DRUG DIFFUSION TRANSPORT THROUGH HUMAN SKIN

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The stratum corneum (SC) forms the outermost layer of the human skin and is essentially a multilamellar lipid milieu punctuated by protein-filled corneocytes that augment membrane integrity and significantly increase membrane tortuosity. The lipophilic character of the SC, coupled with its intrinsic tortuosity, ensure that it almost always provides the principal barrier to the entry of drug molecules into the organism. Drugs can be administered either as suspensions or as solutions and the formulation can range in complexity from a gel or and ointment to a multilayer transdermal path. In this paper, we discuss theoretical principles used to describe transdermal release and we show that relatively simple membrane transport models based on the appropriate solution to the Fick's second law of diffusion can be used to explain drug release kinetics into such a complex biological membrane as the human skin. To apply the Fick's law we introduced into our considerations a brick-and-mortar model with two factors of tortuosity. Assuming that the mortar thickness is variable we also introduced the hindrance factor allowing us to model this variability. Having the modified Fick's equation we presented its general solution and two special cases of this solution frequently applicable in permeation experiments. It seems that the solutions presented herein better approximate the real conditions of drug delivery then these well known.

Key words: drug delivery, human skin, diffusion.

1. Introduction

Fluid flow and diffusion transport within natural tissues play an important role in morphogenesis, metabolism functions and pathogenesis. In the design of new biomaterials mimicking biological tissues, it is well recognized today that a three-dimensional "in vitro" culture better recapitulates physiological cell environment. Fluid flow and solid strain that are imposed within tissue not only affect cell nourishment but also exert on cell mechanical actions such as pressure effects, drag interactions and viscous shear stresses.

Every cell is distinguished from its environment by means of a semipermeable membrane. This membrane plays a crucial role in the ability of the cell to function; the loss of membrane integrity, except for brief periods, would almost certainly lead to the cell's death.

This paper addresses modelling and treatment of mass transport through biological tissues, specially the skin, considered as a porous medium; the mass transport is narrowed down to the diffusion in the skin drug delivery.

The skin drug delivery can be subdivided into topical and transdermal. In a topical delivery the drug is intended to act at skin level, this is indicated for the treatment of skin diseases.

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The aim of transdermal delivery is getting a systemic release and in this case the skin represents a porous barrier that allows drug penetration [1]. The transdermal drug delivery is a viable administration route for potent, not only low-molecular weight therapeutic agents, which has to be precise in the control of drug distribution. This action is specially recommended for many drugs that are difficult to be taken since they must be delivered slowly over a prolonged period to have a beneficial effect [1, 2].

The transdermal drug administration has several interesting advantages over other systemic administration routes such as [2-6]:

- reduction of first-pass drug degradation as the liver is initially bypassed,
- reduction of over dosage peaks that can appear in oral administration,
- existence of variable delivery conditions typical of the gastrointestinal tract.

Most often in the therapy of local and external changes, antibiotics, antifungal drugs, antivirals, glucocorticoids, anti-inflammatory drugs and analgesics, chemotherapeutics, in aesthetic medicine botulinum toxin in the treatment of hyperhidrosis, are administrated transdermally. Systemic effects are characterized by transdermal systems of analgesics and hormonal drugs [5, 6].

One of the oldest drug administration applied since the 1950, acting topically on the skin and systemically, is hydrocortisone, while transdermal administration was applied a bit later [7].

The simplest transdermal formulation consists of a semi-solid vehicle, e.g., an ointment or a cream containing a finely divided suspension of the drug. The control of the drug delivery was first described by Higuchi [8,9] and next developed by Michaels *et al.* [10] and by Bunge [11]. Some theoretical considerations, including the solutions to the Fick's diffusion equation, were presented by Hadgraft [12] and Guy and Hadgraft [13]. Many recent theoretical considerations on the drug diffusion transport through the skin are based on their solutions [14-21].

Motivated by the aforementioned papers, the principle idea of this work is to present a new mathematical model of the skin porosity. The recent ("classical") model of the skin porosity uses a brick-and-mortar model with uniform thickness of the mortar (Fig.2). We would like to propose some modification to this model assuming variable thickness of the mortar (which is closer to the reality) and introducing the so called "hindrance factor" [22].

