Modelling Transdermal Drug Delivery through a Two-layered System

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Abstract: One of the most promising frontiers of bioengineering is the controlled release of a therapeutic drug from a vehicle across the skin (transdermal drug delivery). In order to study the complete process, a multiphase mathematical model describing the dynamics of a substance between two porous coupled media of different properties and extents is presented. A system of partial differential equation describes the diffusion and the reversible binding and unbinding processes in both layers. Additional flux continuity at the interface and clearance conditions into systemic circulation are imposed. A Sturm-Liouville problem is solved and an analytical solution is given in the form of an infinite series expansion. The model points out the role of the diffusion and reaction parameters, which control the complex transfer mechanism and the drug kinetics across the two layers. Drug mass are given and their dependence on the physical parameters are discussed.

1 INTRODUCTION

Systemic delivery of drugs by percutaneous permeation (*transdermal drug delivery* – TDD for short) offers several advantages compared to oral release or hypotermic injection, guarantees a controlled release rate that can provide a constant concentration for a long period of time, improves patient compliance, and represents an attractive alternative to oral administration (Chien, 1992).

Drugs can be delivered across the skin to have an effect on the tissues adjacent to the site of application (topical delivery) or to be effective after distribution through the circulatory system (systemic delivery). While there are many advantages to deliver drugs through the skin, the barrier properties of it provide a significant challenge. To this aim, it is important to understand the mechanism of drug permeation from the delivery device (or vehicle, typically a transdermal patch or medicated plaster, fig. 1) across the skin (Mitragotri et al., 2011; George et al., 2004).

Mathematical modelling for TDD constitutes a powerful predictive tool for fundamental understanding of biotransport processes. In the absence of experiments, many studies have been carried out about TDD, on its efficacy, the optimal design of devices, based on with mathematical models and numerical simulations (Manitz et al., 1998; Addick et al., 1989; Mitragotri et al., 2011). The transdermal release of drug must be carefully tailored to achieve the optimal therapeutic effect and to deliver the correct dose in the required time (Prausniz and Langer, 2008). The pharmacological effects of the drug, tissue accumulation, duration and distribution could potentially have an effect on its efficacy and a delicate balance between an adequate amount of drug delivered over an extended period of time and the minimal local toxicity should be found (Anissimov and Roberts, 2009). Although a large number of mathematical models are available nowadays for drug dynamics in the skin, there is a limited effort to explain the drug delivery mechanism from the vehicle platform. This is a very important issue indeed, since the polymer matrix acts as a drug reservoir, and a strategical design of its microstructural characteristics would improve the release performances (Rim et al., 2005). It is worth to emphasize that the drug elution depends on the properties of the "vehicle-skin" system, taken as a whole, and modelled as a coupled two-layered system. In it, together with diffusive effects, local mass non-equilibrium transfer processes are considered here, due to the drug binding-unbinding phenomena. In both layers these effects, usually neglected or underestimated, play an important role.

In this paper a "vehicle-skin" coupled model is presented and a semi-analytical form is given for drug concentration and mass in the vehicle and the skin at various times. Our mathematical approach is similar

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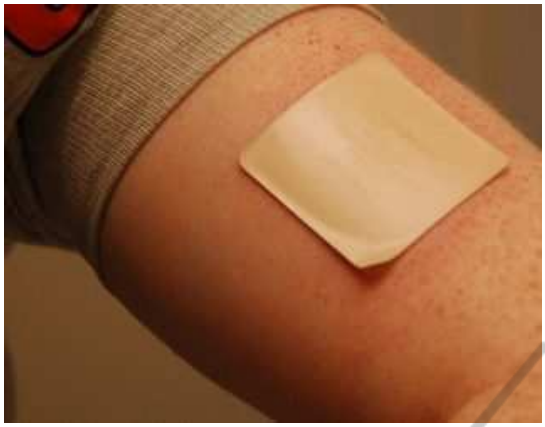

Figure 1: The transdermal patch, a typical vehicle in transdermal drug delivery.

