_{i=d,s}\|e_{i,h}(t)\|_h\\
&\leq 2\Big(\sqrt{2}C_F\big(\sqrt{2}(1+\|c_d(t)\|_\infty)\|c_\ell(t)\|_\infty+\|c_{\ell,h}(t)\|_\infty\big)+1\Big)\sum_{i=d,s}\|e_{i,h}(t)\|_h^2\\
&\quad +C_F^2(1+\|c_d(t)\|_\infty)^2\|e_{\ell,h}(t)\|_h^2\\
&\leq C\Big((1+\|c_d(t)\|_\infty)\|c_\ell(t)\|_\infty+\|c_{\ell,h}(t)\|_\infty+1\Big)\sum_{i=d,s}\|e_{i,h}(t)\|_h^2\\
&\quad +C(1+\|c_d(t)\|_\infty)^2\|e_{\ell,h}(t)\|_h^2
\end{aligned}
\tag{60}
$$

Inserting the upper bounds (55)-(60) in (54), we conclude the existence of a positive constant C, h and t independent, and $m \in \mathbb{N}$ such that

$$
\begin{aligned}
&\frac{d}{dt}\sum_{i=d,s}\|e_{i,h}(t)\|_h^2+2(a_{0,d}-m\epsilon^2)\|D_{-x}e_{d,h}(t)\|_+^2\\
&\quad\leq C\Big((1+\|c_d(t)\|_\infty)\|c_\ell(t)\|_\infty+\|c_{\ell,h}(t)\|_\infty+1\Big)\sum_{i=d,s}\|e_{i,h}(t)\|_h^2\\
&\qquad +C\big(1+\|c_d(t)\|_{C^1[0,R]}^2\big)\|e_{\ell,h}(t)\|_h^2+Ch_{max}^4\sigma(t),
\end{aligned}
\tag{61}
$$

where $\sigma(t)$ is defined by (53). Inequality (61) leads to

$$
\begin{aligned}
&\sum_{i=d,s}\|e_{i,h}(t)\|_h^2+2(a_{0,d}-m\epsilon^2)\int_0^t\|D_{-x}e_{d,h}(\tau)\|_+^2d\tau\\
&\quad\leq \sum_{i=d,s}\|e_{i,h}(0)\|_h^2+C\int_0^t\Big((1+\|c_d(\tau)\|_\infty)\|c_\ell(\tau)\|_\infty+\|c_{\ell,h}(\tau)\|_\infty+1\Big)\sum_{i=d,s}\|e_{i,h}(\tau)\|_h^2d\tau\\
&\qquad +C\int_0^t\Big(\big(1+\|c_d(\tau)\|_{C^1[0,R]}^2\big)\|e_{\ell,h}(\tau)\|_h^2+h_{max}^4\sigma(\tau)\Big)d\tau,
\end{aligned}
$$

for $t \in [0,T]$. Fixing ϵ such that $a_{0,d}-m\epsilon^2>0$ and considering Gronwall Lemma we conclude that there exist two positive constants $C_i, i=1,2$, h and t independent, such that (52) holds.

■

Combing Theorems 1 and 2 we obtain the desired result:

Corollary 2 *Under the conditions of Theorems 1 and 2, if $e_{\ell,h}(0)=e_{d,h}(0)=e_{s,h}(0)=0$, then there exists a positive constant C, h and t independent, such that*

$$
\|e_{\ell,h}(t)\|_h^2+\int_0^t\|D_{-x}e_{\ell,h}(s)\|_+^2ds\leq Ch_{max}^4,
$$

$$
\|e_{d,h}(t)\|_h^2+\|e_{s,h}(t)\|_h^2+\int_0^t\|D_{-x}e_{d,h}(s)\|_+^2ds\leq Ch_{max}^4,
$$

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

■

Remark 1 *The last result shows that the nonlinear finite difference method (25), (23) is second order convergent. We recall that the finite difference method can be seen as a fully discrete finite element method obtained from the variational problem (29), (30) approximating the solvent and dissolved drug using the piecewise linear operator P_h and the solid drug approximated using the piecewise constant operator Q_h and the quadrature rules (31) and (32). Consequently, the last result shows that the fully discrete in space nonlinear finite element method is also second order convergent. This result is unexpected even for linear problems where the approach introduced by Wheeler in [24] has been largely followed in the literature.*

Remark 2 *Theorems 1 and 2 were established assuming that the coefficient functions a_μ, $\mu = \ell, d$, q and f satisfy the assumptions H_{dif}, H_q and H_f, respectively. In the context of the mathematical model introduced in Section 2, a_ℓ is defined by (13) with $D_\ell(c_\ell)$ and $D_v(c_\ell)$ given by (8) and (10), respectively, a_d is given by (9), q is defined by (14) with $\hat{E} = \sum_{j=0}^{m} E_j$, $g'(c_\ell) = \frac{1}{3}\rho_\ell^{\frac{1}{3}}(\rho_\ell - c_\ell)^{-\frac{4}{3}}$ and $ker(t) = \sum_{j=1}^{m} \frac{E_j}{\tau_j} e^{-\frac{t}{\tau_j}}$, and f is given by (7). These functions do not satisfy the assumptions previously mentioned and in order to guarantee the validity of these assumptions new definitions need to be introduced that do not compromise the application of the mathematical model to describe the fluid absorption by a polymeric matrix, the drug dissolution and the drug release.*

We start by the Heaviside function H that was used to define f in (7). This function can be regularized considering for instance

$$H_k(x) = (1 + e^{-2kx})^{-1}, x \in \mathbb{R}, k \in \mathbb{R}^+$$

that, for k large enough, is a good approximation for H. Note that function f replaced by

$$f_k(x, y, z) = H_k(x) k_d \frac{c_{sol} - y}{c_{sol}} z \tag{62}$$

satisfies now the assumption H_f.

The function D_ℓ in (8) is arbitrarily large when $x \to \infty$ that means that the fluid diffusion in the polymer can be arbitrarily large. However this is not phenomenologically observed. As the fluid concentration increases, the diffusion coefficient increases but with an upper bound. Then for given $\gamma, \epsilon > 0$, $D_\ell(x)$ should be replaced by

$$D_{\ell,\gamma}(x) = \begin{cases} D_{\ell e}, & x \geq c_{ext} + \gamma \\ p_1(x), & x \in (c_{ext} - \epsilon, c_{ext} + \gamma) \\ D_{\ell e} e^{-\beta\left(1 - \frac{x}{c_{ext}}\right)}, & x \in (0, c_{ext} - \epsilon) \\ D_{\ell e} e^{-\beta}, & x \leq 0 \end{cases},$$

where p_1 is a polynomial such that $D'_{\ell,\gamma}$ is bounded. We observe that $D_{\ell,\gamma}$ for γ small enough, and when the fluid concentration has not yet reach the equilibrium, is a good approximation for $D_\ell(x), x \in \mathbb{R}$. The same regularization process can be considered for the function a_d defined in (9).

We consider now the functions D_v and $g'(x) = \frac{1}{3}\rho_\ell^{\frac{1}{3}}(\rho_\ell - x)^{-\frac{4}{3}}$ that are used to define the Fickian fluid diffusion coefficient a_ℓ in (13) that depends also on $D_\ell(c_\ell)$. In what concerns D_v, *it is assumed a linear relation with the fluid concentration c_ℓ. It is expected that this coefficient increases with the fluid concentration but it should present a upper bound. This means that, D_v should be replaced by*

$$D_{v,\gamma}(x) = \begin{cases} \dfrac{r^2}{8\hat{\mu}} c_\ell^* & x \geq c_\ell^* + \gamma \\ p_1(x) & x \in (c_\ell^* - \gamma, c_\ell^* + \gamma) \\ \dfrac{r^2}{8\hat{\mu}} x, & x \in [\gamma, c_\ell^* - \gamma] \\ p_2(x), & x \in (-\gamma, \gamma) \\ 0 & x \leq -\gamma \end{cases},$$

where c_ℓ^* is a known fluid concentration, γ is arbitrarily small, and p_1, p_2 are polynomials such that $D_{v,\gamma}(x)$ has bounded derivative. Note that when γ is small $D_{v,\gamma}$ is a good approximation of D_v.

In what concerns $g'(c_\ell)$, that measures the rate of change of the polymeric strain with respect to the fluid concentration, taking into account that $c_\ell = c_{ext} < \rho$, at $x = R$, mathematically we can consider that g is replaced by

$$g_\gamma(x) = \begin{cases} \left(\dfrac{\rho}{\rho - c_{ext}}\right)^{\frac{1}{3}} - 1, & x \geq c_{ext} + \gamma \\ p_1(x), & x \in (c_{ext} - \gamma, c_{ext} + \gamma) \\ \left(\dfrac{\rho}{\rho - x}\right)^{\frac{1}{3}} - 1, & x \in [\gamma, c_{ext} - \gamma] \\ p_2(x), & x \in (-\gamma, \gamma) \\ 0, & x \leq -\gamma \end{cases}.$$

In the definition of g_γ, γ is arbitrarily small, and p_1, p_2 are polynomials such that g_γ has second order bounded derivative.

