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Iontophoresis - estimating the released drug

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Abstract

The use of enhancers to increase the drug molecules penetration into target tissues is an usual technique in drug delivery. In transdermal drug delivery, electric fields are often used to increase the drug transport to the target tissue. In this paper we study the drug delivery from a reservoir which is in contact with a target tissue. We assume that the drug transport in the coupled system is enhanced by a small electric field that generates a convective field. The qualitative behaviour of the system is illustrated and energy estimates for the released drug are obtained.

Key words: Iontophoresis, mathematical model, numerical simulation
MSC 2000: AMS 35B10,35M06

1 Introduction

Intelligent drug delivery devices have been developed during the last decades to deliver drugs in a controlled manner at specific locations. Some of these systems use stimuli-responsive polymers, where the drug is entrapped, that are able to respond to the modification of external environment like electric fields, pH, and temperature. Electric fields are attractive stimulus because they can be precisely controlled, and the drug delivery responses can be predicted.

The use of electric fields as enhancers is popular in transdermal drug delivery where iontophoresis ([1], [4], [5],[6], [8], [10],) and electroploration ([1], [2], [3], [12]), or combination of both, are usual procedures. Drug delivery systems for cancer treatment based in this technology were recently developed ([11]). In this case, the device based on drug-encapsulated nanoparticles is remotely controlled by an electric field to deliver the biological agent in the cancer target tissue (electrochemotherapy)([7]).

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Each of the above applications involves complex phenomena. For instance, in transdermal drug delivery enhanced by an electric field the drug leaves the polymeric matrix, enters the stratum corneum and is transported through the skin to reach the circulatory system. In both media the transport occurs by passive diffusion, electromigration (migration of ions due to the electric field) and electroosmosis (transport due the solvent movement) ([5], [9], [10]).

Let us consider a coupled system: reservoir containing a charged drug and a tissue. In iontophoresis procedure, a small electric field is applied to the coupled system. If the drug molecules are positive, then the anode is in contact with the reservoir and the cathode is in a opposite position. The generated electric field induces a convective field in the system that depends on the drug molecules valence, intensity of the electric field, temperature, electric conductivity of both media and drug diffusion([5],[6]).

The mathematical modelling is a powerful tool that allows a virtual representation of the physical and biological phenomena involved and contributes to the understanding of the role of each phenomenon, the influence of the parameters of the model in its global behaviour and to justify experimental data. Furthermore, it can be used to help the design of new protocols, new drug delivery devices and plan new experiments and treatments.

The main objective of this paper is the mathematical modelling of the drug release from a polymeric matrix and its entrance in the circulatory system when the iontophoresis procedure is used. In this case the drug delivery from polymeric device is enhanced by an electric field of low intensity, which is applied during long periods of time, and its entrance in a target tissue also enhanced by the electric field. The mathematical model is characterized by partial differential equations that describe the transport through the media (polymeric matrix and target tissue) and the evolution of the electric field which is described by the Laplace equation in both media. The electric potential induces a convective field that enhances the drug transport. Then the time-space evolution of the drug in both media is described by convection-diffusion equations and additional conditions: initial, boundary and interface conditions ([6]).

The paper is organized as follows. In Section 2 we present the coupled mathematical model. Solving the coupled problem for the electric field, the convective field is explicitly given and the Laplace-drug equations are replaced by convection-diffusion equations. Energy estimates are obtained in Section 3. Such estimates are used to obtain lower bounds for the released drug. In Section 4 we present some numerical results illustrating the behaviour of the coupled system in different scenarios. We conclude this work by presenting in Section 5 some conclusions.

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2 The Laplace-drug equations

In what follows we assume that the reservoir and the target tissue are isotropic media. This assumption allows the replacement of the 3D physical model: reservoir in contact with the target tissue, by a 1D model. Let $[0, \ell_1]$ be the reservoir and $]\ell_1, \ell_2]$ the target tissue layer. We assume that the left hand side of the reservoir is isolated and the drug molecules that attain the boundary $x = \ell_2$ are immediately removed. In the domains $(0, \ell_1)$ and (ℓ_1, ℓ_2) a diffusion process takes place enhanced by the electric field generated by the applied electric potential ϕ (V) at $x = 0$ and $x = \ell_2$, respectively, ϕ_0 and ϕ_1. We assume that the polymeric matrix of the reservoir and the target tissue have different electric conductivities σ_r and σ_s (S/m), respectively, as well as the drug has different diffusion coefficients in both media, D_r and D_s (m^2/s), respectively.