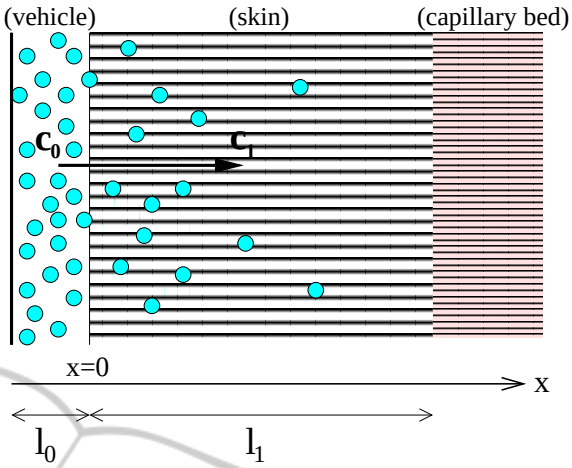

Figure 2: Cross-section of the vehicle and the skin layers. Due to an initial difference of unbounded concentrations c_0 and c_1, a mass flux is established at the interface $x = 0$ and drug diffuses through the skin. At $x = l_1$ the skin-receptor (capillary) is set. Figure not to scale.

to that used to describe drug dynamics from a drug-eluting stent in arterial wall and is based on a two-layer diffusion model (Pontrelli and de Monte, 2010). The simulations, aimed at the design of technologically advanced vehicles, can be used to provide valuable insights into local TDD and to assess experimental procedures to evaluate drug efficacy. A major issue in modelling drug penetration is the assessment of the key parameters defining skin permeability, diffusion coefficients and local mass non-equilibrium transfer rates. A big challenge is the large number of parameters required for an advanced modelling, often not readily available.

2 FORMULATION OF THE PROBLEM

Let us consider a two-layered delivery system constituted by the *vehicle* (the transdermal patch or the film of an ointment), and the *skin* (the stratum corneum followed by the skin-receptor cells and the capillary bed) (fig. 2). The first layer acts as a drug reservoir made of a thin substrate (generally a polymer or a gel) containing a therapeutic drug to be delivered. Because of the small size of the vehicle, most of the mass dynamics occurs along the direction normal to the flat skin surface, we restrict our study to a simplified one-dimensional model. In particular, we consider as x-axis the normal to the skin surface and pointing outwards.

Without loss of generality, let $x_0 = 0$ be the vehicle-skin interface and l_0 and l_1 the thicknesses of the layers, respectively (fig. 2). Either the vehicle and the skin are treated as macroscopically as two homogeneous porous media.

In the vehicle, at initial time, the drug is encapsulated at maximum concentration in solid phase (e.g. nanoparticles) (c_e): in a such (bounded) state, it is unable to be delivered to the tissue. Nevertheless, when the vehicle is applied over the skin, the "in situ" system starts the release process: a fraction of the drug mass is first transferred, in a finite time, to an unbounded – free, biologically available – phase (c_0), and diffuses into the biological tissue (c_1). Similarly, in the skin a part of the unbounded drug is metabolized by the cells and transformed in a bounded state (c_b) (*percutaneous absorption*). Hence, the drug delivery process starts from the vehicle and ends to the skin receptors, with a phase change in a cascade sequence, as schematically represented in fig. 3. Local mass non-equilibrium processes, such as bidirectional drug binding and unbinding phenomena, play a key role in TDD, with characteristic times faster than those of diffusion. A volume-averaged drug concentration $c(x,t)$ (mg/ml) is considered.

In the first layer the process is described by the following equations:

$$\begin{aligned} \frac{\partial c_e}{\partial t} &= -\beta_0 c_e + \delta_0 c_0 && \text{in } (-l_0, 0) \\ \frac{\partial c_0}{\partial t} &= D_0 \frac{\partial^2 c_0}{\partial x^2} + \beta_0 c_e - \delta_0 c_0 && \text{in } (-l_0, 0) \end{aligned} \qquad (1)$$

where D_0 (cm^2/s) is the diffusion coefficient of the unbounded solute, $\beta_0 \geq 0$ and $\delta_0 \geq 0$ are the unbinding and binding rate constants in the vehicle, respectively (s^{-1}).