Using the introduced functions, we replace a_μ by $a_{\mu,\gamma}$, for $\mu = \ell, d$. The first part of the condition H_{dif} on the diffusion coefficient a_ℓ means that the Fickian component $D_{\ell,\gamma}$ should dominate the non Fickian one $\hat{E} D_{v,\gamma} g'_\gamma$. Let q_γ be defined as in (14) replacing D_v and g' by $D_{v,\gamma}$ and g'_γ, respectively. The function q_γ satisfies the assumption H_q.

Finally, we remark that Theorems 1 and 2 are established assuming that $c_s(t) \in C[0, R]$, $c_d, c_\ell \in H^3(0, R)$ and $f(c_s(t), c_d(t), c_\ell(t)) \in H^2(0, R)$ that should be replaced now by $f_k(c_s(t), c_d(t), c_\ell(t)) \in H^2(0, R)$ defined in (62).

5 An IMEX method

Let $\{t_m, m = 0, \ldots, M\}$ be a uniform grid in $[0, T]$ with $t_m - t_{m-1} = \Delta t$ for $m = 1, \ldots, M$, $t_0 = 0$ and $T = t_M$. By D_{-t} we denote the usual backward finite difference operator in time and by $c_{\ell,h}^m, c_{d,h}^m$ and $c_{s,h}^m$ we represent the approximation for $c_\ell(t_m), c_d(t_m)$ and $c_s(t_m)$, defined by the following implicit-explicit Euler's method

$$\begin{aligned} D_{-t} c_{\ell,h}^{m+1} &= D_x^*\big(a_\ell(M_h c_{\ell,h}^m) D_{-x} c_{\ell,h}^{m+1}\big) + \Delta t \sum_{j=0}^{m} D_x^*\big(q(t_{m+1}, t_j, M_h c_{\ell,h}^j, M_h c_{\ell,h}^m) D_{-x} c_{\ell,h}^j\big), \\ D_{-t} c_{d,h}^{m+1} &= D_x^*\big(a_d(M_h c_{\ell,h}^m) D_{-x} c_{d,h}^{m+1}\big) + f(c_{s,h}^m, c_{d,h}^m, c_{\ell,h}^m) \\ D_{-t} c_{s,h}^{m+1} &= -f(c_{s,h}^m, c_{d,h}^m, c_{\ell,h}^m), \end{aligned} \quad (63)$$

in $\overline{\Omega}_h - \{x_N\}$ and for $m = 0, \dots, M-1$, with the initial conditions

$$\begin{array}{l} c^0_{\ell,h}(x_i) = c_{\ell,0}(x_i), \\ c^0_{d,h}(x_i) = 0, \\ c^0_{s,h}(x_i) = c_{s,0}(x_i), \end{array} \tag{64}$$

for $i = 0, \dots, N-1$, and the boundary conditions

$$\begin{array}{l} M_h(a_\ell(M_h c^{j-1}_{\ell,h})D_{-x}c^j_{\ell,h})(x_1) = M_h(a_d(M_h c^{j-1}_{\ell,h})D_{-x}c^j_{d,h})(x_1) = 0, \\ c^j_{\ell,h}(x_N) = c_{ext}, \\ c^j_{d,h}(x_N) = 0, \end{array} \tag{65}$$

for $j = 0, \dots, M$.

The finite difference scheme (63) is deduced considering in (22) explicit discretization for the diffusion coefficients and for the dissolution reactions, an implicit discretization for the diffusion terms and the rectangular quadrature rule to discretize the integral term.

The numerical method (63), (64), (65) can also be written in the following form

(S_ℓ) $(I - \Delta t A_\ell(c^m_{\ell,h}))c^{m+1}_{\ell,h} = F_{\ell,m,\Delta_t}(c^0_{\ell,h}, \dots, c^m_{\ell,h})$,

(S_d) $(I - \Delta t A_d(c^m_{\ell,h}))c^{m+1}_{d,h} = \Delta_t F_d(c^m_{d,h}, c^m_{s,h}, c^m_{\ell,h})$,

(S_s) $c^{m+1}_{s,h} = c^m_{s,h} - \Delta_t F_d(c^m_{d,h}, c^m_{s,h}, c^m_{\ell,h})$

where $A_i(c^m_{\ell,h}) \in \mathbb{R}^{N\times N}, i = \ell, d$, and $F_{\ell,m,\Delta t}(c^0_{\ell,h}, \dots, c^m_{\ell,h}), F_d(c^m_{d,h}, c^m_{s,h}, c^m_{\ell,h}) \in \mathbb{R}^N$ are convenient matrices and vectors, respectively, and $c^0_{i,h}, i = d, \ell, s$, are given. For each $m = 0, \dots, M-1$, if $\Delta t \le C h^2_{min}$, for convenient C, matrix $I - \Delta t A_\ell(c^m_{\ell,h})$ is nonsingular and then (S_ℓ) has a unique solution. Consequently, as $I - \Delta t A_d(c^m_{\ell,h})$ is also nonsingular, (S_i), $i = d, s$, have also a unique solution.

We observe that as done in Section 3 this finite difference method can be seen as a fully discrete in time and space finite element method: for $m = 1, \dots, M$, find $c^m_{\ell,h} \in V^*_h$, $c^m_{d,h} \in V^*_{h,0}$, $c^m_{s,h} \in V_{h,0}$, such that $c^m_{\ell,h}(x_N) = c_{ext}$ and

$$\begin{array}{l} (D_{-t}c^{m+1}_{\ell,h}, v_h)_h = -(a_\ell(M_h c^m_{\ell,h})D_{-x}c^{m+1}_{\ell,h}, D_{-x}v_h)_+ \\ \qquad\qquad -\Delta t \displaystyle\sum_{j=0}^{m}(q(t_{m+1}, t_j, M_h c^j_{\ell,h}, M_h c^m_{\ell,h})D_{-x}c^j_{\ell,h}, D_{-x}v_h)_+, \forall v_h \in V_{h,0} \\ (D_{-t}c^{m+1}_{d,h}, w_h)_h = -(a_d(M_h c^m_{\ell,h})D_{-x}c^{m+1}_{d,h}, D_{-x}w_h)_+ + (f(c^m_{s,h}, c^m_{d,h}, c^m_{\ell,h}), w_h)_h, \forall w_h \in V_{h,0}, \\ (D_{-t}c^{m+1}_{s,h}, p_h)_h = -(f(c^m_{s,h}, c^m_{d,h}, c^m_{\ell,h}), p_h)_h, \forall p_h \in V_{h,0}, \end{array} \tag{66}$$

with the initial conditions

$$\begin{array}{l} (c^0_{\ell,h}, v_h)_h = (c_{\ell,0}, v_h)_h, \forall v_h \in V_{h,0}, \\ (c^0_{d,h}, w_h)_h = 0, \forall w_h \in V_{h,0}, \\ (c^0_{s,h}, p_h)_h = (c_{s,0}, p_h), \forall p_h \in V_{h,0}. \end{array} \tag{67}$$

In the next result we establish that there is an unconditional convergence for $c^m_{\ell,h}$.

