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Transdermal iontophoresis—A quantitative and qualitative study

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ABSTRACT

The use of enhancers to increase the drug molecules penetration into target tissues is a usual technique in drug delivery. In transdermal drug delivery, electric fields are often used to increase the drug transport through the skin. In this paper we study a drug delivery mechanism from a reservoir which is in contact with the skin. We assume that the drug transport in the coupled system is enhanced by a small electric field that induces a convective field. We establish energy estimates for the coupled system and we propose a semi-analytical discrete coupled model that mimics the continuous model. The qualitative behaviour of the system is illustrated.

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 the external environment (like electric fields, pH and temperature). Electric fields are an interesting type of 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 [1–6] and electroporation [1,7–9] or a combination of both, are usual procedures. Drug delivery systems for cancer treatment based on this technology were recently developed [10]. 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, see [11]). Each of the above applications involves complex phenomena. For instance, in transdermal drug delivery, enhanced by an electric field, the drug and its solvent vehicle 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) [3,6,12].

In an iontophoresis procedure, a small electric field is applied to the coupled system to enhance the drug transport. If the drug molecules are positively charged, then the anode is in contact with the reservoir and the cathode is in the opposite position. The anode will repel the positively charged drug into the skin. If the drug is negatively charged it will be placed under the cathode that will repel it into the skin. The generated electric field induces a convective flux in the system that depends on the drug molecules valence, intensity of the electric field, temperature, electric conductivity of both media and drug diffusion [3,4]. In this case, the anode is called the active electrode and the cathode the passive electrode.

We are interested in studying transdermal iontophoretic applications consisting of a coupled system having a reservoir containing a charged drug and a tissue, see Fig. 1.

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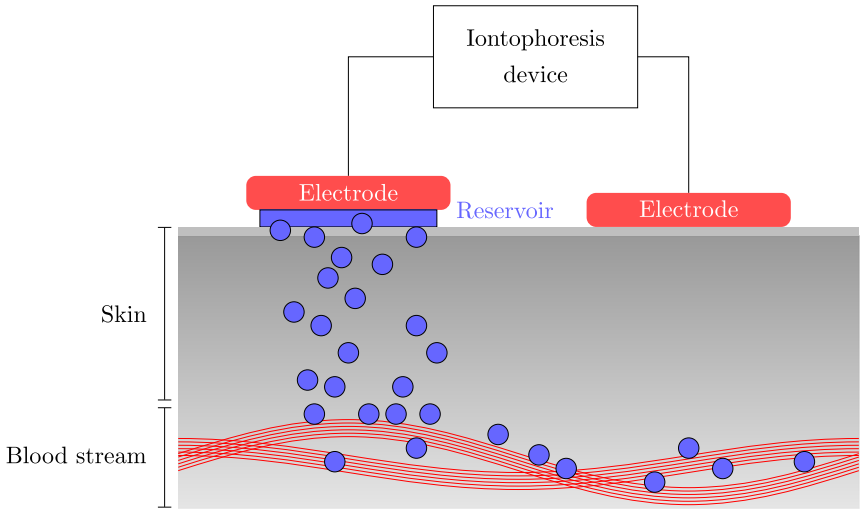

Fig. 1. Drug delivery system for the skin enhanced by an electric potential.

In this case, the polymeric reservoir is in contact with the skin which is a multilayered tissue: epidermis (100 μm), dermis (2–3 mm) and subcutaneous tissue. These three layers have different histological characteristics and functions, however, to simplify the mathematical model, we represent the skin as one layer. The electric field is generated by a potential of low intensity applied during long periods of time. The drug transport occurs by passive diffusion and convection caused by the potential gradient.

The main goal of this paper is the study of a mathematical model that describes the drug transport through the reservoir and the target tissue, under the effect of an electric field. In pursuing this, one of the main contributions of this work is a stability analysis that allows to calculate an upper bound for the L^2-norm of the global (target tissue and reservoir) concentration. This allows to derive an upper bound for the global mass of drug in the system. As a consequence, a lower bound for the absorbed mass will be established. The considered model is a two-layer simplification of the multi-layered model introduced in [13], in the case of a perfect contact between reservoir and skin. 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. A numerical method that mimics the qualitative behaviour of the continuous model is introduced and studied in Section 4. In Section 5 we present some numerical results illustrating the behaviour of the coupled system in different scenarios. In Section 6 some conclusions are presented.

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 $\phi(V)$ 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. We also assume that the diffusion coefficients of the drug in both media are represented, respectively, by D_r and D_s (m^2/s).

The drug transport in the polymeric matrix occurs by passive diffusion and convection induced by the electric field $E = -\nabla\phi$. Let J_r be the drug mass flux. By the Nernst–Planck equation we have

$$J_r = -D_r \nabla c_r - v_r c_r, \tag{1}$$

where c_r denotes the drug concentration (g/m^3) in the polymeric matrix and v_r (m/s) stands for the mean velocity of the solvent vehicle in the reservoir. Let J_s represent the drug mass flux in the skin. By the Nernst–Planck equation we have

$$J_s = -D_s \nabla c_s - v_s c_s + v_{sol} c_s, \tag{2}$$

where c_s denotes the drug concentration in the target tissue. The convective velocity v_{sol}, caused by the electric field, represents the average velocity of the solvent vehicle. The convective velocities v_k, $k = r, s$, are given by the Nernst–Einstein

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