Similarly, in the second layer, the drug dynamics is governed by a similar reaction-diffusion equation:

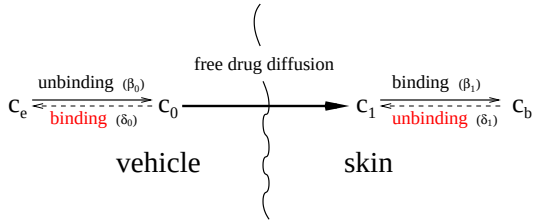

Figure 3: A diagram showing the schematic mechanism of percutaneous drug absorption in the vehicle-skin system. A unbinding (resp. binding) reaction occurs in the vehicle (resp. in the skin). Reverse reactions are possible in both layers. Diffusion occurs only in the free phases c_0 and c_1.

$$\begin{aligned} \frac{\partial c_1}{\partial t} &= D_1 \frac{\partial^2 c_1}{\partial x^2} - \beta_1 c_1 + \delta_1 c_b \qquad \text{in } (0, l_1) \\ \frac{\partial c_b}{\partial t} &= \beta_1 c_1 - \delta_1 c_b \qquad \text{in } (0, l_1) \end{aligned} \tag{2}$$

where D_1 is the effective diffusivity of unbounded drug, $\beta_1 \geq 0$ and $\delta_1 \geq 0$ are the binding and unbinding rate constants in the skin, respectively.

To close the previous bi-layered mass transfer system of eqns. (1)-(2), flux and flux continuity conditions have to be assigned at the vehicle-skin interface:

$$\begin{aligned} D_0 \frac{\partial c_0}{\partial x} &= D_1 \frac{\partial c_1}{\partial x} \\ -D_1 \frac{\partial c_1}{\partial x} &= P(c_0 - c_1) \qquad \text{at } x = 0 \end{aligned}$$

with P the skin permeability coefficient (cm/s). No mass flux passes between the vehicle and the surrounding and we impose a no-flux condition:

$$D_0 \frac{\partial c_0}{\partial x} = 0 \qquad \text{at } x = -l_0$$

Finally, a boundary condition has to be imposed at the skin-receptor (capillary bed) boundary. At this point the elimination of drug by capillary system follows first-order kinetics:

$$K_{cl} c_1 + D_1 \frac{\partial c_1}{\partial x} = 0 \qquad \text{at } x = l_1$$

where K_{cl} is the skin-capillary clearance per unit area (cm/s). The initial conditions are:

$$\begin{aligned} c_e(x,0) &= C_e \qquad & c_0(x,0) &= 0 \\ c_1(x,0) &= 0 \qquad & c_b(x,0) &= 0 \end{aligned}$$

2.1 Dimensionless Equations

All the variables and the parameters are now normalized to get easily computable dimensionless quantities as follows:

$$\begin{aligned} \bar{x} &= \frac{x}{l_1} \qquad & \bar{t} &= \frac{D_1}{(l_1)^2} t \qquad & \bar{c_i} &= \frac{c_i}{C_e} \\ \gamma &= \frac{D}{D_1} \qquad & \phi &= \frac{P l_1}{D_1} \qquad & K &= \frac{K_{cl} l_1}{D_1} \\ \bar{\beta} &= \frac{\beta (l_1)^2}{D_1} \qquad & \bar{\delta} &= \frac{\delta (l_1)^2}{D_1} \end{aligned}$$