The drug transport occurs by passive diffusion and by a convective field induced by the electric field $E = -\nabla\phi$. Then, neglecting the electroosmosis transport, the drug mass flux in the reservoir J_r and in the target tissue J_s are given by the Nernst-Planck equation

$$J_i = -D_i \nabla c_i + v_i c_i, i = r, s, \tag{1}$$

where c_i denotes the drug concentration (g/m^3) in the medium $i = r, s$, and v_i is given by the Nernst-Einstein equation

$$v_i = \frac{D_i z F}{R T_i} \nabla \phi_i, i = r, s, \tag{2}$$

where z denotes the valence of the drug molecules, R the Faraday constant $(9.6485 \times 10^4 Coulomb/mol)$, T_i the temperature (K) in the medium i, and R de gas constant $(8.31446 J/(K mol))$.

From the previous considerations, the electric potential $\phi_i, i = r, s$, are described by the two equations

$$\begin{cases} \sigma_r \nabla \phi_r = 0 \text{ in } (0, \ell_1) \\ \phi_r(0) = \phi_0, \end{cases} \tag{3}$$

and

$$\begin{cases} \sigma_r s \nabla \phi_s = 0 \text{ in } (\ell_1, \ell_2) \\ \phi_s(\ell_2) = \phi_1, \end{cases} \tag{4}$$

coupled with the transition condition

$$\begin{cases} \phi_r(\ell_1) = \phi_s(\ell_1) \text{ (continuity of the potential)} \\ \\ \sigma_r \nabla \phi_r(\ell_1) = \sigma_s \nabla \phi_s(\ell_1) \text{ (continuity of the electric field).} \end{cases} \tag{5}$$

The time-space drug evolution is described by the mass conservation law

$$\frac{\partial c_i}{\partial t} + \nabla J_i = 0, \; i = r, s, \tag{6}$$

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coupled with the Nernst-Planck equation (1). Then, for $c_i, i = r, s$, we obtain

$$\begin{cases} \dfrac{\partial c_r}{\partial t} + \nabla(v_r c_r) = \nabla(D_r \nabla c_r) \text{ in } (0, \ell_1) \times \mathbb{R}^+, \\ \\ D_r \nabla c_r(0,t) - v_r c_r(0,t) = 0, t \in \mathbb{R}^+, \end{cases} \tag{7}$$

and

$$\begin{cases} \dfrac{\partial c_s}{\partial t} + \nabla(v_s c_s) = \nabla(D_s \nabla c_s) \text{ in } (\ell_1, \ell_2) \times \mathbb{R}^+, \\ \\ c_s(\ell_2, t) = 0, t \in \mathbb{R}^+. \end{cases} \tag{8}$$

System (7), (8) is complemented with the interface conditions

$$\begin{cases} c_r(\ell_1, t) = c_s(\ell_1, t) \text{ (continuity of the concentration)}, \\ \\ J_r(\ell_1, t) = J_s(\ell_1, t) \text{ (continuity of the mass flux)}, \end{cases} \tag{9}$$

and initial condition

$$\begin{cases} c_r(x, 0) = c_{r,0}, x \in (0, \ell_1), \\ \\ c_s(x, 0) = 0, x \in (\ell_1, \ell_2). \end{cases} \tag{10}$$

Condition (10) means that the reservoir is initially with a homogeneous drug distribution and the target tissue is empty.

