MODELLING AND NUMERICAL SIMULATION OF PERCUTANEOUS PENETRATION OF CHEMICAL MOLECULES AFTER FINITE DOSING

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Abstract

We present a mathematical model of transient transdermal penetration of drugs after finite dosing. In this case skin is exposed to small doses of chemicals, i.e., the volume applied per area is small and exposure times are variable. The lipophilic flufenamic acid and the hydrophilic caffeine are used as test compounds. The relevant input parameters have been determined experimentally. The quality of the model has been evaluated by comparing the concentration-depth-profiles of the experiment with those of the simulation. The results from the experiment and the simulation are in good agreement. Moreover, the significance of lateral diffusion has been studied in a simplified model with a reduced computational complexity which was derived using the method of homogenization.

Introduction

Modelling and numerical simulation of percutaneous penetration of chemical molecules is an attractive alternative to reduce the number of in-vitro and in-vivo experiments. As the availability of human and animal skin is limited, there is an increasing need for in-silico methods in the cosmetics industry and in transdermal drug delivery as well as in the risk assessment of dermal exposures to toxic compounds. At present, predictions are largely made using QSARs or compartmental models. These models do not provide detailed information such as, e.g., transient concentration-depth profiles. Therefore, our mathematical approach is based on diffusion models, which consist of partial differential equations describing drug distribution in space and time according to Fick's laws of diffusion. Previously, an in-silico model of skin penetration under infinite dose conditions was presented [1,2]. This model was based on experimentally determined input parameters. Here, we present an extended two-dimensional non-steady-state model of skin penetration under finite dose conditions. The quality of the model has been evaluated by comparing the concentration-depth-profiles of the experiment with those of the simulation.

Model Geometries

As in previous studies [1,2] drug transport through skin (stratum corneum (SC) and deeper skin layers (DSL)) is simulated on a brick-and-mortar geometry which was extended by an additional homogeneous compartment for the living epidermis and dermis. The membrane consists of clusters of quadrilateral base cells, each of them corresponding to a corneocyte embedded in a lipid layer, cf. Fig. 1.

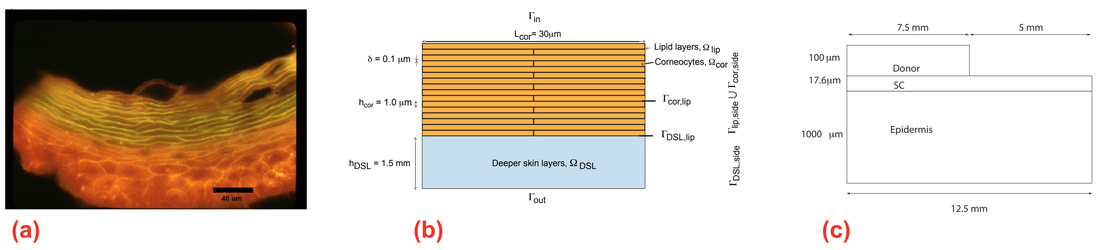

Figure 1. (a) Micrograph of human SC and viable epidermis (from [3]); (b) Brick-and-mortar model of human SC and DSL (from [2]); (c) Cross-section of diffusion cell.

By periodic alignment of flattened base cells in all space dimensions, we obtain a domain consisting of N = 16 vertical layers, which stretches infinitely into the horizontal direction. The characteristic parameters are: cell length L_{cor} = 30 µm, cell height h_{cor} = 1 µm, and lipid channel diameter d_{lip} = 0.1 µm. In order to represent finite dose and outflow conditions, a compartment for the vehicle (h_{veh} = 100 µm) and for the deeper skin layers (h_{dsl} = 1500 µm) are added on top and bottom respectively, cf. Fig. 1, (c).

Model Equations and Experimental Summary

The mass transport in all phases is modelled using the heat equation, which assumes a Fickian diffusion process in all phases:

$$\frac{\partial c_i(x,t)}{\partial t} = div\left[D_i \nabla c_i(x,t)\right] \qquad (1)$$

for all times $t > 0$ and points x in all phases $i \in \{veh,lip,cor,dsl\}$. Here, c_i denotes the concentration in phase i, and D_i is a constant coefficient characterizing the diffusivity of the respective phase. Additionally, we must impose transmission conditions on the interface between the phases: Since the chemical potential is continuous at equilibrium, the concentration is discontinuous, and due to conservation of mass, the flux across the interface must be continuous. Hence, we have

$$D_i \nabla c_i(x,t)\vec{n} + D_j \nabla c_j(x,t)\vec{n} = 0 \quad and \quad c_i = K_{i,j} c_j \qquad (2)$$

for $t > 0$ and $x \in \Gamma_{i,j}$. The symbol $\vec{n}$ denotes a normal vector of the interface Γ. Zero flux conditions are assumed on all boundaries except for the outward surface of the DSL, where perfect sink conditions are applied. In the beginning, t = 0, all substance is distributed homogeneously in the vehicle.