Theorem 3 *Let $c_{\ell,h}^m \in V_{h,0}^*$ be defined by the fluid part of the discrete IBVP (63)-(65). Let us suppose that H_{dif} and H_q hold, and c_ℓ defined by the fluid part of the IBVP (1), (2), (3) is such that*

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

Then, there exist positive constants $C_i, i=1,2$, h and t independent, such that, for $h \in \Lambda$, $\Delta_t > 0$, the error $E_{\ell,h}^m = R_h c_\ell(t_m) - c_{\ell,h}^m$, $m=0,\dots,M$, satisfies

$$\begin{aligned} \|E_{\ell,h}^{m+1}\|_h^2 + \quad & \Delta t \sum_{j=0}^{m+1} \|D_{-x}E_{\ell,h}^j\|_+^2 \leq C_1\Big(\|E_{\ell,h}^0\|_h^2 + \Delta t\|D_{-x}E_{\ell,h}^0\|_+^2\Big) \\ & + C_2 T_{tru}(\Delta t^2, h_{max}^4), \end{aligned} \tag{68}$$

for $m=0,\dots,M-1$, and

$$\begin{aligned} T_{tru}(\Delta t^2, h_{max}^4) = & \Delta t^2\Big(\|c_\ell\|_{H^1(0,T,C^1[0,R])}^2\big(1+\|c_\ell\|_{H^1(0,T,C[0,R])}^2\big) \\ & + \|c_\ell\|_{H^2(0,T,C[0,R])}^2\big(1+\Delta_t\|c_\ell\|_{C^1([0,T],C[0,R])}^2\big)\Big) \\ & + h_{max}^4\Big(\|c_\ell\|_{C^1([0,T],H^2(0,R))}^2 + \|c_\ell\|_{C([0,T],H^3(0,R))}^2\big(1+\|c_\ell\|_{C([0,T],H^2(0,R))}^2\big)\Big) \end{aligned}$$

Proof: It can be shown that

$$\begin{aligned} (D_{-t}E_{\ell,h}^{m+1}, E_{\ell,h}^{m+1})_h = \quad & -(a_\ell(M_hR_hc_\ell(t_m))D_{-x}R_hc_\ell(t_{m+1}), D_{-x}E_{\ell,h}^{m+1})_+ \\ & +(a_\ell(M_hc_{\ell,h}^m)D_{-x}c_{\ell,h}^{m+1}, D_{-x}E_{\ell,h}^{m+1})_+ \\ & -\Delta t\sum_{j=0}^{m}(q(t_{m+1},t_j,M_hR_hc_\ell(t_j),M_hR_hc_\ell(t_m))D_{-x}R_hc_\ell(t_j), D_{-x}E_{\ell,h}^{m+1})_+ \\ & +\Delta t\sum_{j=0}^{m}(q(t_{m+1},t_j,M_hc_{\ell,h}^j,M_hc_{\ell,h}^m)D_{-x}c_{\ell,h}^j, D_{-x}E_{\ell,h}^{m+1})_+ \\ & +\sum_{j=1}^{5} T_{h,j}^m, \end{aligned} \tag{69}$$

with

$$T_{h,1}^m = (D_{-t}R_hc_\ell(t_{m+1}) - R_h\frac{\partial c_\ell}{\partial t}(t_{m+1}), E_{\ell,h}^{m+1})_h, \tag{70}$$

$$T_{h,2}^m = (R_h\frac{\partial c_\ell}{\partial t}(t_{m+1}) - \big(\frac{\partial c_\ell}{\partial t}(t_{m+1})\big)_h, E_{\ell,h}^{m+1})_h, \tag{71}$$

$$T_{h,3}^m = -(a_\ell(\widehat{c}_\ell(t_m))\widehat{\frac{\partial c_\ell}{\partial x}}(t_{m+1}) - a_\ell(M_hR_hc_\ell(t_m))D_{-x}R_hc_\ell(t_{m+1}), D_{-x}E_{\ell,h}^{m+1})_+, \tag{72}$$

$$\begin{aligned} T_{h,4}^m = \quad & -(\int_0^{t_{m+1}} q(t_{m+1},s,\widehat{c}_\ell(s),\widehat{c}_\ell(t_{m+1}))\widehat{\frac{\partial c_\ell}{\partial x}}(s)ds, D_{-x}E_{\ell,h}^{m+1})_+ \\ & +\Delta t\sum_{j=0}^{m}(q(t_{m+1},t_j,\widehat{c}_\ell(t_j),\widehat{c}_\ell(t_{m+1}))\widehat{\frac{\partial c_\ell}{\partial x}}(t_j), D_{-x}E_{\ell,h}^{m+1})_+ \end{aligned} \tag{73}$$

and

$$T^m_{h,5} = \begin{array}{l} -\Delta t \sum_{j=0}^{m} (q(t_{m+1}, t_j, \widehat{c_\ell}(t_j), \widehat{c_\ell}(t_{m+1})) \widehat{\frac{\partial c_\ell}{\partial x}}(t_j), D_{-x} E^{m+1}_{\ell,h})_+ \\ -(q(t_{m+1}, t_j, M_h R_h c_\ell(t_j), M_h R_h c_\ell(t_m)) D_{-x} R_h c_\ell(t_j), D_{-x} E^{m+1}_{\ell,h})_+. \end{array} \tag{74}$$

To get an upper bound for $|T^m_{h,1}|$ we observe that posing as done before $h_{1/2} = \frac{h_1}{2}$

$$\begin{aligned} T^m_{h,1} &= \sum_{i=0}^{N-1} h_{i+1/2} \frac{1}{\Delta t} \big(c_\ell(x_i, t_{m+1}) - c_\ell(x_i, t_m) - \Delta t \frac{\partial c_\ell}{\partial t}(x_i, t_{m+1}) \big) E^{m+1}_{\ell,h}(x_i) \\ &= \sum_{i=0}^{N-1} h_{i+1/2} \frac{1}{\Delta t} \big(v(1) - v(0) - v'(1) \big) E^{m+1}_{\ell,h}(x_i), \end{aligned}$$

where $v(s) = c_\ell(x_i, t_m + s\Delta t)$, $i = 0, \ldots, N-1$, $s \in [0,1]$. Let $F : W^{2,1}(0,1) \to \mathbb{R}$ be the linear function defined by $F(w) = w(1) - w(0) - w'(1), w \in W^{2,1}(0,1)$. As $W^{2,1}(0,1)$ is embedded in $C^1[0,1]$, F is bounded. Furthermore, for $w(s) = 1, s$, $F(w) = 0$. Then by Bramble-Hilbert lemma, there exists a positive constant C independent of w such that

$$|F(w)| \leq C |w|_{W^{2,1}(0,1)}, \forall w \in W^{2,1}(0,1),$$

where $|.|_{W^{2,1}(0,1)}$ denotes the usual semi-norm in $W^{2,1}(0,1)$. Consequently we obtain

$$\begin{aligned} |T^m_{h,1}| &\leq C\sqrt{\Delta t} \Big(\sum_{i=1}^{N-1} h_{i+1/2} \int_{t_m}^{t_{m+1}} \big(\frac{\partial^2 c_\ell}{\partial t^2}(x_i, t) \big)^2 dt \Big)^{1/2} \| E^{m+1}_{\ell,h} \|_h \\ &\leq C \Delta t \| c_\ell \|^2_{H^2(t_m, t_{m+1}, C[0,R])} + \epsilon^2 C_P \| D_{-x} E^{m+1}_{\ell,h} \|^2_+. \end{aligned} \tag{75}$$

for $\epsilon \neq 0$, and C is a positive constant that depends on $\dfrac{1}{\epsilon^2}$.

Following the construction of the spatial discretization error upper bounds for the semi-discrete approximation done in Theorem 1, the next upper bounds can be established, where C is a positive constant depending on ϵ, and h, Δ_t independent

$$\begin{aligned} |T^m_{h,2}| \leq & \; C h^4_{max} \left\| \frac{\partial c_\ell}{\partial t}(t_{m+1}) \right\|^2_{H^2(0,R)} + \epsilon^2 \| D_{-x} E^{m+1}_{\ell,h} \|^2_+ \\ \leq & \; C h^4_{max} \| \, c_\ell \|^2_{C^1([0,t_{m+1}], H^2(0,R))} + \epsilon^2 \| D_{-x} E^{m+1}_{\ell,h} \|^2_+, \end{aligned} \tag{76}$$

$$\begin{aligned} |T^m_{h,3}| \leq & \; C h^4_{max} \Big(\| c_\ell \|^2_{C([0,t_{m+1}], H^2(0,R))} \| c_\ell \|^2_{C([0,t_{m+1}], C^1[0,R])} + \| c_\ell \|^2_{C([0,t_{m+1}], H^3(0,R))} \Big) \\ & + \epsilon^2 \| D_{-x} E^{m+1}_{\ell,h} \|^2_+ \\ & \leq C h^4_{max} \big(\| c_\ell \|^2_{C([0,t_{m+1}], C^1[0,R])} + 1 \big) \| c_\ell \|^2_{C([0,t_{m+1}], H^3(0,R))} + \epsilon^2 \| D_{-x} E^{m+1}_{\ell,h} \|^2_+. \end{aligned} \tag{77}$$