By omitting the bar for simplicity, the mass transfer problem (1)-(2) in the two-layered system can be now written in dimensionless form as:

$$\begin{aligned} \frac{\partial c_e}{\partial t} &= -\beta_0 c_e + \delta_0 c_0 \qquad & \text{in } (-l_0, 0) \\ \frac{\partial c_0}{\partial t} &= \gamma_0 \frac{\partial^2 c_0}{\partial x^2} + \beta_0 c_e - \delta_0 c_0 \qquad & \text{in } (-l_0, 0) \\ \frac{\partial c_1}{\partial t} &= \gamma_1 \frac{\partial^2 c_1}{\partial x^2} - \beta_1 c_1 + \delta_1 c_b \qquad & \text{in } (0, 1) \\ \frac{\partial c_b}{\partial t} &= \beta_1 c_1 - \delta_1 c_b \qquad & \text{in } (0, 1) \end{aligned} \tag{3}$$

and the following interface and B.C.'s:

$$\begin{aligned} \frac{\partial c_0}{\partial x} &= 0 \qquad & \text{at } x = -l_0 \\ \gamma_0 \frac{\partial c_0}{\partial x} &= \gamma_1 \frac{\partial c_1}{\partial x} \qquad & \text{at } x = 0 \\ -\gamma_1 \frac{\partial c_1}{\partial x} &= \phi(c_0 - c_1) \qquad & \text{at } x = 0 \\ K c_1 + \gamma_1 \frac{\partial c_1}{\partial x} &= 0 \qquad & \text{at } x = 1 \end{aligned} \tag{4}$$

supplemented with the initial condition:

$$\begin{aligned} c_e(x,0) &= 1 \qquad & c_0(x,0) &= 0 \\ c_1(x,0) &= 0 \qquad & c_b(x,0) &= 0 \end{aligned} \tag{5}$$

3 METHOD OF SOLUTION

Preliminarily, we note that the solution of the linear non-homogeneous ODE (3.1) is:

$$\begin{aligned} c_e(x,t) &= \exp(-\beta_0 t) \\ &+ \exp(-\beta_0 t) \int_0^t \exp(\beta_0 \tau) \delta_0 c_0(x,\tau) d\tau \end{aligned}$$

By considering the correspondent homogeneous problem, it turns out that c_e can be expressed as a

function of c_0. Similarly, from eqn. (3.4), c_b can be expressed as a function of c_1

$$c_b(x,t) = \exp(-\delta_1 t) \int_0^t \exp(\delta_1 \tau) \beta_1 c_1(x,\tau) d\tau$$

Let us find a solution for c_0 and c_1 by separation of variables

$$c_0(x,t) = X_0(x) G_0(t) \qquad c_1(x,t) = X_1(x) G_1(t)$$

As a consequence of the previous remark, the homogeneous part of c_e and c_b can be also separated by the same eigenvector set as:

$$c_e(x,t) = X_0(x) G_e(t) \qquad c_b(x,t) = X_1(x) G_b(t)$$

If $X_0 \neq 0$, $X_1 \neq 0$, the previous problem becomes:

$$\begin{cases} \dfrac{dG_e}{dt} = -\beta_0 G_e + \delta_0 G_0 \\ \dfrac{1}{\gamma_0 G_0} \left[\dfrac{dG_0}{dt} - (\beta_0 G_e - \delta_0 G_0) \right] = \dfrac{X_0''}{X_0} = -\lambda_0^2 \end{cases} \tag{6}$$

$$\begin{cases} \dfrac{dG_b}{dt} = -\delta_1 G_b + \beta_1 G_1 \\ \dfrac{1}{\gamma_1 G_1} \left[\dfrac{dG_1}{dt} - (\delta_1 G_b - \beta_1 G_1) \right] = \dfrac{X_1''}{X_1} = -\lambda_1^2 \end{cases} \tag{7}$$

where λ_0 and λ_1 have to be computed. We have a solution for X_i in the form (Pontrelli and de Monte, 2010):

$$X_0(x) = a_0 \cos(\lambda_0 x) + b_0 \sin(\lambda_0 x)$$

$$X_1(x) = a_1 \cos(\lambda_1 x) + b_1 \sin(\lambda_1 x)$$

By enforcing the boundary-interface conditions (4):

$$a_0 \sin(\lambda_0 l_0) + b_0 \cos(\lambda_0 l_0) = 0$$

$$\gamma_0 \lambda_0 b_0 - \gamma_1 \lambda_1 b_1 = 0$$

$$\phi(a_0 - a_1) + \gamma_1 \lambda_1 b_1 = 0$$

$$[K\cos(\lambda_1) - \gamma_1 \lambda_1 \sin(\lambda_1)]\, a_1 + [K\sin(\lambda_1) + \gamma_1 \lambda_1 \cos(\lambda_1)]\, b_1 = 0$$