3 The drug delivery

Solving the potential problems (3), (4) and (5) we easily obtain

$$\begin{cases} \phi_r(x) = \dfrac{\phi_1 - \phi_0}{\ell_1 + \frac{\sigma_r}{\sigma_s}(\ell_2 - \ell_1)} x + \phi_0, \ x \in [0, \ell_1], \\ \\ \phi_s(x) = \dfrac{\sigma_r}{\sigma_s} \dfrac{\phi_1 - \phi_0}{\ell_1 + \frac{\sigma_r}{\sigma_s}(\ell_2 - \ell_1)} (x - \ell_2) + \phi_1, \ x \in [\ell_1, \ell_2]. \end{cases} \tag{11}$$

From (11) and (2) we deduce the convective velocities

$$\begin{cases} v_r = \dfrac{D_r z F}{R T_r} \dfrac{\phi_1 - \phi_0}{\ell_1 + \frac{\sigma_r}{\sigma_s}(\ell_2 - \ell_1)} \\ \\ v_s = \dfrac{D_s z F}{R T_s} \dfrac{\sigma_r}{\sigma_s} \dfrac{\phi_1 - \phi_0}{\ell_1 + \frac{\sigma_r}{\sigma_s}(\ell_2 - \ell_1)} \end{cases} \tag{12}$$

We introduce now the weak formulation of the initial boundary value coupled problem (7), (8), (9) and (10). To do that we define the following space $V = \{w \in H^1(0, \ell_2) : w(\ell_2) = 0\}$.

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The weak solution for the previous problem is a function $c \in L^2(\mathbb{R}^+, V) \cap C^1(\mathbb{R}^+, L^2(0, \ell_2))$ such that

$$(c'(t), w) - (vc(t), \nabla w) = (D\nabla c(t), w), t \in \mathbb{R}^+, \forall w \in V, \tag{13}$$

where $(.,.)$ denotes the usual inner product in $L^2(0, \ell_2)$, and

$$c(0) = c_{r,0} \text{ in } [0, \ell_1], \ c(0) = 0 \text{ in } (\ell_1, \ell_2]. \tag{14}$$

Then the drug distribution is defined by

$$c_r(t) = c(t) \text{ in } [0, \ell_1], \ c_s(t) = c(t) \text{ in } [\ell_1, \ell_2].$$

In (13) D and v are defined by

$$D = \begin{cases} D_r, \ x \in (0, \ell_1), \\ \\ D_s, \ x \in (\ell_1, \ell_2), \end{cases} \qquad D = \begin{cases} v_r, \ x \in (0, \ell_1), \\ \\ v_s, \ x \in (\ell_1, \ell_2). \end{cases}$$

To study the stability of the weak problem we recall that the following Friedrich-Poincaré inequality

$$\|w\|^2 \leq \frac{\ell_2^2}{2} \|\nabla w\|^2, \ w \in V, \tag{15}$$

holds. In the next results we establish energy estimates for $c(t)$:

Theorem 1 *If $c \in L^2(\mathbb{R}, V) \cap C^1(\mathbb{R}^+, L^2(0, \ell_2))$ is a solution of (13), (14) then*

$$\|c(t)\|^2 \leq e^{(-\frac{2}{\ell_2^2} \min_{i=r,s} D_i + \max_{i=r,s} \frac{v_i^2}{D_i})t} \|c(0)\|^2, t \in \mathbb{R}_0^+. \tag{16}$$

Proof: Takin in (13) $w = c(t)$ we have

$$\frac{d}{dt}\|c(t)\|^2 = -2\|\sqrt{D}\nabla c(t)\|^2 + 2(vc(t), \nabla c(t)). \tag{17}$$

As

$$2(vc(t), \nabla c(t)) \leq \sum_{i=r,s}^{2} \Big(v_i^2 \frac{1}{2\epsilon_i^2} \|c(t)\|_i^2 + 2\epsilon_i^2 \|\nabla c(t)\|_i^2 \Big),$$

with $\epsilon \neq 0$, where $\|.\|_i$, for $i = r, s$, denotes the L^2 norm in the reservoir and in the target tissue, respectively, we deduce

$$\frac{d}{dt}\|c(t)\|^2 \leq \sum_{i=r,s} \Big((-2D_i + 2\epsilon_i^2) \|\nabla c(t)\|_i^2 + v_i^2 \frac{1}{2\epsilon_i^2} \|c(t)\|_i^2.$$

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If we fix now $\epsilon_i^2 = \frac{1}{2}D_i$, then we establish

$$\frac{d}{dt}\|c(t)\|^2 \leq \sum_{i=r,s}\Big(D_i\|\nabla c(t)\|_i^2 + \frac{v_i^2}{D_i}\|c(t)\|_i^2\Big),$$

that implies

$$\frac{d}{dt}\|c(t)\|^2 \leq -\min_{i=r,s} D_i\|\nabla c(t)\| + \max_{i=r,s}\frac{v_i^2}{D_i}\|c(t)\|^2.$$

Applying the inequality (15) we obtain

$$\frac{d}{dt}\|c(t)\|^2 \leq \Big(-\frac{2}{\ell_2^2}\min_{i=r,s} D_i + \max_{i=r,s}\frac{v_i^2}{D_i}\Big)\|c(t)\|^2$$

that leads to (16).