To establish an estimate for $T^m_{h,4}$, and to simplify the presentation let $q_I(s) = q(t_{m+1}, s, \widehat{c_\ell}(s), \widehat{c_\ell}(t_{m+1})) \widehat{\frac{\partial c_\ell}{\partial x}}(s)$, $s \in [0, t_{m+1}]$. We easily get

$$|T^m_{h,4}| \leq \sum_{j=0}^{m} \| \int_{t_j}^{t_{j+1}} q_I(s) ds - \Delta t q_I(t_j) \|_+ \| D_{-x} E^{m+1}_{\ell,h} \|_+,$$

where $\int_{t_j}^{t_{j+1}} q_I(s)ds - \Delta t q_I(t_j) = \Delta t\big(\int_0^1 w(\mu)d\mu - w(0)\big)$, with $w(\mu) = q_I(t_j + \mu\Delta t), \mu \in [0,1]$.
As there exists a positive constant C such that

$$|\int_0^1 v(\mu)d\mu - v(0)| \leq C\int_0^1 |v'(\mu)|d\mu, \forall v \in W^{1,1}(0,1),$$

we obtain

$$\begin{aligned}
|T^m_{h,4}| &\leq C\Delta t\sum_{j=0}^m \| \int_{t_j}^{t_{j+1}} |q_I'(s)|ds\|_+\|D_{-x}E^{m+1}_{\ell,h}\|_+ \\
&\leq C\Delta t\sum_{j=0}^m \sqrt{\Delta t}\Big(\int_{t_j}^{t_{j+1}} \|q_I'(s)\|^2_+ds\Big)^{1/2}\|D_{-x}E^{m+1}_{\ell,h}\|_+ \\
&\leq C\Delta t\Big(\int_0^{t_{m+1}} \|q_I'(s)\|^2_+ds\Big)^{1/2}\|D_{-x}E^{m+1}_{\ell,h}\|_+ \\
&\leq C\Delta t^2\Big(\|c_\ell\|^2_{C([0,t_{m+1}],C^1[0,R])}\|c_\ell\|^2_{H^1(0,t_{m+1},C[0,R])} + \|c_\ell\|^2_{H^1(0,t_{m+1},C^1[0,R])}\Big) + \epsilon^2\|D_{-x}E^{m+1}_{\ell,h}\|^2_+ \\
&\leq C\Delta t^2\|c_\ell\|^2_{H^1(0,t_{m+1},C^1[0,R])}\big(1 + \|c_\ell\|^2_{H^1(0,t_{m+1},C[0,R])}\big) + \epsilon^2\|D_{-x}E^{m+1}_{\ell,h}\|^2_+,
\end{aligned} \tag{78}$$

where the last inequality is obtained using that $C([0,t_{m+1}],C^1[0,R])$ is embedded in $H^1(0,t_{m+1},C^1[0,R])$.

Finally, for $T^m_{h,5}$ we have $T^m_{h,5} = A + B$ with

$$\begin{aligned}
A = \ & -\Delta t\sum_{j=0}^m (q(t_{m+1},t_j,\widehat{c_\ell}(t_j),\widehat{c_\ell}(t_{m+1}))\widehat{\frac{\partial c_\ell}{\partial x}}(t_j), D_{-x}E^{m+1}_{\ell,h})_+ \\
& -(q(t_{m+1},t_j,M_hR_hc_\ell(t_j),M_hR_hc_\ell(t_{m+1}))D_{-x}R_hc_\ell(t_j), D_{-x}E^{m+1}_{\ell,h})_+
\end{aligned}$$

and

$$\begin{aligned}
B = \ & -\Delta t\sum_{j=0}^m (q(t_{m+1},t_jM_hR_hc_\ell(t_j),M_hR_hc_\ell(t_{m+1}))D_{-x}R_hc_\ell(t_j), D_{-x}E^{m+1}_{\ell,h})_+ \\
& -(q(t_{m+1},t_j,M_hR_hc_\ell(t_j),M_hR_hc_\ell(t_m))D_{-x}R_hc_\ell(t_j), D_{-x}E^{m+1}_{\ell,h})_+.
\end{aligned}$$

For A we have

$$\begin{aligned}
|A| &\leq C\Delta t h^2_{max}\sum_{j=0}^m \Big(\big(\|c_\ell(t_j)\|_{H^2(0,R)} + \|c_\ell(t_{m+1})\|_{H^2(0,R)}\big)\|c_\ell(t_j)\|_{C^1[0,R]} \\
&\qquad + \|c_\ell(t_j)\|_{H^3(0,R)}\Big)\|D_{-x}E^{m+1}_{\ell,h}\|_+ \\
&\leq C\Delta t h^4_{max}\sum_{j=0}^m \Big(\big(\|c_\ell(t_j)\|^2_{H^2(0,R)} + \|c_\ell(t_{m+1})\|^2_{H^2(0,R)}\big)\|c_\ell(t_j)\|^2_{C^1[0,R]} \\
&\qquad + \|c_\ell(t_j)\|^2_{H^3(0,R)}\Big) + \epsilon^2\|D_{-x}E^{m+1}_{\ell,h}\|^2_+ \\
&\leq C h^4_{max}\Big(\big(\|c_\ell\|^2_{C([0,t_{m+1}],H^2(0,R))} + \|c_\ell(t_{m+1})\|^2_{H^2(0,R)}\big)\|c_\ell\|^2_{C([0,t_{m+1}],C^1[0,R])} \\
&\qquad + \|c_\ell\|^2_{C([0,t_{m+1}],H^3(0,R))}\Big) + \epsilon^2\|D_{-x}E^{m+1}_{\ell,h}\|^2_+ \\
&\leq C h^4_{max}\big(1 + \|c_\ell\|^2_{C([0,t_{m+1}],H^2(0,R))}\big)\|c_\ell\|^2_{C([0,t_{m+1}],H^3(0,R))} + \epsilon^2\|D_{-x}E^{m+1}_{\ell,h}\|^2_+.
\end{aligned}$$

It can be shown that for B we have

$$
\begin{aligned}
|B| \leq\ & C\Delta t \sum_{j=0}^{m} \|c_\ell(t_j)\|_{C^1[0,R]} \|M_h(R_h c_\ell(t_{m+1}) - R_h c_\ell(t_m))\|_+ \|D_{-x}E_{\ell,h}^{m+1}\|_+ \\
& \leq C\Delta t \sum_{j=0}^{m} \|c_\ell(t_j)\|_{C^1[0,R]} \Delta t \|c_\ell\|_{C^1([t_m,t_{m+1}],C[0,R])} \|D_{-x}E_{\ell,h}^{m+1}\|_+ \\
& \leq C\Delta t^2 \|c_\ell\|^2_{C([0,t_m],C^1[0,R])} \|c_\ell\|^2_{C^1([t_m,t_{m+1}],C[0,R])} + \epsilon^2 \|D_{-x}E_{\ell,h}^{m+1}\|_+^2.
\end{aligned}
$$

Considering the upper bounds for A and B we obtain

$$
\begin{aligned}
|T_{h,5}^m| \ & \leq C\Big(h_{max}^4\big(1 + \|c_\ell\|^2_{C([0,t_{m+1}],H^2(0,R))}\big)\|c_\ell\|^2_{C([0,t_{m+1}],H^3(0,R))} \\
& \quad +\Delta t^2 \|c_\ell\|^2_{C([0,t_m],C^1[0,R])} \|c_\ell\|^2_{C^1([t_m,t_{m+1}],C[0,R])}\Big) \\
& \quad +2\epsilon^2 \|D_{-x}E_{\ell,h}^{m+1}\|_+^2.
\end{aligned}
\tag{79}
$$

Inserting the error bounds (75)-(79) in (69) and taking into account that

$$
\begin{aligned}
& -(a_\ell(M_h R_h c_\ell(t_m)) D_{-x} R_h c_\ell(t_{m+1}) - a_\ell(M_h c_{\ell,h}^m) D_{-x} c_{\ell,h}^{m+1}, D_{-x}E_{\ell,h}^{m+1})_+ \\
& \quad \leq -(a_{0,\ell} - \epsilon^2)\|D_{-x}E_{\ell,h}^{m+1}\|_+^2 + \frac{M_\ell^2}{4\epsilon^2}\|c_\ell\|^2_{C([0,t_{m+1}],C^1[0,R])}\|E_{\ell,h}^m\|_h^2,
\end{aligned}
$$

and

$$
\begin{aligned}
& -\Delta t \sum_{j=0}^{m} \big(q(t_{m+1}, t_j, M_h R_h c_\ell(t_j), M_h R_h c_\ell(t_m)) D_{-x} R_h c_\ell(t_j) \\
& \qquad -q(t_{m+1}, t_j, M_h c_{\ell,h}^j, M_h c_{\ell,h}^m)\big) D_{-x} c_{\ell,h}^j, D_{-x}E_{\ell,h}^{m+1})_+ \\
& \quad \leq \frac{M_q^2}{4\epsilon^2}\Delta t^2 \Big(\sum_{j=0}^{m} \|c_\ell(t_j)\|_{C^1[0,R]}\big(\|E_{\ell,h}^j\|_h + \|E_{\ell,h}^m\|_h\big) + \|D_{-x}E_{\ell,h}^j\|_+\Big)^2 + \epsilon^2\|D_{-x}E_{\ell,h}^{m+1}\|_+^2 \\
& \quad \leq \Delta t \frac{M_q^2 T}{\epsilon^2}\big(2C_P\|c_\ell\|^2_{C([0,t_m],C^1[0,R])} + \frac{1}{2}\big)\sum_{j=0}^{m}\|D_{-x}E_{\ell,h}^j\|_+^2 + \epsilon^2\|D_{-x}E_{\ell,h}^{m+1}\|_+^2,
\end{aligned}
$$