2. Skin as a porous biomembrane

The skin being the body's first defense against infection should not be treated – in general – as a homogenous medium. Even in a very basic description, human skin in made of multiple constituent composite layers (Milington and Wilkinson, [23]), each providing specific function with varying thickness. A schematic representation of human skin is shown in Fig.1.
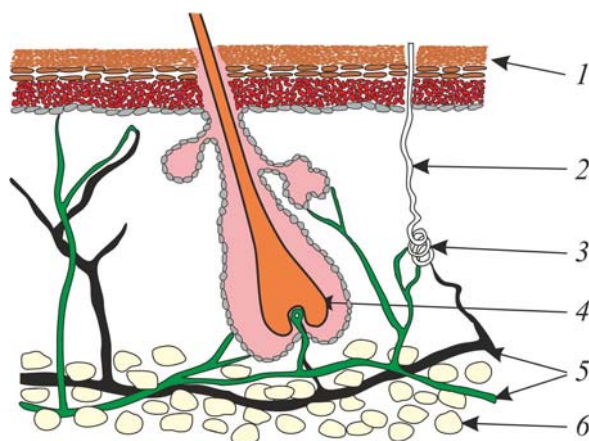

Fig.1.   Schematic representation of the skin; 1 – stratum corneum, 2 – sweat duct, 3 – sweat gland, 4 – hair follicle, 5 – blood vessels, 6 – fat lobule.

The outer skin layer, the epidermis, is without vasculature and acts as a protective barrier preventing molecular transport. The epidermis is a foundation of viable living cells being a transition to flat dead cells at its outer surface. The thin outermost layer of the epidermis is called the "stratum corneum" (SC) and it is most resistive to drug transport through the skin.

Below the epidermis there is a highly vascular inner skin layer, the dermis, that is characterized by a the large network of capillaries with high blood flow rates exceeding several times the metabolic requirements. The primary reason of such high perfusion rates in the dermis is to regulate body temperature. The dermis is also characterized by high collagen content, that provides the skin with its structural support.

Below the dermis there lies a thermally insulative fatty layer that also acts to conserve body heat. The skin, at most sites on the body, is perforated by appendageal pathways in the form of sweat glands and hair follicles.

The SC is composed of $15-20$ layers of corneocytes, that is flat dead cell shells, which are interconnected by a lipid lamellar bilayer structure in a crystallinegel phase. Transport circumventing the barrier function of the SC is primarily associated to occur within the lamellar lipid structure of the SC (Bouwstra *et al.* [24]; Madison [25]). The thin SC corneocytes-lipid porous matrix (Fig.2) may be conceptualized as a brick-and-mortar structure in which the highly impermeable corneocyte cells are represented by the brick and the slightly less impermeable intercellular lipid lamellar bilayers are represented by the mortar.
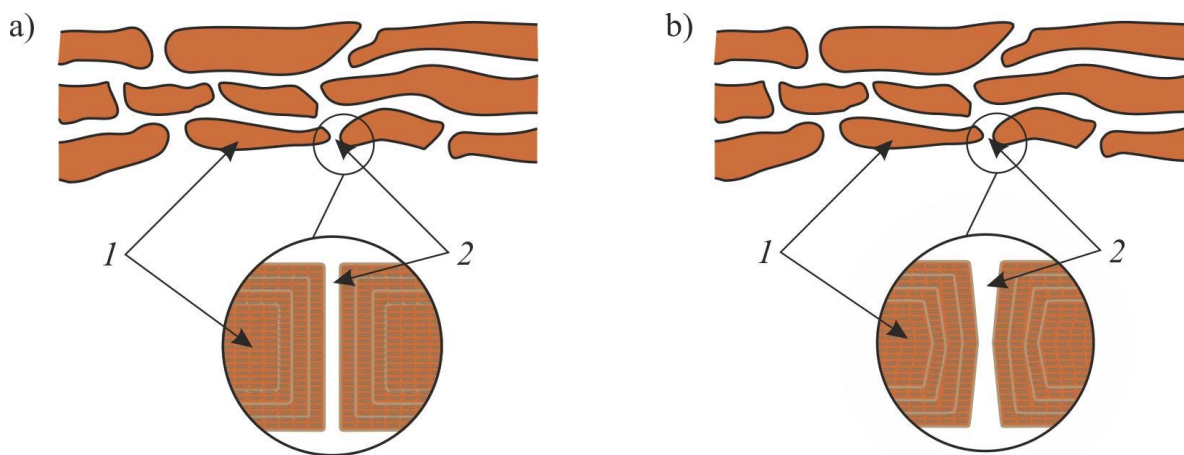

Fig.2.   Schematic representation of the stratum corneum (SC); 1 – corneocyte, 2 – lipid bilayers, a) scheme hitherto accepted, b) scheme just now proposed.