A non trivial solution exist only if the determinant of the coefficient matrix is zero, i.e.:

$$\begin{aligned} &\gamma_1 \lambda_1 \left(\gamma_1 \lambda_1 \sin(\lambda_1) - K\cos(\lambda_1)\right) \\ &\times \left[\gamma_0 \lambda_0 \sin(\lambda_0 l_0) - \phi \cos(\lambda_0 l_0)\right] \\ &- \gamma_0 \phi \lambda_0 \sin(\lambda_0 l_0) \left(K\sin(\lambda_1) + \gamma_1 \lambda_1 \cos(\lambda_1)\right) = 0 \end{aligned} \tag{8}$$

The four time dependent functions G_0, G_1, G_e, G_b have to be determined from

$$\frac{d}{dt} \begin{pmatrix} G_e \\ G_0 \end{pmatrix} = \begin{pmatrix} -\beta_0 & \delta_0 \\ \beta_0 & -\delta_0 - \gamma_0 \lambda_0^2 \end{pmatrix} \begin{pmatrix} G_e \\ G_0 \end{pmatrix} \tag{9}$$

$$\frac{d}{dt} \begin{pmatrix} G_b \\ G_1 \end{pmatrix} = \begin{pmatrix} -\delta_1 & \beta_1 \\ \delta_1 & -\beta_1 - \gamma_1 \lambda_1^2 \end{pmatrix} \begin{pmatrix} G_b \\ G_1 \end{pmatrix} \tag{10}$$

Denoting by $\mu_\pm$ (resp. $\nu_\pm$) the eigenvalues of the matrices in eqns. (9) and (10). The general solution of the previous system is:

$$\begin{aligned} G_e(t) &= c_1 \frac{\delta_0}{\beta_0 + \mu_+} \exp(\mu_+ t) + c_2 \frac{\delta_0}{\beta_0 + \mu_-} \exp(\mu_- t) \\ G_0(t) &= c_1 \exp(\mu_+ t) + c_2 \exp(\mu_- t) \\ G_1(t) &= c_3 \exp(\nu_+ t) + c_4 \exp(\nu_- t) \\ G_b(t) &= c_3 \frac{\beta_1}{\delta_1 + \nu_+} \exp(\nu_+ t) + c_4 \frac{\beta_1}{\delta_1 + \nu_-} \exp(\nu_- t) \end{aligned}$$

with:

$$\begin{aligned} \mu_\pm &= \frac{-(\beta_0 + \delta_0 + \gamma_0 \lambda_0^2) \pm \sqrt{(\beta_0 + \delta_0 + \gamma_0 \lambda_0^2)^2 - 4\gamma_0 \beta_0 \lambda_0^2}}{2} \\ \nu_\pm &= \frac{-(\beta_1 + \delta_1 + \gamma_1 \lambda_1^2) \pm \sqrt{(\beta_1 + \delta_1 + \gamma_1 \lambda_1^2)^2 - 4\gamma_1 \delta_1 \lambda_1^2}}{2} \end{aligned} \tag{11}$$

It is easily seen that $\mu_\pm$ and $\nu_\pm$ are real and negative. A necessary condition to guarantee continuity of fluxes at $x = 0$ is that $\mu_\pm = \nu_\pm$.