we obtain

$$
\begin{aligned}
& \|E_{\ell,h}^{m+1}\|_h^2 + 2\Delta t(a_{0,\ell} - \epsilon^2(7 + C_P))\|D_{-x}E_{\ell,h}^{m+1}\|_+^2 \\
& \qquad \leq \|E_{\ell,h}^m\|_h^2 \\
& \qquad +2\Delta t^2 \frac{TM_q^2}{\epsilon^2}\big(2C_P\|c_\ell\|^2_{C([0,t_{m+1}],C^1[0,R])} + \frac{1}{2}\big)\sum_{j=0}^{m}\|D_{-x}E_{\ell,h}^j\|_+^2 + \Delta t T_{er}(m),
\end{aligned}
\tag{80}
$$

with

$$
\begin{aligned}
T_{er}(m) \ & = C\Big(\Delta t\|c_\ell\|^2_{H^2(t_m,t_{m+1},C[0,R])}(1 + \Delta_t\|c_\ell\|^2_{C^1([t_m,t_{m+1}],C^1[0,R])}) + h_{max}^4\Big(\|c_\ell\|^2_{C^1([0,t_{m+1}],H^2(0,R))} \\
& \quad +\|c_\ell\|^2_{C([0,t_{m+1}],H^3(0,R))}\big(1 + \|c_\ell\|^2_{C([0,t_{m+1}],H^2(0,R))}\big)\Big) \\
& \quad +\Delta t^2\|c_\ell\|^2_{H^1(0,t_{m+1},C^1[0,R])}\big(1 + \|c_\ell\|^2_{H^1(0,t_{m+1},C[0,R])}\big)\Big).
\end{aligned}
\tag{81}
$$

Let ϵ be defined by $\epsilon^2 = \dfrac{a_{0,\ell}}{2(7+C_P)}$. Then (80) is equivalent to

$$\|E_{\ell,h}^{m+1}\|_h^2 + \Delta t a_{0,\ell}\|D_{-x}E_{\ell,h}^{m+1}\|_+^2 \leq \|E_{\ell,h}^m\|_h^2 + \Delta t^2\gamma\sum_{j=0}^m \|D_{-x}E_{\ell,h}^j\|_+^2 + \Delta t T_{er}(m), \tag{82}$$

with

$$\gamma = \frac{4TM_q^2(7+C_P)}{a_{0,\ell}}\big(2C_P\|c_\ell\|^2_{C([0,T],C^1[0,R])} + \frac{1}{2}\big).$$

Then, for $m = 0,\dots,M-1$, from (82) we deduce

$$\begin{aligned}&\|E_{\ell,h}^{m+1}\|_h^2 + \Delta t\sum_{j=0}^{m+1}\|D_{-x}E_{\ell,h}^j\|_+^2\\ &\leq \frac{1}{\min\{1,a_{0,\ell}\}}\Big(\|E_{\ell,h}^0\|_h^2 + a_{0,\ell}\Delta_t\|D_{-x}E_{\ell,h}^0\|_+^2 + \Delta t\sum_{j=0}^m T_{er}(j)\Big)\\ &\quad + \sum_{j=0}^m \Delta t^2\frac{\gamma}{\min\{1,a_{0,\ell}\}}\sum_{k=0}^j\|D_{-x}E_{\ell,k}^k\|_+^2.\end{aligned} \tag{83}$$

Inequality (84) leads to

$$\begin{aligned}&\|E_{\ell,h}^{m+1}\|_h^2 + \Delta t\sum_{j=0}^{m+1}\|D_{-x}E_{\ell,h}^j\|_+^2\\ \leq\ &\frac{1}{\min\{1,a_{0,\ell}\}}\Big((1+a_{0,\ell})\big(\|E_{\ell,h}^0\|_h^2 + \Delta t\|D_{-x}E_{\ell,h}^0\|_+^2\big)\\ &\quad + \Delta t\sum_{j=0}^m T_{er}(j)\Big)e^{(m+1)\Delta t\frac{\gamma}{\min\{1,a_{0,\ell}\}}}\end{aligned} \tag{84}$$

where

$$\begin{aligned}\Delta t\sum_{j=0}^m T_{er}(j) \quad &\leq C\Big(\Delta t^2\|c_\ell\|^2_{H^2(0,T,C[0,R])}\big(1+\Delta_t\|c_\ell\|^2_{C^1([0,T],C[0,T])}\big) + h_{max}^4\Big(\|c_\ell\|^2_{C^1([0,T],H^2(0,R))}\\ &\quad + \|c_\ell\|^2_{C([0,T],H^3(0,R))}\big(1+\|c_\ell\|^2_{C([0,T],H^2(0,R))}\big)\Big)\\ &\quad + \Delta t^2\|c_\ell\|^2_{H^1(0,T,C^1[0,R])}\big(1+\|c_\ell\|^2_{H^1(0,T,C[0,R])}\big)\Big).\end{aligned} \tag{85}$$

From (84) and (85), we conclude (68).

■

Corollary 3 *Under the condition of Theorem 3, there exist an upper bound Δt_0 for the time step Δt and a positive constant C, Δt and h independent, such that*

$$\|E_{\ell,h}^m\|_h^2 + \Delta t\sum_{j=0}^m\|D_{-x}E_{\ell,h}^j\|_+^2 \leq C\Big(\|E_{\ell,h}^0\|_h^2 + \Delta t\|D_{-x}E_{\ell,h}^0\|_+^2 + h_{max}^4 + \Delta t^2\Big), m = 0,\dots,M, \tag{86}$$

for $\Delta t \in (0,\Delta t_0)$ and $h \in \Lambda$.

Corollary 3 states that if we have null a initial error $E^0_{\ell,h}$ then

$$\|E^m_{\ell,h}\|_h^2 + \Delta t \sum_{j=0}^{m} \|D_{-x}E^j_{\ell,h}\|_+^2 \leq C\big(h^4_{max} + \Delta t^2\big), m = 1, \ldots, M.$$

This result can be seen in two different perspectives: in finite difference and finite element methods. As we stated before, the finite difference method for the solvent concentration defined in (63)-(65) can be also seen as a fully discrete in time and space finite element method for the solvent concentration defined in (66), (67). Consequently, the last result is unexpected in the two different contexts, even for linear case.

As in the semi-discrete case, to conclude the accuracy of the dissolved and solid drugs, we need to establish uniform boundness in time and space of the of the solvent approximation. To conclude such property we need to impose a condition on the nonuniform grids in space and also on the time step size Δt. We remark that, as we will see in what follows, we do not need to impose null initial error for the solvent.

Corollary 4 *Let us suppose that the conditions of Theorem 3 hold and let* $\|E^0_{\ell,h}\|_h \leq C\sqrt{h_{max}}$ *and* $\|D_{-x}E^0_{\ell,h}\|_+ \leq C\sqrt{h_{max}}$. *If there exist positive constants* C_u *and* C_s *such that*

$$\frac{h_{max}}{h_{min}} \leq C_u, h \in \Lambda, \tag{87}$$

$$\frac{\Delta t}{h^2_{min}} \leq C_s, h \in \Lambda, \tag{88}$$

where $h_{min} = \min\{h_i, i = 1, \ldots, N\}$, *and for* h_{max} *small enough, then there exists a positive constant,* C_ℓ, Δt *and* h *independent, such that*

$$\|c^m_{\ell,h}\|_\infty \leq C_\ell, \tag{89}$$

for $m = 0, \ldots, M$, $\Delta t \in (0, \Delta t_0]$ *and* $h \in \Lambda$.

Proof: As we have

$$\begin{aligned} \|c^m_{\ell,h}\|^2_\infty &\leq 2\|E^m_{\ell,h}\|^2_\infty + 2\|R_h c_\ell(t_m)\|^2_\infty, \\ &\leq \tfrac{4}{h_{min}}\|E^m_{\ell,h}\|^2_h + 2\|R_h c_\ell(t_m)\|^2_\infty, \end{aligned}$$

considering (86), we obtain

$$\begin{aligned} \|c^m_{\ell,h}\|^2_\infty &\leq \frac{4C}{h_{min}}\big(h^2_{max} + \Delta t h_{max} + h^4_{max} + \Delta t^2\big) + 2\|R_h c_\ell(t_m)\|^2_\infty \\ &\leq 4C\Big(h_{max}\frac{h_{max}}{h_{min}} + \Delta t\frac{h_{max}}{h_{min}} + h^3_{max}\frac{h_{max}}{h_{min}} + \Delta t^{3/2}\sqrt{\frac{\Delta t}{h^2_{min}}}\Big) + 2\|R_h c_\ell(t_m)\|^2_\infty. \end{aligned}$$

Taking into account the conditions (87) and (88) we conclude (89).