Experimental reference is provided by a Franz cell diffusion experiment. Flufenamic acid (lipophilic, ionizable) and Caffeine (hydrophilic) are used as model compounds, and applied to the skin in an aqueous vehicle. Values for the diffusion coefficients D_{SC}, D_{DSL} and D_{lip} and the partition coefficients $K_{lip/veh}$, $K_{cor/lip}$ and $K_{DSL/lip}$ were determined previously for the infinite dose case [1]. This infinite dose database could also be used for the finite dose setup considered here. The diffusion in the vehicle is assumed to be non-rate-limiting ($D_{veh} \gg D_{lip}$). Tape stripping experiments are conducted following [4]. Skin samples are incubated for 0.25 h, 0.5 h, 3 h, 6 h for flufenamic acid and 0.083 h, 2 h, 6 h, 12 h for caffeine. The surface load for both substances was < 10 mg/cm^2 in order to get finite dose conditions.

Homogenization Results

The application of homogenization theory can significantly reduce the computational cost of modelling transdermal diffusion through the skin membrane. We have used the model of Muha et al., [5], to estimate the influence of lateral diffusion in SC and epidermis over time for the lipophilic compound flufenamic acid, cf. Fig. 2, (a)-(c). The calculated fraction in the lateral compartment is approx. 1 % in the SC and approx. 15 % in the epidermis.

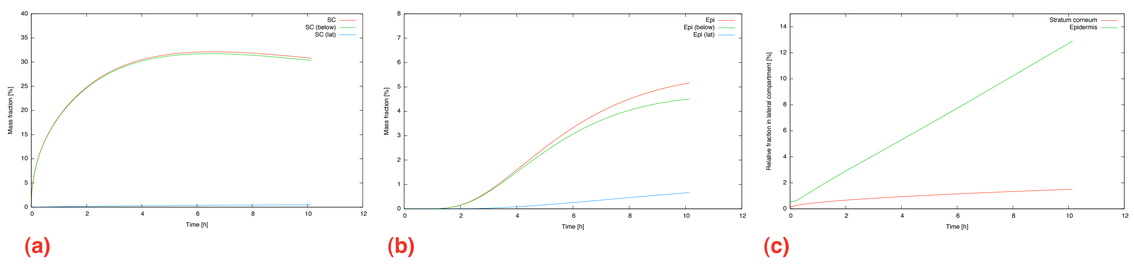

Figure 2. Homogenization results for the lateral diffusion over time for flufenamic acid. (a) Lateral diffusion in stratum corneum ; (b) Lateral diffusion in epidermis; (c) Relative fraction in lateral compartment (SC, epidermis)

Results and Discussion

Experimentally determined (red) and calculated (green) concentration-SC-depth profiles are shown for both compounds, flufenamic acid (Fig. 3, (a)-(d)) and caffeine (Fig. 4, (a)-(d)). We obtained a good agreement between simulation and experiment.

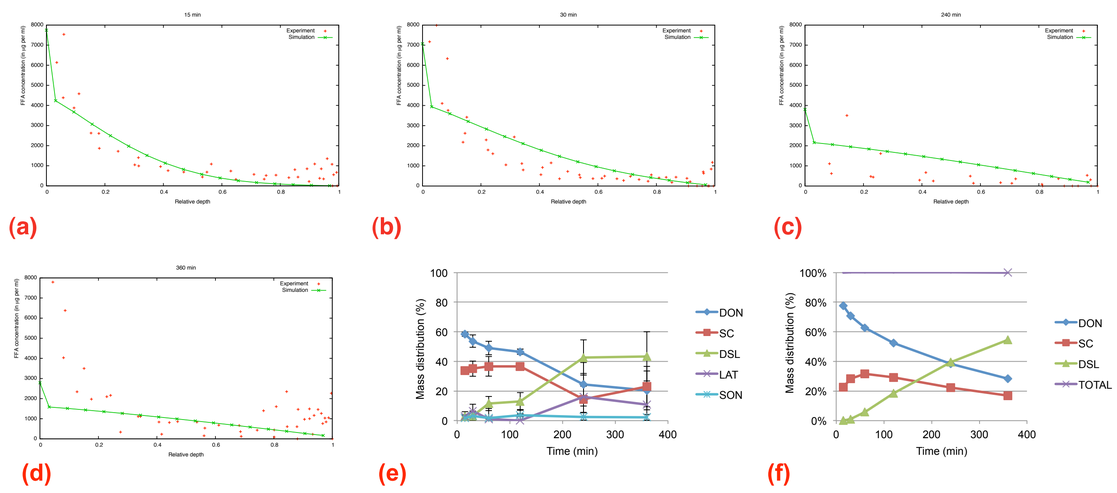

Figure 3. Flufenamic acid: Concentration-SC-depth profiles at (a) t = 0.25 h; (b) t = 0.5 h; (c) t = 3 h; (d) t = 6 h; (e) Distribution of mass over time: Experiment; (f) Distribution of mass over time: Simulation.

