Mathematical Biosciences 257 (2014) 96–103

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

A two-phase two-layer model for transdermal drug delivery and percutaneous absorption

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ARTICLE INFO

Article history:
Available online 14 May 2014

Keywords:
Diffusion–reaction equation
Transdermal drug delivery
Percutaneous absorption
Binding–unbinding
Local mass non-equilibrium

ABSTRACT

One of the 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 two-phase mathematical model describing the dynamics of a substance between two coupled media of different properties and dimensions is presented. A system of partial differential equations describes the diffusion and the binding/unbinding processes in both layers. Additional flux continuity at the interface and clearance conditions into systemic circulation are imposed. An eigenvalue problem with discontinuous coefficients 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 masses are given and their dependence on the physical parameters is discussed.

1. Introduction

Transdermal drug delivery (TDD for short) is an approach used to deliver drugs through the skin for therapeutic purposes as an alternative to oral, intravascular, subcutaneous and transmucosal routes. Various TDD technologies are possible including the use of suitable drug formulations, carriers such as nanoparticles and penetration enhancers to facilitate drug delivery and transcutaneous absorption.[1] TDD offers several advantages compared to other traditional delivery methods: controlled release rate, noninvasive administration, less frequent dosing, and simple application without professional medical aids, improving patient compliance. For these reasons it represents a valuable and attractive alternative to oral administration [1].

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 TDD, the skin's barrier properties 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 [2]. In TDD, the drug should be absorbed to an adequate extent and rate in order to achieve and maintain uniform, systemic, effective levels throughout the duration of use. TDD must be carefully tailored to achieve the optimal therapeutic effect and to deliver the correct dose in the required time [3]. 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 [4]. Most drugs do not penetrate skin at rates sufficient for therapeutic efficacy and this restrictive nature limits the use of the transdermal route to molecules of low molecular weight and with moderate lipophilicity. In general, the first skin layer, the stratum corneum, presents most of the resistance to diffusive transport into skin. Thus, once the drug molecules cross it, transfer into deeper dermal layers and systemic uptake occurs in a relatively short time. In order to speed up transdermal permeation of drugs in the stratum corneum, new delivery techniques are currently under investigation, for example the use of chemical enhancers or microneedles and techniques such as ultrasound, electroporation and iontophoresis [3,5].

Mathematical modeling for TDD constitutes a powerful predictive tool for the fundamental understanding of biotransport processes, and for screening processes and stability assessment of

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[1] The term "drug delivery" refers to the release of drug from a polymeric platform where it is initially contained. The name "percutaneous absorption" is generally related to the same process viewed from the perspective of the living tissue where the drug is directed to.

http://dx.doi.org/10.1016/j.mbs.2014.05.001
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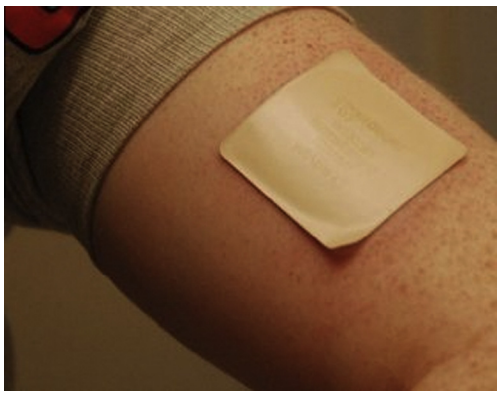

Fig. 1. The transdermal patch, a typical vehicle in transdermal drug delivery.

new formulations. In the absence of experiments, a number of mathematical models and numerical simulations have been carried out regarding TDD, its efficacy and the optimal design of devices [6–9]. Recent extensive reviews deal with various aspects of transdermal delivery at different scales [2,10–12]. In general, drug absorption into the skin occurs by passive diffusion and most of the proposed models consider this effect only. On the other hand, 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 an optimal design of its microstructural characteristics would improve the release performances [13]. For example, in the vehicle, the dissolution of the drug from encapsulated to free phase occurs at a given reaction rate. Another relevant feature in TDD is the similar binding/unbinding process through the receptor sites in the skin. These drug association–dissociation aspects are often neglected or underestimated by most authors who consider purely diffusive systems in the skin or in the vehicle [20,21]. One exception is the work of Anissimov et al. [2,4], where a linear reversible binding is considered, but the vehicle is taken into account only through a boundary condition of the first kind. However, it is worth emphasizing that the drug elution depends on the properties of the "vehicle-skin" system, taken as a whole, and modeled as a coupled two-layered system.