■

In the next result we study the accuracy of the solution of (63), (64), (65). As the reaction term is discretized explicitly, conditional convergence is established.

Theorem 4 *Let us suppose that the assumptions H_{dif} and H_f hold, and the solution c_ℓ, c_d and c_s of the IBVP (1), (2), (3) is such that*

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

$$c_d \in H^2(0,T,C([0,R])) \cap C^1([0,T],H^2(0,R) \cap C([0,T],H^3(0,R) \cap H^1_{0,R}(0,R)),$$

$$c_s \in H^2(0,T,C([0,R])),$$

$$f(c_s,c_d,c_\ell) \in C([0,T],H^2(\Omega)) \cap H^1(0,T,C[0,R]).$$

For $h \in \Lambda$, let $c^m_{\ell,h}, c^m_{d,h} \in V^*_{h,0}$, $c^m_{s,h} \in V_{h,0}$, be the corresponding discrete approximations defined by (63), (64), (65) and $E^m_{i,h} = R_h c_i(t_m) - c^m_{i,h}, m = 0,\ldots,M$, $i = d,\ell,s$, be the global errors. Then there exists an upper bound for the time step $\Delta t_{0,d}$ and positive constants $C_i, i = 1,2$, h and Δt independent, such that for $\Delta t \in (0, \Delta t_{0,d})$, we have

$$\sum_{i=d,s} \|E^{m+1}_{i,h}\|^2_h + \Delta t \sum_{j=0}^{m+1} \|D_{-x}E^j_{d,h}\|^2_+ \leq C_1\Big(\sum_{i=d,s} \|E^0_{i,d}\|^2_h + \|D_{-x}E^0_{d,h}\|^2_+\Big) \\ +\Delta t \sum_{j=0}^{m} \|E^j_{\ell,h}\|^2_h + T_{tru,d}(\Delta t^2, h^4_{max})\Big) e^{C_2(\theta(c_{\ell,h})+1)} \tag{90}$$

for $j = 0,\ldots,M-1$.

In (90), $T_{tru,d}(\Delta t^2, h^4_{max})$ is defined by

$$\begin{aligned} T_{tru,d}(\Delta t^2, h^4_{max}) = \;& \Delta t^2\big(\|c_d\|^2_{H^2(0,T,C[0,R])} + \|c_s\|^2_{H^2(0,T,C[0,R])} \\ & + \|c_\ell\|^2_{H^1(0,T,C[0,R])}\|c_d\|^2_{C([0,T],C^1[0,R])} + \|f\|^2_{H^1(0,T,C[0,R])}\big) \\ & + h^4_{max}\big((1 + \|c_\ell\|^2_{C([0,T],H^2(0,R))})\|c_d\|^2_{C^1([0,T],H^2(0,R))} \\ & + \|c_d\|^2_{C([0,T],H^3(0,R))} + \|f\|^2_{C([0,T],H^2(0,R))}\big), \end{aligned}$$

and $\theta(c_{\ell,h})$ is given by

$$\theta(c_{\ell,h}) = C_\theta\Big(\big(1 + \|c_d\|_{C([0,T],C[0,R])}\big)\|c_\ell\|_{C([0,T],C[0,R])} + \max_{m=0,\ldots,M} \|c^m_{\ell,h}\|_\infty\Big)^2, \tag{91}$$

where C_θ is a positive constant, h and Δt independent.

Proof: Following the proof of Theorems 2 and 3, it can be shown that for the global error of the dissolved and solid drug concentrations, $E^m_{d,h}, E^m_{s,h}$, respectively, we have

$$\sum_{i=d,s} \|E^{m+1}_{i,h}\|^2_h + \Delta t(a_{d,0} - 5\epsilon^2)\|D_{-x}E^{m+1}_{d,h}\|^2_+ \leq \big(1 + \Delta t\theta_\epsilon(c_{\ell,h})\big) \sum_{i=d,s} \|E^m_{i,h}\|^2_h \\ +\Delta t\sigma\|E^m_{\ell,h}\|^2_h + 2\Delta t\epsilon^2 \sum_{i=d,s} \|E^{m+1}_{i,h}\|^2_h + \Delta t T_{er,d}(m), \tag{92}$$

for $m = 0,\ldots,M$, where

$$\sigma_\epsilon = 2\frac{M_d^2}{\epsilon^2}\|c_d\|^2_{C([0,T],C^1(\overline{\Omega}))} + \frac{2}{\epsilon^2}(1 + \|c_d\|_{C([0,T],C[0,R])})^2,$$

$$\theta_\epsilon(c_{\ell,h}) = \frac{4}{\epsilon^2}C_F^2\Big(\sqrt{2}\big(1+\|c_d\|_{C([0,T],C[0,R])}\big)\|c_\ell\|_{C([0,T],C[0,R])} + \max_{m=0,\dots,M}\|c_{\ell,h}^m\|_\infty\Big)^2 \tag{93}$$

ϵ is an arbitrary nonzero constant, and

$$\begin{aligned} T_{er,d}(m) = \; & C\Big(\Delta t\big(\|c_d\|^2_{H^2(t_m,t_{m+1},C[0,R])} + \|c_s\|^2_{H^2(t_m,t_{m+1},C[0,R])} \\ & \qquad + \|c_\ell\|^2_{H^1(t_m,t_{m+1},C[0,R])}\|c_d\|^2_{C([0,T],C^1[0,R])} + \|f\|^2_{H^1(t_m,t_{m+1},C[0,R])}\big) \\ & + h^4_{max}\big(\|c_d\|^2_{C^1([0,T],H^2(0,R))}\|c_\ell\|^2_{C([0,T],H^2(0,R))}\big)\|c_d\|^2_{C([0,T],H^2(0,R))} \\ & \qquad + \|c_d\|^2_{C([0,T],H^3(0,R))} + \|f\|^2_{C([0,T],H^2(0,R))}\big)\Big), \end{aligned}$$

where $f(x,t) = f(c_s(x,t), c_d(x,t), c_\ell(x,t)), x \in [0,R], t \in [0,T]$, C is a positive constant, h and Δt independent, depending on $\frac{1}{\epsilon^2}$.

Let ϵ be fixed by $\epsilon^2 = \frac{a_{0,d}}{10}$. Then from (92) we obtain

$$\begin{aligned} \sum_{i=d,s}\|E_{i,d}^{m+1}\|_h^2 + \Delta t\frac{a_{0,d}}{2}\|D_{-x}E_{d,h}^j\|_+^2 \leq & (1+\Delta t\theta(c_{\ell,h}))\sum_{i=d,s}\|E_{i,h}^m\|_h^2 + \Delta t\sigma\|E_{\ell,h}^m\|_h^2 \\ & + \Delta t\frac{a_{0,d}}{5}\sum_{i=d,s}\|E_{i,h}^{m+1}\|_h^2 + \Delta t T_{er,d}(m), \end{aligned} \tag{94}$$

where $\theta(c_{\ell,h})$ is defined by (91) for a convenient positive constant C_θ, and

$$\sigma = C_\sigma\big(\|c_d\|^2_{C([0,T],C^1(\overline{\Omega}))} + (1+\|c_d\|_{C([0,T],C[0,R])})^2\big),$$

where C_σ is a convenient positive constant. The two positive constants C_θ and C_σ are h and Δt independent.