4 A SPECIAL CASE

We develop here the solution for a particular combination of parameters, being the general case addressed in a forthcoming paper. Under the assumption that

$$\delta_1 = \beta_0 \qquad \delta_0 = \beta_1$$

and

$$\gamma_0 \lambda_0^2 = \gamma_1 \lambda_1^2 \tag{12}$$

we have, from eqn. (11):

$$\mu_\pm = \nu_\pm$$

The nonlinear eqn. (8) is solved together with (12) to get λ_0^k and λ_1^k, $k = 1, 2, \ldots$. Correspondingly, we have a countable set of eigenfunctions X_0^k, X_1^k $k = 1, 2, \ldots$. Finally, the solution of the our problem is given by the linear superposition of the fundamental solution:

$$
\begin{aligned}
c_e(x,t) = & \sum_k X_0^k(x)\left(A_k\frac{\delta_0}{\beta_0+\mu_+^k}\exp(\mu_+^k t)\right.\\
& \left. + B_k\frac{\delta_0}{\beta_0+\mu_-^k}\exp(\mu_-^k t)\right)\\
c_0(x,t) = & \sum_k X_0^k(x)\left(A_k\exp(\mu_+^k t)+B_k\exp(\mu_-^k t)\right)\\
c_1(x,t) = & \sum_k X_1^k(x)\left(A_k\exp(\mu_+^k t)+B_k\exp(\mu_-^k t)\right)\\
c_b(x,t) = & \sum_k X_1^k(x)\left(A_k\frac{\beta_1}{\delta_1+\mu_+^k}\exp(\mu_+^k t)\right.\\
& \left. + B_k\frac{\beta_1}{\delta_1+\mu_-^k}\exp(\mu_-^k t)\right) \qquad (13)
\end{aligned}
$$

The constants A_k, B_k are found by applying the initial condition. First of all, from eqn (13.2) and (13.3) it follows that $B_k = -A_k$. Let us impose the initial condition on the (13.1) and (13.4), i.e:

$$
\begin{aligned}
&\sum_k A_k X_0^k(x)\left(\frac{\delta_0}{\beta_0+\mu_+^k}-\frac{\delta_0}{\beta_0+\mu_-^k}\right)=1\\
&\sum_k A_k X_1^k(x)\left(\frac{\beta_1}{\delta_1+\mu_+^k}-\frac{\beta_1}{\delta_1+\mu_-^k}\right)=0 \qquad (14)
\end{aligned}
$$

By truncating the series to M terms, by collocating in M points, we solve the system (14) is solved to get the constants $A_k, k = 1,...,M$.

The analytical form of the solution given by eqns. (13) allows an easy computation of the drug mass (per unit of area) as integral of the concentration over the correspondent layer:

$$M(t) = \int c(x,t)dx$$

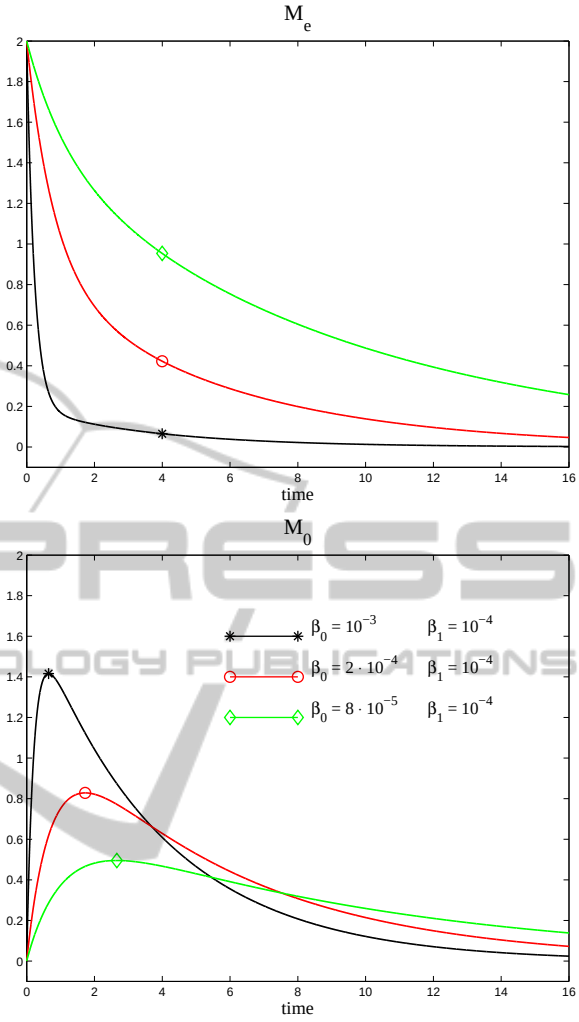

Figure 4: Time histories of the drug mass M_e and M_0 in the vehicle for three values of β_0 (s^{-1}).