■

From Theorem 1 we conclude the stability of the IVP (13), (14) and if $c, \tilde{c} \in L^2(\mathbb{R}, V) \cap C^1(\mathbb{R}^+, L^2(0,\ell_2))$ are solutions of this problem then $c = \tilde{c}$.

The upper bound (16) can be used to study the qualitative behavior of the drug mass inside of the coupled system and the absorbed drug. Let

$$M(t) = \int_0^{\ell_2} c(t)\,dx, t \in \mathbb{R}_0^+,$$

be the drug mass in the coupled system.
As

$$M(t) \leq \sqrt{\ell_2}\|c(t)\|,$$

from Theorem 1 we obtain an upper bound for such mass.

Corollary 1 *Under the assumptions of Theorem 1,*

$$M(t) \leq \sqrt{\ell_2}e^{\frac{1}{2}(-\frac{2}{\ell_2^2}\min_{i=r,s} D_i + \max_{i=r,s}\frac{v_i^2}{D_i})t}\|c(0)\|,\ t \in \mathbb{R}_0^+. \tag{18}$$

Moreover, if

$$\frac{\max_{i=r,s}\frac{v_i^2}{D_i}}{D_i} < \frac{2}{\ell_2^2}, i = r, s, \tag{19}$$

then

$$\lim_{t\to\infty} M(t) = 0 \ \ \textit{exponentially.} \tag{20}$$

■

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Let $M_{abs}(t)$ be the absorbed mass. We have

$$M_{abs}(t) = M(0) - M(t), t \in \mathbb{R}_0^+.$$

and consequently

$$M_{abs}(t) \geq M(0) - \sqrt{\ell_2} e^{\frac{1}{2}(-\frac{2}{\ell_2^2}\min_{i=r,s} D_i + \max_{i=r,s} \frac{v_i^2}{D_i})t} \|c(0)\|, t \in \mathbb{R}_0^+. \tag{21}$$

We remark that condition (19) can be a reasonable assumption at least for thin reservoirs where ℓ_1 is small.

To obtain a second estimate for $M(t)$, we need to improve the estimate (16). From (17) we deduce

$$\frac{d}{dt}\|c(t)\|^2 \leq -2 \min_{i=r,s} D_i \|\nabla c(t)\|^2 + 2 \max_{i=r,s} v_i \|c(t)\| \|\nabla c(t)\|,$$

that leads to

$$\frac{d}{dt}\|c(t)\|^2 \leq \Big(-2 \min_{i=r,s} D_i + \sqrt{2}\ell_2 \max_{i=r,s} v_i \Big) \|\nabla c(t)\|^2.$$

Assuming that

$$\frac{v_i}{D_i} < \frac{2\sqrt{2}}{\ell_2}, i = r, s, \tag{22}$$

we obtain

$$\frac{d}{dt}\|c(t)\|^2 \leq \Big(-2 \min_{i=r,s} D_i + \sqrt{2}\ell_2 \max_{i=r,s} v_i \Big) \frac{\ell_2^2}{2} \|c(t)\|^2,$$

and finally

$$\|c(t)\|^2 \leq e^{\ell_2^2(-2\min_{i=r,s} D_i + \sqrt{2}\ell_2 \max_{i=r,s} v_i)t} \|c(0)\|^2, t \in \mathbb{R}_0^+. \tag{23}$$

From the previous considerations we conclude that under the condition (22), we have

$$M(t) \leq \sqrt{\ell_2} e^{\frac{\ell_2^2}{2}(-2\min_{i=r,s} D_i + \sqrt{2}\ell_2 \max_{i=r,s} v_i)t} \|c(0)\|, t \in \mathbb{R}_0^+, \tag{24}$$

and

$$M_{abs}(t) \geq M(0) - \sqrt{\ell_2} e^{\frac{\ell_2^2}{2}(-2\min_{i=r,s} D_i + \sqrt{2}\ell_2 \max_{i=r,s} v_i)t} \|c(0)\|, t \in \mathbb{R}_0^+. \tag{25}$$

The condition (22) is less restrictive than the condition (19) and the upper bound of (18) for the drug mass in the reservoir- target tissue is grater than the upper bound in (24). To conclude this section we finally observe that the estimates (21) and (25) allow the evaluation of lower bounds for the absorbed mass $M_{abs}(t)$ provided that such lower bounds are positive.