Inequality (94) leads to

$$\begin{aligned} (1-\Delta t\frac{a_{0,d}}{5})\sum_{i=d,s}\|E_{i,h}^{m+1}\|_h^2 + \Delta t\frac{a_{0,d}}{2}\sum_{j=0}^{m+1}\|D_{-x}E_{d,h}^j\|_+^2 \leq & (1+\frac{a_{0,d}}{2}\Delta t)\Big(\sum_{i=d,s}\|E_{i,h}^0\|_h^2 + \|D_{-x}E_{d,h}^0\|_+^2\Big) \\ & + \big(\theta(c_{\ell,h}) + \frac{a_{0,d}}{5}\big)\Delta t\sum_{j=0}^m\sum_{i=d,s}\|E_{i,h}^j\|_h^2 + \sigma\Delta t\sum_{j=0}^m\|E_{\ell,h}^j\|_h^2 + \Delta t\sum_{j=0}^m T_{er,d}(j), \end{aligned} \tag{95}$$

for $j = 0,\dots,M-1$. Then there exists an upper bound for the time step size $\Delta t_0 = \frac{5}{a_{0,d}}$, such that, for $\Delta t \in (0, \Delta t_0)$, we deduce

$$\begin{aligned} & \sum_{i=d,s}\|E_{i,h}^{m+1}\|_h^2 + \Delta t\sum_{j=0}^{m+1}\|D_{-x}E_{d,h}^j\|_+^2 \\ & \quad \leq \frac{1}{\min\{1-\Delta t\frac{a_{0,d}}{5}, \frac{a_{0,d}}{2}\}}\Big((1+\frac{a_{0,d}}{2}\Delta t)\Big(\sum_{i=d,s}\|E_{i,d}^0\|_h^2 + \|D_{-x}E_{d,h}^0\|_+^2\Big) \\ & \quad + \sigma\Delta t\sum_{j=0}^m\|E_{\ell,h}^j\|_h^2 + \Delta t\sum_{j=0}^m T_{er,d}(j)\Big) + \Delta t\frac{\theta(c_{\ell,h}) + \frac{a_{0,d}}{5}}{\min\{1-\Delta t\frac{a_{0,d}}{5}, \frac{a_{0,d}}{2}\}}\sum_{j=0}^m\sum_{i=d,s}\|E_{i,h}^j\|_h^2, \end{aligned} \tag{96}$$

for $j = 0,\dots,M-1$.

Finally, from (96) we conclude (90).

■

Combining Corollaries 3 and 4 with Theorem 4 we can state the following result:

Corollary 5 *Under the assumptions of Theorems 3 and 4, if* Λ *is such that* $h \in \Lambda$, *satisfis the condition (87), then there exist an upper bound for the time step size* $\Delta t_{\ell,d}$ *such that, for* $\Delta t \in (0, \Delta t_{\ell,d}$, *and a positive constant* C, h *and* Δt *independent, such that*

$$\sum_{i=d,s} \|E_{i,h}^m\|_h^2 + \Delta t \sum_{j=0}^{m} \|D_{-x} E_{d,h}^j\|_+^2 \le C \Big(\sum_{i=d,\ell,s} \|E_{i,h}^0\|_h^2 + \sum_{i=d,\ell} \|D_{-x} E_{i,d}^0\|_+^2 + h_{max}^4 + \Delta t^2 \Big), \tag{97}$$

for $m = 0, \dots, M$. ∎

6 Numerical simulation

This section aims to illustrate the main results of this work: Theorems 1 and 2 for the semi-discrete approximation defined by (22), (23) and (24), and Theorems 3 and 4 for the IMEX approximation defined by (63), (64) and (65).

In order to consider a differential problem with a known solution, we replace the problem described by (1)-(3), by a modified problem obtained by adding in each partial differential equation a reaction term R_i, $i = \ell, d, s$.

Let c_ℓ be the solvent concentration solution of the modified problem defined by $c_\ell(x,t) = e^{-\frac{t}{150}} \tilde{C}(x) + \phi(t)$, with $\phi(t) = c_{ext}(1 - e^{-\frac{t}{150}})$ and

$$\tilde{C}(x) = \left(1 - \frac{1}{m}\right)(c_{ext} - 1)\frac{r^2}{R^2} + \frac{c_{ext} - 1}{m} + \frac{|ax - R|^{\sigma+1}}{(aR - R)^{\sigma+1}} + \frac{a\,R^\sigma(\sigma+1)}{(aR - R)^{\sigma+1}}(x - R),$$

where we consider the values $a = 3$, $m = 10$ and $\sigma = 1.7$. In this definition, $R = 1\ mm$ is the radius of polymeric platform and the exterior solvent concentration $c_{ext} = 755.74\ kg/m^3$ is considered constant. Notice that $x = \frac{R}{a}$ is a critical point and $c_\ell \in H^3(\Omega)$ satisfies the hypothesis of Theorem 3.

Let c_d be the solid drug concentration solution of the modified problem defined by $c_d(x,t) = g(x,\, t)\,\psi(t)$, with

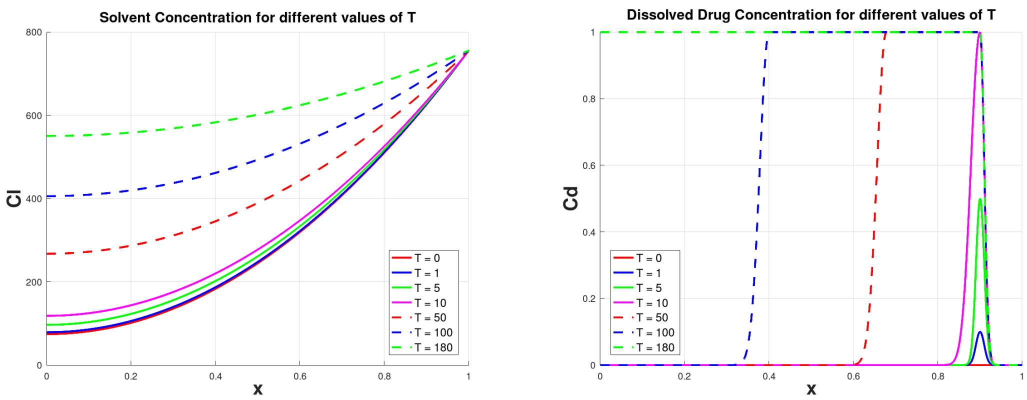
$$g(x,\,t) = \begin{cases} exp\left(-\dfrac{(x - a_0)^2 + |x - a_0|^{\sigma+1}}{2 \cdot 10^{-4}}\right), & \text{if } x \ge a_0 \\ 1, & \text{if } a_2(t) < x < a_0 \\ exp\left(-\dfrac{(x - a_2(t))^2 + |x - a_2(t)|^{\sigma+1}}{2 \cdot 10^{-4}}\right), & \text{if } x \le a_2(t) \end{cases}$$

and $\psi(t) = \begin{cases} \frac{t}{\tilde{t}}, & \text{if } t < \tilde{t} \\ 1, & \text{if } t \ge \tilde{t} \end{cases}$. In this definition, we consider $\tilde{t} = 10\ s$ and $a_0 = 0.9\ mm$. The $a_2(t)$ function is given by $a_2(t) = \begin{cases} a_0, & \text{if } t < \tilde{t} \\ a_0 - \dfrac{(t - \tilde{t})}{t_1}, & \text{if } \tilde{t} \le t \le t_1, \end{cases}$ where $t_1 = T_{max} = 180s$. Notice that $c_d \in H^3(\Omega)$ satisfies the hypothesis of Theorem 4.

Finally, we consider c_s the solid drug concentration solution of the modified problem defined by $c_s(x,t) = \left(1 + \dfrac{t}{5 \times 10^{-5}}\; e^{-k\left(\frac{10}{4} - \frac{tx}{30}\right)}\right)^{-1}$ where $k = 10$ is a constant.

Figure 1 illustrates the behaviour of solvent concentration and dissolved drug concentration in time. As T increases, increases the solvent concentration in the polymeric structure and increases the dissolved drug concentration in the polymeric regions filled with fluid. A sharp decreases can be seen near the boundary because all the dissolved drug that attains the polymeric boundary is immediately removed from this region (homogeneous Dirichlet boundary condition at polymeric boundary).

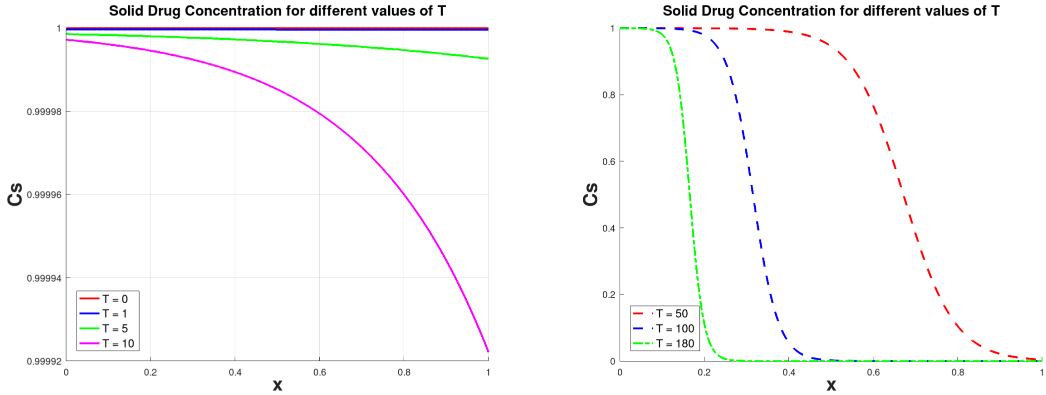
Figure 2 illustrates the behavior of solid drug concentration at initial times and values of T close to $T_{max} = 180\ s$. The behavior of the solid drug is the opposite of the behavior of the dissolved drug. Note with a such behavior these theoretical concentration solutions describe a phenomenological meaningful drug release problem.