Traditional drug deliveries often result in low efficacy and unintentional treatment of healthy tissues. Oral intake may result in drug denaturation in the gastro-intestinal track; drugs consisting of water soluble molecules may degrade before reaching intended locations of treatment. Injection of drugs into the circulatory system may result in lower selectivity level of the drug's region influence. Transdermal drug delivery is one method that allows localized delivery by transporting the drug directly through the skin to the desired target, as it is necessary, for example, in chemotherapy for drugs with a high toxicity.

3. Diffusion through brick-and-mortar structure

The representation of the SC matrix consisting of a symmetric brick-and-mortar model was introduced at first by Michaels *et al.* [10] in which the interstitial horizontal lengths between vertical spaces are all of the same length (Fig.3a). A nonsymmetric variation of this model was introduced by Johnson *et al.* [14]; this model describes more accurately the lateral diffusive path by using an offset, ω, that is defined as the ratio of long, d_L, to short, d_S, lateral diffusion path lengths (Fig.3.b). This offset is equal to $\omega = d_L/d_S$; for the symmetric model the offset is equal to $\omega = 1$.
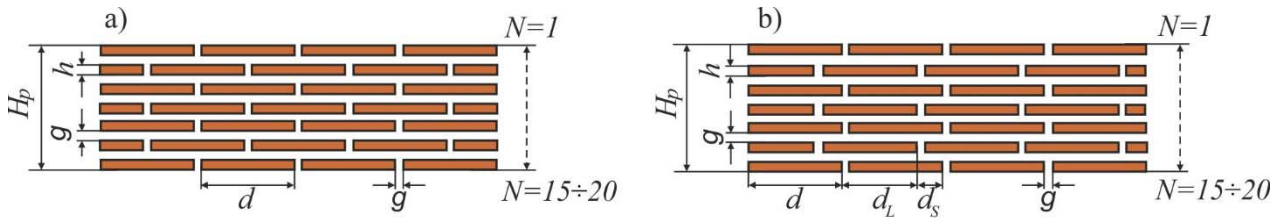
Fig.3. Brick-and-mortar representations of the SC matrix: a) symmetric, b) nonsymmetric.
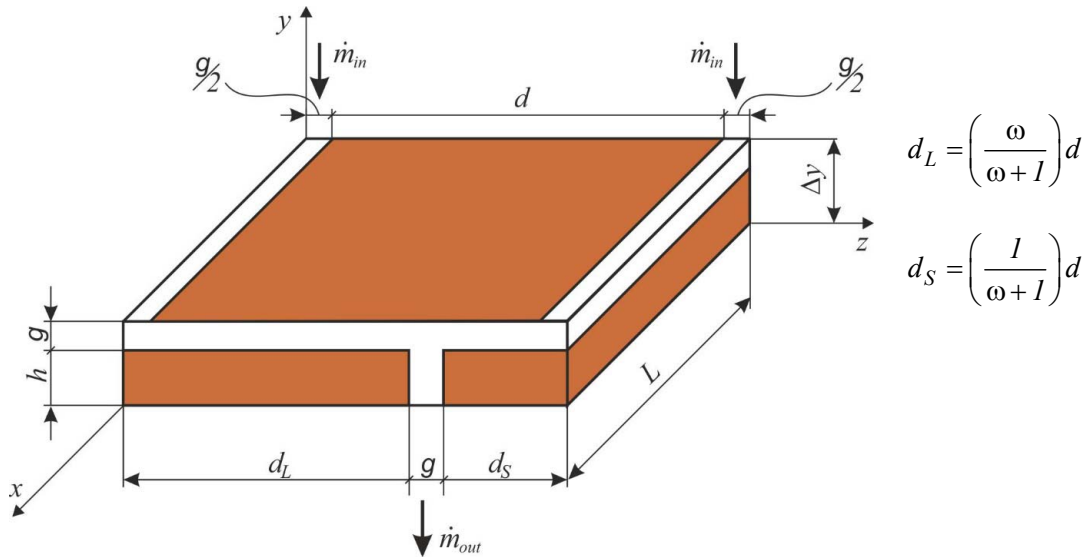

$$d_L = \left(\frac{\omega}{\omega+1}\right)d$$

$$d_S = \left(\frac{1}{\omega+1}\right)d$$

Fig.4. Schematic view of a slice of the SC matrix.