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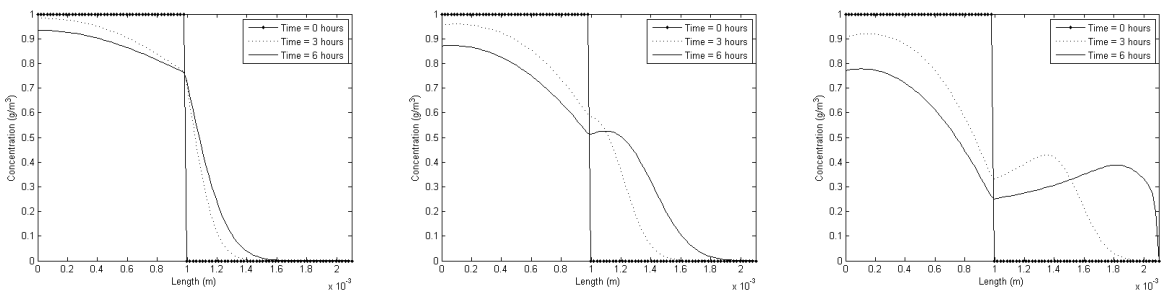
4 Numerical results

In this section we illustrate the behaviour of the drug concentration in the reservoir and target tissue as well as the released drug in different scenarios. We consider $\ell_1 = 9.87\times10^{-4}$, $\ell_2 = 2.1 \times 10^{-3}(m)$ and $D_1 = 10^{-11}$ and $D_2 = 10^{-12}$, $\sigma_1 = 1.5 \times 10^{-5}$, $\sigma_2 = 10^{-7}$, $c(x,0) = 1, x \in (0,\ell_1)$, $c(x,0) = 0, x \in (\ell_1,\ell_2)$. The scenarios are defined considering different applied potentials taking always $\phi_0 = 0$. The numerical results were obtained using a second order finite difference scheme with a uniform grid.

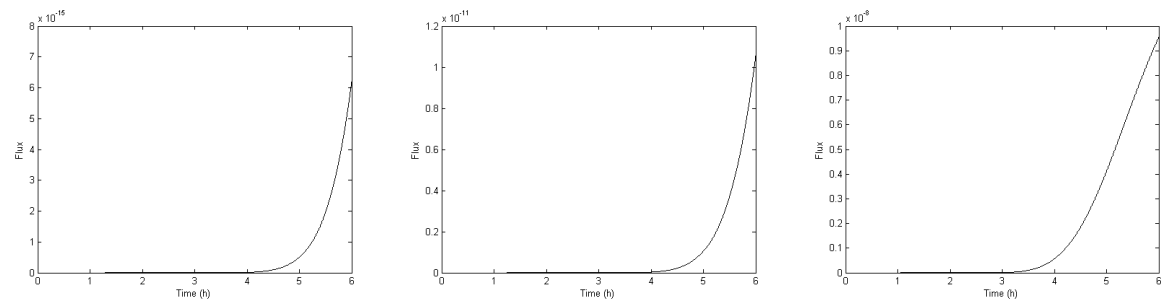
In Figure 1 we present the concentration profiles for $\phi_1 = 0, 0.5$ and 1.5. The increase of the applied potential increases de convective transport and consequently, as time increases, less drug concentration remains in the reservoir and in the target tissue.



(a) (b) (c)

Figure 1: Drug concentration in the coupled system for $\phi_1 = 0$ (a), $\phi_1 = 0.5$(b) and $\phi_1 = 1.5$ (c).

In Figure 2 we illustrate the drug flux at the boundary $x = \ell_2$. The mass flux increases when the applied potential increases.