5 NUMERICAL SIMULATIONS AND RESULTS

A common difficulty in modelling physiological processes is the identification of reliable estimates of the model parameters. Experiments of TDD are prohibitively expensive or impossible in vivo and the only available source are data from literature. The physical problem depends on a large number of parameters, each of them may vary in a finite range, with a variety of combinations and limiting cases. The model constants cannot be chosen independently from each other and there is a compatibility range of them. For simplicity, the following physical parameters are kept fixed for simulations in TDD (Simon and Loney, 2005; Kubota et al., 2002; Anissimov and Roberts, 2009):

$$
\begin{aligned}
&D_0 = 10^{-8} cm^2/s \qquad && D_1 = 10^{-9} cm^2/s\\
&P = 10^{-6} cm/s && K_{cl} = 10^3 cm/s
\end{aligned}
$$

The thickness of the vehicle is set as: $l_0 = 40\mu m$, whereas the limit of the skin layer (l_1) is estimated by the following considerations. Strictly speaking, in a diffusion-reaction problem the concentration vanishes asymptotically at infinite distance. However, for computational purposes, the concentration is damped out (within a given tolerance) over a finite distance at a given time. Such a distance ("penetration length" d^*) critically depends on the diffusive properties of the two-layered medium, and in particular, is related to the ratio $\frac{D_0}{D_1}$. By taking $l_1 < d^*$ the condition (4.4) is imposed erroneously before it should be. Any truncation of the domain before d^* is arbitrary and does not ensure a conservative model. On the other hand, tak-

ing $l_1 > d^*$ the condition (4.4) is verified, but leads to an overdetermined system. The precise concept and the estimation of the penetration distance in two and multiple layer systems is given in (Pontrelli and de Monte, 2010). All series appearing in the eqn. (13) and following have been truncated at a number of terms $M = 50$.

The concentration is decreasing inside each layer, being possibly discontinuous at the interface, and vanishes at a distance that is within the stratum corneum, at all times. Due to the relatively large value of D_0 and to the small l_0, the concentration profiles are almost flat in the vehicle, with levels reduced in time, and have a decreasing behavior in the skin layer.

The effect of local mass non-equilibrium is studied by varying the values of the on-off reaction rates β_0 and β_1. The mass M_e is exponentially decreasing in the vehicle, and M_0 it is first increasing up to some upper bound and then decaying asymptotically (fig. 4). The relative size of $\beta_0 = \delta_1$ and $\beta_1 = \delta_0$ affects the transfer binding/unbinding processes, thus influencing the mechanism of the whole dynamics. The occurrence and the magnitude of the drug peak depends on the combination and the relative extent of the diffusive and reaction parameters. The outcomes of the simulation provides valuable indicators to assess whether drug reaches target tissue, and to optimize the dose capacity in the vehicle. For example, fig. 5 shows that a lower value of the unbinding parameter β_0 guarantees a more prolonged and uniform release. On the other way around, a large value of β_0 is responsible for a localized peaked distribution followed by a faster decay.