Figure 4 shows one slice of the SC matrix; here $\dot{m}_{in}$ and $\dot{m}_{out}$ are, respectively, the drug mass flow rates into and out of the slice of the SC. Assuming that mass transport is restricted to the intercellular regions of the SC and following Kushner *et al.* [26] (see also [21]) we may write the mass balance for the flowing permeant (drug solute) in the form

$$\frac{1}{\tau_v}\frac{\partial F(y,t)}{\partial y} = \varphi_p \frac{\partial C(y,t)}{\partial t} \tag{3.1}$$

where

$\tau_v = \dfrac{d+g+h}{g+h}$ is the volume tortuosity factor,

$\varphi_p = \dfrac{g}{d+g}$ is the porosity of the SC,

$F(y,t)$ is the mass flux,

$C(y,t)$ is the drug concentration.

Taking into account that the real mortars (intercellular regions of the SC) are not regular let us introduce the so called "hindrance factor" (Walicka *et al.* [22]) considering the irregularity of the mortar. Then Eq.(3.1) takes the form

$$\frac{\psi}{\tau_v}\frac{\partial F(y,t)}{\partial y} = \varphi_p \frac{\partial C(y,t)}{\partial t}$$

(3.2)

where ψ is the hindrance factor.

Note that some mathematical considerations on the flows of Newtonian and non-Newtonian fluids through irregular capillary tubes and fissures one may find in [27, 28].

Consider now the diffusive mass flow rate of the drug delivered through the intercellular regions of the SC; according to Johnson *et al.* [14] it may be evaluated as (see also [21])

$$F(y,t) = \frac{\varphi_p D}{\tau_f}\frac{\partial C(y,t)}{\partial y}.$$

(3.3)

or, after introducing the hindrance factor

$$F(y,t) = \frac{\varphi_p \psi}{\tau_f}\frac{\partial C(y,t)}{\partial y}.$$

(3.4)

where

D is the diffusion coefficient,

$$\tau_f = \frac{d_{lat} + g + h}{g + h} \text{ is the flux tortuosity factor,}$$

$$\frac{1}{d_{lat}} = \frac{1}{d_l} + \frac{1}{d_s},$$

or

$$d_{lat} = \frac{\omega}{(1+\omega)^2}d \text{ is the lateral diffusion path length.}$$

Now substituting Eq.(3.4) into Eq.(3.2) yields the final form of the Fick second law of diffusion through the irregular intercellular regions of the SC

$$\frac{dC}{dt} = \frac{\psi^2 D}{\tau_v \tau_f}\frac{\partial^2 C}{\partial y^2}$$

(3.5)

or in a more general form

$$\frac{\partial C}{\partial t} + (\bar{\upsilon}\nabla)C = \frac{\psi^2 D}{\tau_v \tau_f}\frac{\partial^2 C}{\partial y^2},$$

(3.6)

where $\bar{\upsilon}$ is the velocity vector of the flow in the SC intercellular regions.

One of more general forms of this equation proposed by Picioreanu *et al.* [29] is as follows

$$\frac{\partial C}{\partial t} + (\bar{\upsilon}\nabla)C = \text{div}(\varepsilon D \text{grad} C) + \Phi,$$

(3.7)

where ε is the coefficient of concentration and Φ is the source field of diffusion.

Different variants of this equation have been discussed by many researchers, except early cited also by DiMicco and Sah [30], Barta and Maroudas [31], Klein and Sah [32], who discussed diffusion and drug transport in a human articular cartilage.

Note that in the case of the absence of flow $(\bar{\upsilon}=0)$, Eq.(3.6) takes the form of Eq.(3.5).