The method used in the present study follows the mathematical approach developed in a series of previously published papers which successfully describe drug dynamics form an eluting stent embedded in an arterial wall [14–17]. In these papers, we proposed a number of models of increasing complexity to explain the diffusion–advection-reaction release mechanism of a drug from the stent coating to the wall, constituted of a number of contiguous homogeneous media of different properties and extents. Separation of variables leads to an eigenvalue problem with discontinuous coefficients and an exact solution is given in terms of infinite series expansion and is based on a two- or multi-layer diffusion model. In the wake of these papers, a two-layer two-phase coupled model for TDD has been recently presented and a semi-analytical solution has been proposed for drug concentration and mass in the vehicle and the skin at various times, for special values of the parameters [18].

In the present paper we extend the above study and remove some of the simplifying assumptions, obtaining a solution in a more general form. Together with diffusive effects, the drug dissolution process in the polymer constituting the vehicle platform and the reversible drug binding process in the skin are also addressed. A solution of the Fick-type reaction–diffusion equations (reduced problem) serves as the building block to construct a space–time dependent solution for the general equations (full problem). A major issue in modeling TDD is the assessment of the key parameters defining skin permeability, diffusion coefficients, drug dissociation and association rates. Lacking experimental data and reliable estimates of the model parameters, we carry out a systematic sensitivity analysis over a feasible range of parameter values. The results of the simulations provide valuable insights into local TDD and can be used to assess experimental procedures to evaluate drug efficacy, for an optimal control strategy in the design of technologically advanced transdermal patches.

2. Formulation of the problem

To model TDD, let us consider a two-layered system composed of: (i) the *vehicle* (the transdermal patch or the film of an ointment), and (ii) the *skin* (the stratum corneum followed by the skin-receptor cells and the capillary bed) (Fig. 2). The drug is stored in the vehicle, a reservoir consisting of a polymeric matrix. This is enclosed on one side with an impermeable backing and having on the other side an adhesive in contact with the skin. A rate-controlling membrane protecting the polymer matrix may exist. In this configuration, the first layer is shaped as a planar slab that is in direct contact with the skin, the second layer. As most of the mass dynamics occurs along the direction normal to the 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 oriented with the positive direction outwards the skin. Without loss of generality, let $x_0 = 0$ be the vehicle-skin interface and l_0 and l_1 the thicknesses of the vehicle and skin layers respectively (Fig. 2). The vehicle and the skin are both treated from a macroscopic perspective so that they are represented as two homogeneous media.

Initially, the drug is encapsulated at maximum concentration within the vehicle in a bound phase (e.g. nanoparticles or crystalline form) (c_e): in a such state, it is unable to be delivered to the tissue. Then, a fraction of this drug ($\beta_0 c_e$) is transferred, through an unbinding process, to an unbound – free, biologically available – phase (c_0), and conversely, a part of the free drug ($\delta_0 c_0$) is transferred by a binding process to the bound state, in a dynamic equilibrium (Fig. 3). Also, at the same time, another fraction of free drug (c_0) begins to diffuse into the adjacent skin (c_1) *(delivery)*. Similarly, in the skin – the release medium – a part of the unbound drug ($\beta_1 c_1$) is metabolized by the cell receptors and transformed in a bound state (c_b) (*absorption*), and with the reverse unbinding process ($\delta_1 c_b$) again in a unbound phase. Thus, the drug

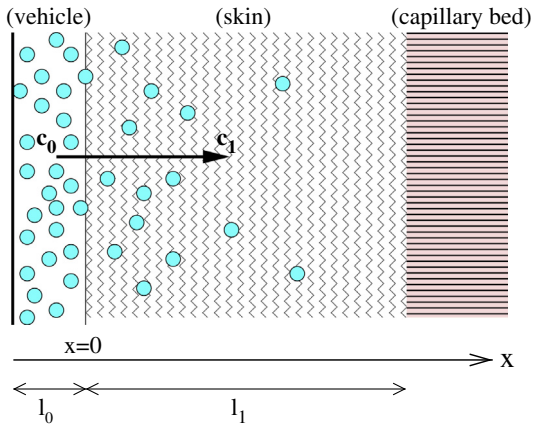

Fig. 2. Cross-section of the vehicle and the skin layers, geometrical configuration and reference system in TDD. Due to an initial difference of free drug concentrations c_0 and c_1, a mass flux is established at the interface and drug diffuses through the skin. At a distance $x = l_1$ the skin-receptor (capillary bed) is present where all drug is assumed to be absorbed. Figure not to scale.