(a) (b) (c)

Figure 2: Drug flux at $x = \ell_2$ for $\phi_1 = 0$ (a), $\phi_1 = 0.5$(b) and $\phi_1 = 1.5$ (c).

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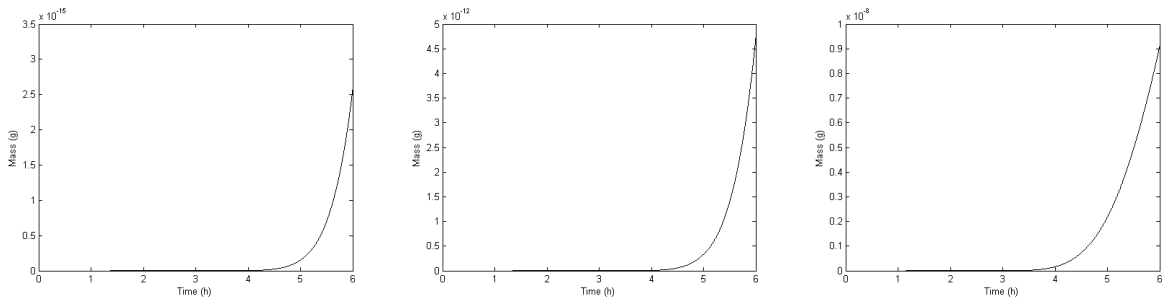
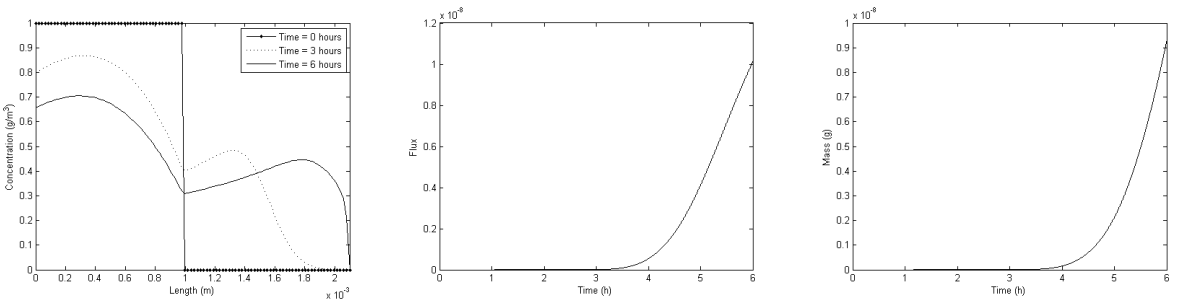
In Figure 3 we plot the absorbed mass drug. These plots are consistent with the previous behaviours of the concentration and flux exhibit in Figures 1, 2.



(a) (b) (c)

Figure 3: Drug flux at $x = \ell_2$ for $\phi_1 = 0$ (a), $\phi_1 = 0.5$(b) and $\phi_1 = 1.5$ (c).

Finally we illustrate the influence of the electric conductivity coefficients. In Figure 4 we plot the drug concentrations, the mass flux at $x = \ell_2$ and the released mass for $\sigma_r = 0.5 \times 10^{-5}$. We observe that a lower electric conductivity in the reservoir can lead to an increase of the released mass. In this case we obtain $M_{abs}(6h) = 9.271 \times 10^{-9}$ while $M_{abs}(6h) = 9.082 \times 10^{-9}$ for $\sigma = 1.5 \times 10^{-5}$. These results were obtained for $\phi_0 = 0, \phi_1 = 1.5$.



(a) (b) (c)

Figure 4: Drug concentrations (a), mass flux at $x = \ell_2$ (b) and the released mass (c).

5 Conclusion

In this paper the mathematical model that describes the drug evolution in the coupled reservoir-target tissue is studied when the drug transport is enhanced by an applied electric

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field. We assume that the applied potential is stationary and is described by a coupled system that admits an explicit solution. As the electric field generates a convective field, the drug transport occurs by passive diffusion and convection.

The convection-diffusion drug system was studied and its stability was concluded under different assumptions on the parameters of the model. The energy estimates were used to obtain estimates for the drug in the coupled system and for the released drug. Such estimates can be used to design iontophoretic systems with a prescribed behaviour. The obtained results need to be numerically validated.

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