The factors τ_v and τ_f are given for one lipid layer; in the case of N corneocyte layers and of $(N-1)$ intercellular lateral lipid layers in the SC, the expressions for τ_v and τ_f are given by Kushner et al. [26]

$$\tau_v = \frac{(N-1)d + Nh + (N-1)g}{Nh + (N-1)g}, \tag{3.8}$$

$$\tau_f = \frac{(N-1)\dfrac{\omega}{(1+\omega)^2}d + Nh + (N-1)g}{Nh + (N+1)g}. \tag{3.9}$$

The hindrance factor for human skin takes the values from the bracket $0.8 \leq \psi \leq 1$.

4. Diffusion transport through the stratum corneum

Taking into account the fact that the flow in the brick-and-mortar fissure is a one-dimensional flow we may rewrite Eq.(3.6) in the following form

$$\frac{\partial C}{\partial t} + |\bar{\upsilon}|\frac{\partial C}{\partial y} = \frac{\psi^2 D}{\tau_v \tau_f}\frac{\partial^2 C}{\partial y^2}. \tag{4.1}$$

This equation should be solved for the general case with the following boundary and initial conditions

$$C(y=0,t)=C_1, \quad C(y=H_p,t)=C_2, \quad C(y,t=0)=C_0, \tag{4.2}$$

where C_1 is the bulk concentration on the receiver side of the SC, C_2 is the bulk concentration on the donor side of the SC and C_0 is the initial concentration of the drug within the intercellular lipids of the SC. Note that $y=0$ corresponds to the outlet of the stratum corneum, whereas $y=H_p$ corresponds to the inlet of the stratum corneum.

Introducing the non-dimensional magnitudes

$$\tilde{C} = \frac{C}{C_2}, \quad \tilde{y} = \frac{y}{H_p}, \quad \alpha = \frac{|\bar{\upsilon}|H_p\tau_v\tau_f}{\psi^2 D}, \quad \tilde{t} = \frac{\psi^2 D}{\tau_v\tau_f H_p^2}t, \tag{4.3}$$

one may rewrite Eq.(4.1) as follows

$$\frac{\partial \tilde{C}}{\partial \tilde{t}} + \alpha\frac{\partial \tilde{C}}{\partial \tilde{y}} = \frac{\partial^2 \tilde{C}}{\partial \tilde{y}^2}. \tag{4.4}$$

4.1. Steady-state diffusion through the SC

First, let us consider the steady-state diffusion through the SC. The Fick's equation (4.4) for the steady-state case is as follows

$$\frac{d^2\tilde{C}}{d\tilde{y}^2} = \alpha \frac{d\tilde{C}}{d\tilde{y}}.$$

(4.5)

Solving this equation with the boundary conditions (4.2), one obtains

$$\tilde{C} = \tilde{C}_1 + \frac{\tilde{C}_2 - \tilde{C}_1}{1 - e^\alpha}\left(1 - e^{\alpha\tilde{y}}\right)$$

(4.6a)

or

$$C = C_1 + \frac{C_2 - C_1}{1 - e^\alpha}\left(1 - e^{\alpha\frac{y}{H_p}}\right).$$

(4.6b)

Note that for $\alpha \to 0$, there is

$$\tilde{C} = \tilde{C}_1 + \left(\tilde{C}_2 - \tilde{C}_1\right)\tilde{y},$$

(4.7a)

or

$$C = C_1 + \left(C_2 - C_1\right)\frac{y}{H_p};$$

(4.7b)

therefore the diffusion distribution is linear.

4.2. Non-steady state diffusion through the SC

Let us rewrite Eq.(4.4) as follows

$$\frac{\partial\tilde{C}}{\partial\tilde{t}} = \frac{\partial^2\tilde{C}}{\partial\tilde{y}^2} - \alpha\frac{\partial\tilde{C}}{\partial\tilde{y}}.$$

(4.8)

A standard method of obtaining the solution of a partial differential equation of second order is to assume that the variables are separable (Kącki [33]; Crank [34]). Applying this method (called the method of separation of variables) one obtains the following solution [21]

$$\tilde{C} = \tilde{C}_1 + \frac{\tilde{C}_2 - \tilde{C}_1}{1 - e^\alpha}\left(1 - e^{\alpha\tilde{y}}\right) + \sum_{m=1}^{\infty} A_m \sin\left(m\pi\tilde{y}\right)\exp\left(\frac{\alpha}{2}\tilde{y} - \lambda_m^2\tilde{t}\right) +$$

$$+\tilde{C}_0\sum_{m=1}^{\infty}\frac{8m\pi}{\alpha^2 + 4\left(m\pi\right)^2}\left(e^{-\frac{\alpha}{2}}\cos\left(m\pi\right) - 1\right)\sin\left(m\pi\tilde{y}\right)\exp\left(\frac{\alpha}{2}\tilde{y} - \lambda_m^2\tilde{t}\right),$$