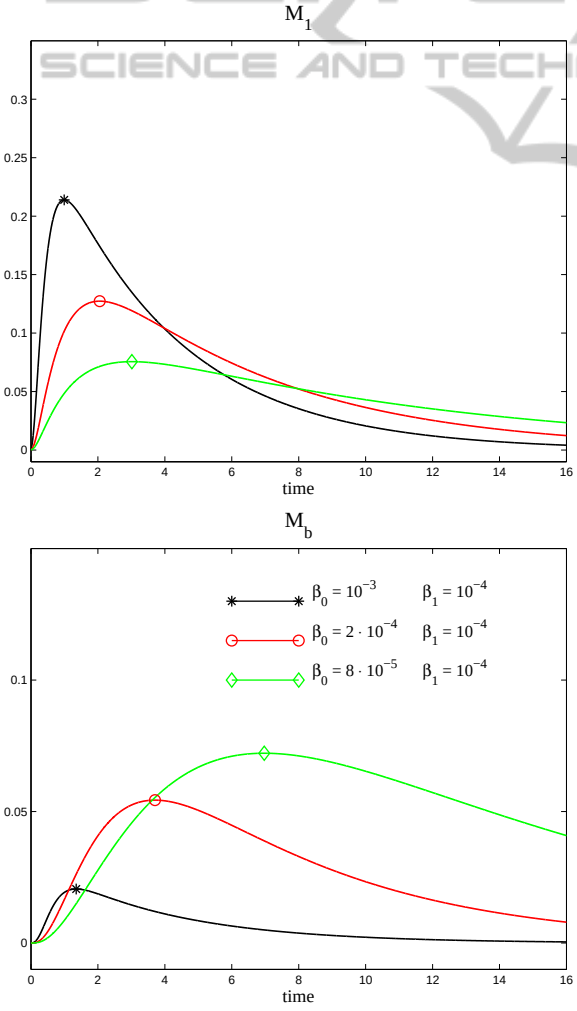

Figure 5: Time histories of the drug mass M_1 and M_b in the vehicle for three values of β_0 (s^{-1}).

The present TDD model constitutes a simple tool that can help in designing and in manufacturing new vehicle platforms that guarantee the optimal release for an extended period of time.

6 CONCLUSIONS

In the last decades, transdermal delivery has emerged as an attractive alternative and an efficient route for drug administration. A mathematical model of drug delivery by percutaneous permeation is presented in this paper. To account the various aspects of drug dynamics from the vehicle across the skin, a multiphase two-layered model is developed and a semi-analytic solution for drug concentration is proposed.

The model incorporates the binding reversible process and can be employed to study the effects of the various parameters that control the vehicle-skin delivery system. This can be of interest in the design of smarter devices in order to get the optimal therapeutic effect by releasing the correct dose in the required time.

Although limited to a simple one-dimensional case, the results of the numerical simulations can offer a useful tool to estimate the performance of the delivery devices.

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REFERENCES

Addick, W., Flynn, G., Weiner, N., and Curl, R. (1989). A mathematical model to describe drug release from thin topical applications. *Int. J. Pharm.*, 56:243–248.

Anissimov, Y. and Roberts, M. (2009). Diffusion modelling of percutaneous absorption kinetics: effects of a slow equilibration process within stratum corneum on absorption and desorption kinetics. *J. Pharm. Science*, 98:772–781.

Chien, Y. (1992). *Novel drug delivery systems*. M. Dekker Inc.

George, K., Kubota, K., and Twizell, E. (2004). A two-dimensional mathematical model of percutaneous drug absorption. *Biomed. Eng. Online*, 3:18:567–578.

Kubota, K., Dey, F., Matar, S., and Twizell, E. (2002). A repeated dose model of percutaneous drug absorption. *Appl. Math. Modell*, 26:529–544.

Manitz, R., Lucht, W., Strehmel, K., Weiner, R., and Neubert, R. (1998). On mathematical modeling of dermal and transdermal drug delivery. *J. Pharm. Sciences*, 87:873–879.

Mitragotri, S., Anissimov, Y., Bunge, A., and al. (2011). Mathematical models of skin permeability: an overview. *Int. J. Pharm.*, 418:115–129.

Pontrelli, G. and de Monte, F. (2010). A multi-layer porous wall model for coronary drug-eluting stents. *Int. J. Heat Mass Transf.*, 53:3629–3637.

Prausniz, M. and Langer, R. (2008). Transdermal drug delivery. *Nat. Biotechnol.*, 26 (11):1261–1268.

Rim, J. E., Pinsky, P., and van Osdol, W. (2005). Finite element modeling of coupled diffusion with partitioning in transdermal drug delivery. *Ann. Biomed. Eng.*, 33 (10):1422–1438.

Simon, L. and Loney, N. (2005). An analytical solution for percutaneous drug absorption: application and removal of the vehicle. *Math. Biosci.*, 197:119–139.