In Fig. 3, (e)-(f) the experimentally determined and calculated mass distribution over time is shown for flufenamic acid (FFA). For this compound we have a significant faster donor depletion in the experiment compared to the simulation. This is possibly due to the rapid uptake of donor solution into the stratum disjunctum, the uppermost compartment of the SC. This fast uptake is not considered in the simulation. Possibly therefore, we have an underestimate in simulation for the mass of FFA in the SC. Furthermore, the mass of FFA in the DSL is overestimated in the simulation because of a high fraction of FFA in the lateral compartment. Therefore, we have calculated the lateral diffusion for the model skin membrane using the method of homogenization, cf. Fig. 2, (a)-(c). The calculated fraction in the lateral compartment is approx. 1 % in the SC and approx. 15 % in the DSL .

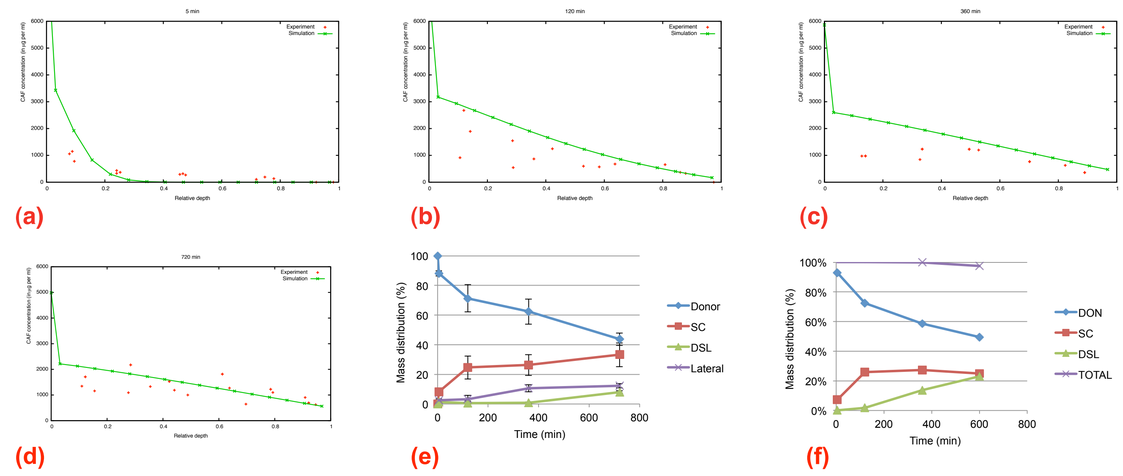

Figure 4. Caffeine: Concentration-SC-depth profiles at (a) t = 0.083 h; (b) t = 2 h; (c) t = 6 h; (d) t = 12 h; (e) Distribution of mass over time: Experiment; (f) Distribution of mass over time: Simulation.

Experimentally determined and calculated mass distribution curves for caffeine are shown in Fig. 4, (e)-(f). In the case of caffeine we have no significant donor depletion in the experiment compared to the simulation results shown for FFA (Fig. 3, (e)-(f)). This is possibly due to the fast diffusion of the hydrophilic caffeine through the corneocytes.

For the detailed computation of percutaneous penetration of chemical molecules after finite dosing a software tool based on the simulation system UG and on the framework for visual programming, VRL, has been implemented [6].

Conclusion

A straight-forward extension of an in-silico model previously used to describe transport under infinite dose conditions turns out to be useful also in a finite dose context. Based on the anatomical structure the stratum corneum should be modelled as two separate domains, stratum disjunctum and stratum conjunctum. Work is in progress to further extend the model. In contrast to earlier work, e.g., [7], the model does not rely on parameter fitting. In future work it will be quantified, how the two-dimensional simplification of the in-silico model differs from the three-dimensional setup. This will allow to study the influence of lateral diffusion in greater detail. Furthermore, the refined in-silico model is capable not only to describe diffusion, but also additional effects such as different vehicles, adsorption, metabolism, and enhancement by co-permeation. Investigations with the refined in-silico model are in progress and are an important area for future studies.

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