(4.9)

where

$$A_m = \frac{8m\pi}{\alpha^2 + 4(m\pi)^2} \left[\left(\tilde{C}_1 + \frac{\tilde{C}_2 - \tilde{C}_1}{1 - e^\alpha} \right) \left(e^{-\frac{\alpha}{2}} \cos(m\pi) - 1 \right) - \frac{\tilde{C}_2 - \tilde{C}_1}{1 - e^\alpha} \left(e^{\frac{\alpha}{2}} \cos(m\pi) - 1 \right) \right],$$

(4.10)

$$\lambda_m^2 = \frac{1}{4} \left[\alpha^2 + 4(m\pi)^2 \right].$$

Note that for $\alpha \to 0$, A_m tends towards

$$A_m = \frac{2}{m\pi} \left[\tilde{C}_2 \cos(m\pi) - \tilde{C}_1 \right]$$

(4.11)

and the solution given by Eq.(4.9) approaches the form (Crank [34])

$$\tilde{C} = \tilde{C}_1 + \left(\tilde{C}_2 - \tilde{C}_1 \right) \tilde{y} + \frac{2}{\pi} \sum_{m=1}^{\infty} \frac{\tilde{C}_2 \cos(m\pi) - \tilde{C}_1}{m} \sin(m\pi\tilde{y}) \exp\left(-\lambda_m^2 \tilde{t}\right) +$$

$$+ \frac{4\tilde{C}_0}{\pi} \sum_{m=0}^{\infty} \frac{\sin(2m+1)\pi\tilde{y}}{2m+1} \exp\left(-\lambda_{2m+1}^2 \tilde{t}\right),$$

(4.12)

where

$$\lambda_m^2 = (m\pi)^2, \qquad \lambda_{2m+1}^2 = \left[(2m+1)\pi \right]^2.$$

(4.13)

4.3. Mass transport in non-steady state diffusion

The total amount of mass per unit area, $M(t)$, delivered across the SC is given by a time integral over the flux $F(y,t)$

$$M(t) = \int_0^t F(y = 0, t) dt = \frac{\varphi_p \psi}{\tau_f} \int_0^t \left[D \frac{\partial C(y,t)}{\partial y} \right]_{y=0} dt.$$

(4.14)

Substitution of the dimensional form of Eq.(4.12) and integration over time yields

$$M(t) = \frac{\varphi_p \psi D t}{\tau_f H_p} (C_2 - C_1) + \frac{2\varphi_p \psi \tau_v H_p}{\pi^2} \sum_{m=1}^{\infty} \frac{C_2 \cos(m\pi) - C_1}{m^2} \left[1 - \exp\left(-\frac{\psi^2 D m^2 \pi^2 t}{\tau_v \tau_f H_p^2} \right) \right] +$$

$$+ \frac{4\varphi_p \psi C_0 \tau_v H_p}{\pi^2} \sum_{m=0}^{\infty} \frac{1}{(2m+1)^2} \left[1 - \exp\left(-\frac{\psi^2 D (2m+1)^2 \pi^2 t}{\tau_v \tau_f H_p^2} \right) \right].$$

(4.15)

For the special case when $C_1 = C_0 = 0$, which is frequently applicable to permeation experiments, Eq.(4.15) can be further simplified

$$M(t) = \frac{\varphi_p \tau_v H_p C_2}{6\psi} \left\{ \frac{6\psi^2 D t}{\tau_v \tau_f H_p^2} - 1 - \frac{12}{\pi^2} \sum_{m=1}^{\infty} \frac{(-1)^m}{m^2} \exp\left(-\frac{\psi^2 D m^2 \pi^2 t}{\tau_v \tau_f H_p^2} \right) \right\}.$$

(4.16)

Here it was assumed that (Korn and Korn, [35])

$$\cos(m\pi) = (-1)^m, \qquad \sum_{m=1}^{\infty} \frac{(-1)^m}{m^2} = -\frac{\pi^2}{12}.$$