(a) Solvent concentration

(b) Dissolved drug concentration

Figure 1: Solvent concentration and dissolved drug concentration for $T = 0, 1, 5, 10, 50, 100$ and 180 s



(a) $T = 0, 1, 5$ and 10 (b) $T = 50, 100$ and 180

Figure 2: Solid drug Concentration for different values of T

Example 1 *In what follows we intend to illustrate Theorems 1 and 2 for the semi-discrete approximation defined by* (22), (23) *and* (24). *The time integration of the modified IBVP obtained from* (22), (23)*and* (24) *introducing convenient reaction terms to get a problem with the introduced solution, was performed in block using an explicit embedded Runge-Kutta (4,5) included in the © Matlab ode suite with the code ode45 [21]. We consider the final time $T = 5$ s and the time grid $\{t_m, m = 0, \cdots, M\}$ with variable step size less than $\Delta t_{max} = 1 \times 10^{-1}$ s. In order to avoid the nonlinearity of the modified system, we calculate σ and the diffusion coefficients D_ℓ, D_d and D_v considering the solvent concentration at previous times. The integral term of first equation was approximated using the trapezoidal rule.*

In the computation of the convergence orders of the numerical approximations obtained as described before, we consider

$$\|E_{i,h}\|_H = \max_{m=0,\ldots,M} \sqrt{\|E_{i,h}^m\|_h^2 + \sum_{j=0}^{m} \Delta t_j \|D_{-x} E_{i,h}^j\|_+^2}, \ \ \textit{for } i = \ell, d, \tag{98}$$

$$\|E_{s,h}\|_h = \max_{m=0,\ldots,M} \|E_{s,h}^m\|_h, \tag{99}$$

and the rates

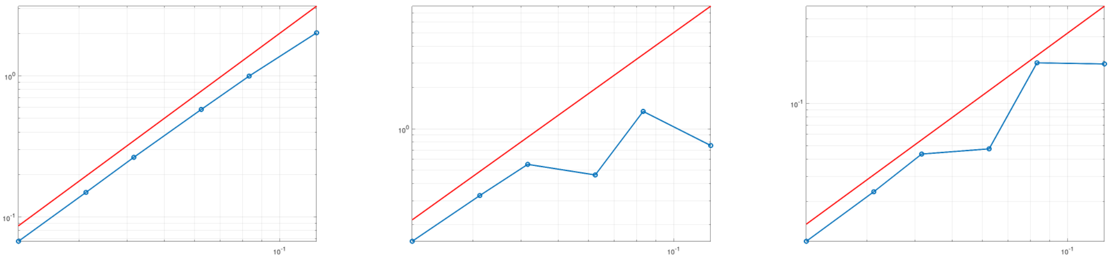
$$Rate_i = \frac{\log \frac{\|E_{i,h}\|_h}{\|E_{i,\tilde{h}}\|_{\tilde{h}}}}{\log \frac{h_{max}}{\tilde{h}_{max}}}, \ i = \ell, d, s. \tag{100}$$

In Table 1 we present the errors $E_{i,h}, i = \ell, d, s$, and the corresponding convergence rates.

$h_{max}(approx.)$	$\|E_{\ell,h}\|_H$	$Rate_l$	$\|E_{d,h}\|_H$	$Rate_d$	$\|E_{s,h}\|_h$	$Rate_s$
1.2500×10^{-1}	2.0177	–	7.5616×10^{-1}	–	1.9104×10^{-1}	–
8.3333×10^{-2}	9.9617×10^{-1}	1.7408	1.3401	−1.4113	1.9456×10^{-1}	−0.0450
6.2500×10^{-2}	5.7778×10^{-1}	1.8934	4.6153×10^{-1}	3.7052	4.7313×10^{-2}	4.9151
4.1666×10^{-2}	2.6463×10^{-1}	1.9257	5.5137×10^{-1}	−4.3865	4.3432×10^{-2}	0.2111
3.1250×10^{-2}	1.4929×10^{-1}	1.9897	3.2682×10^{-1}	1.8179	2.3372×10^{-2}	2.1538
2.0833×10^{-2}	6.7265×10^{-2}	1.9663	1.5182×10^{-1}	1.8909	1.0357×10^{-2}	2.0071

Table 1: Errors $\|E_{i,h}\|_H$ for $i = \ell, d$, $\|E_{s,h}\|_h$ and the corresponding convergence rates.

In Figure 3 we plot the logarithm of the error norms (in blue) and a line with a slope 2 (in red).



(a) Solvent Concentration (b) Dissolved Drug Concentration (c) Solid Drug Concentration

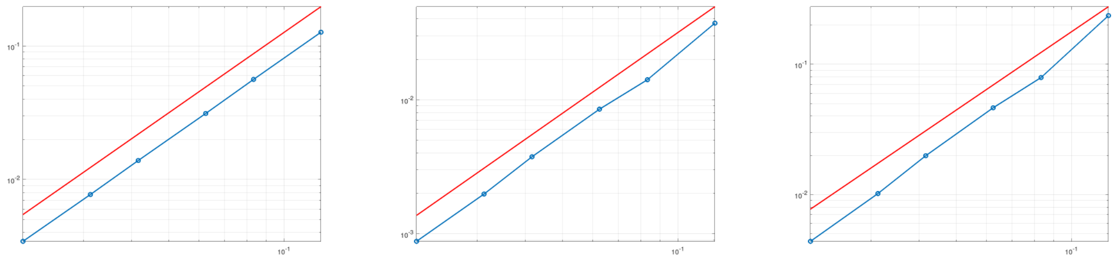
Figure 3: Plot of the logarithmic of the errors on H-norm

Example 2 *In what follows we illustrate Theorems 3 and 4 for the IMEX approximation defined by* (63)*,* (64) *and* (65) *but introducing in this problem the reaction terms as before.*

Table 2 includes the errors $e_{i,h}, i = \ell, d, s$, and the corresponding convergence rates. In Figure 4 we plot the logarithm of the error norms.

$h_{max}(approx.)$	$\|e_{\ell,h}\|_h$	$Rate_l$	$\|e_{d,h}\|_h$	$Rate_d$	$\|e_{s,h}\|_h$	$Rate_s$
1.2500×10^{-1}	1.2654×10^{-1}	–	3.7206×10^{-2}	–	2.3699×10^{-1}	–
8.3333×10^{-2}	5.6080×10^{-2}	2.0069	1.4082×10^{-2}	2.3960	7.9176×10^{-2}	2.7038
6.2500×10^{-2}	3.1175×10^{-2}	2.0409	8.4988×10^{-3}	1.7554	4.6400×10^{-2}	1.8574
4.1666×10^{-2}	1.3865×10^{-2}	1.9982	3.7525×10^{-3}	2.0162	1.9864×10^{-2}	2.0924
3.1250×10^{-2}	7.7157×10^{-3}	2.0374	1.9808×10^{-3}	2.2209	1.0165×10^{-2}	2.3287
2.0833×10^{-2}	3.4440×10^{-3}	1.9893	8.7965×10^{-4}	2.0020	4.3674×10^{-3}	2.0834

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



(a) Solvent Concentration (b) Dissolved Drug Concentration (c) Solid Drug Concentration

Figure 4: Plot of the logarithmic of the errors on H-norm

7 Conclusions

In this paper we consider the numerical analysis of a semi-discrete approximation and an IMEX approximation for the quasilinear initial boundary value problem (1), (2) and (3) that are defined by (22), (23) and (24) and (63), (64) and (65), respectively. It should be noticed that the nonlinear IBVP (1), (2) and (3) can be used to describe the drug release from a polymeric platform loaded with drug in the solid state when the drug reservoir is imbedded in a solvent.

Theorems 1 and 2, for the semi-discrete approximation, and Theorems 3 and 4, for the IMEX approximation, are the main contributions of the present paper. It should be pointed out that the smooth version of Theorems 1 and 2 were previously obtained in [4]. In the new results we assume that the fluid concentration and the dissolved drug concentration are in $H^3(0, R)$. The main ingredient in the convergence analysis for nonsmooth solutions is the Bramble-Hilbert Lemma [5] introduced in the convergence analysis of FDM or of fully discrete FEM in [2] and [12].

It is important to remark that, to obtain the convergence results for dissolved and solid drugs concentrations, the uniform boundness of the numerical approximations for the solvent concentrations has an important role. This boundness is established in both scenarios from the error estimates and imposing smoothness assumptions on the spatial grid, for the semi-discrete approach, and on spatial and time grids in the IMEX approach. Numerical experiments illustrating the proved theoretical rates of convergence are also included.

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