Equation (4.16) describes mass transport across a rate-controlling membrane and it is identical with the equation describing diffusion across the SC in situations where drug release from a transdermal drug delivery system is rapid and transport across the stratum corneum is the rate-limiting step before fast entry into the viable epidermis. At the long time values, the exponential terms tend to zero and the full solution can be approximated by

$$M(t) = \frac{\varphi_p \tau_v H_p C_2}{\psi} \left(\frac{\psi^2 Dt}{\tau_v \tau_f H_p^2} - \frac{1}{6} \right). \tag{4.17}$$

The shortest lag time describing the time necessary to reach steady-state diffusion is essential for the drug delivery through the skin. This time can be evaluated by setting $M(t) = 0$ in Eq.(4.17), which yields

$$t_{lag} = \frac{\tau_v \tau_f H_p^2}{6\psi^2 D}. \tag{4.18}$$

When the time t reaches the value $(t = t_{lag})$, the diffusion may be described by Eqs (4.7). This case of drug release represents the so called "lag effect".

A different drug release called "burst effect" arises when $C_1 = 0$, $C_2 = C_0$, then the expression describing drug release is given by

$$M(t) = \frac{\varphi_p \tau_v H_p C_2}{6\psi} \left\{ \frac{6\psi^2 Dt}{\tau_v \tau_f H_p^2} + 2 + \frac{12}{\pi^2} \sum_{m=1}^{\infty} \frac{1}{m^2} \exp\left(-\frac{\psi^2 Dm^2\pi^2 t}{\tau_v \tau_f H_p^2} \right) \right\}. \tag{4.19}$$

At the long time values there is

$$M(t) = \frac{\varphi_p \tau_v H_p C_2}{\psi} \left(\frac{\psi^2 Dt}{\tau_v \tau_f H_p^2} + \frac{1}{3} \right). \tag{4.20}$$

Having general solution (4.12) of the Fick's equation it is possible to find other particular solutions for different boundary and initial conditions. These solutions may be found in the literature. Note that most of these solutions consider only straight mortar fissures without their tortuosity. Any of these solutions does not make allowance for variable cross section (variable thickness) of the mortar fissures.

5. Conclusions

In the paper, we have focussed on analytical solutions of the Fick's equation describing mass diffusion through the porous membrane. These solutions have the advantage that the terms in the equations can be clearly related to physical parameters within the drug transport system. Some analytical solutions

have the drawback of being limited to systems having relatively simple geometries and boundary conditions. On the other hand, it seems that numerical methods are considerably more powerful and can be used to model more complex situations which more closely resemble those encountered experimentally [34]. More complex mathematical models that represent release into a biologically realistic membrane, e.g., taking into account the structural heterogeneity, and which incorporate diffusion in three-dimensions and any time-dependent variation of the boundary conditions will have to employ advanced analytical methods of solutions.

The aim of this paper was to improve the analytical method using a brick-and-mortar model, with uniform thickness of the mortar, describing the porosity of the stratum corneum. This aim was achieved by two steps dependent on:

- the introduction of two tortuosity factors,
- the introduction of the hindrance factor.

The influence of tortuosity on mass transport in porous media is well known but in drug diffusion transport tortuosity is rarely taken into account.

The hindrance factor represents the influence of variable thickness of the mortar fissure on the mass transport in porous medium. Introduction of this factor allows us to consider the fissure variability in a simple way.

It seems that the proposed methods of solution will contribute to a broader use of the analytical methods for a better understanding of drug diffusion transport through the skin.

Nomenclature

C – drug concentration
D – diffusion coefficient
d – length of a corneocyte slice
d_{lat} – lateral diffusion path length
d_l – long lateral diffusion path length
d_s – short lateral diffusion path length
F – mass flux
g – thickness of a lipid layer
H_p – thickness of the SC matrix
h – thickness of a corneocite slice
l – width of a corneocite slice
$M(t)$ – total amount of mass
m – mass
$\dot{m}$ – mass flow rate
N – number of corneocyte layers
SC – stratum corneum
t – time
$\bar{\upsilon}$ – velocity vector
$|\bar{\upsilon}|$ – value of one-dimensional velocity
φ_p – porosity of the SC
τ_f – flux tortuosity factor
τ_v – volume tortuosity factor
ψ – hindrance factor

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