Non Steady-state Descriptions of Drug Permeation Through Stratum Corneum. I. The Biphasic Brick-and-Mortar Model

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Purpose. The diffusion equation should be solved for the non-steady-state problem of drug diffusion within a two-dimensional, biphasic stratum corneum membrane having homogeneous lipid and corneocyte phases.

Methods. A numerical method was developed for a brick-and-mortar SC-geometry, enabling an explicit solution for time-dependent drug concentration within both phases. The lag time and permeability were calculated.

Results. It is shown how the barrier property of this model membrane depends on relative phase permeability, corneocyte alignment, and corneocyte-lipid partition coefficient. Additionally, the time-dependent drug concentration profiles within the membrane can be observed during the lag and steady-state phases.

Conclusions. The model SC-membrane predicts, from purely morphological principles, lag times and permeabilities that are in good agreement with experimental values. The long lag times and very small permeabilities reported for human SC can only be predicted for a highly-staggered corneocyte geometry and corneocytes that are 1000 times less permeable than the lipid phase. Although the former conclusion is reasonable, the latter is questionable. The elongated, flattened corneocyte shape renders lag time and permeability insensitive to large changes in their alignment within the SC. Corneocyte/lipid partitioning is found to be fundamentally different to SC/donor partitioning, since increasing drug lipophilicity always reduces both lag time and permeability.

KEY WORDS: stratum corneum; barrier function; diffusion equation; non steady-state model.

INTRODUCTION

The diffusion equation has no analytical solution for the problem of drug permeation through a membrane of human stratum corneum (SC) because of the latter's heterogeneous morphology. It shows upwards of ten approximately-parallel layers of elongated, flattened and keratinized corneocytes (1). The intercellular domains are filled with an extended lipid bilayer structure, composed primarily of fatty acids, cholesterol and sphingolipids (2). These bilayers are continuous and arranged more-or-less parallel to the corneocyte surfaces (3). The phase behavior of these lipids is complex, but appears to be that of a lamellar gel (4), possibly incorporating local liquid-crystalline areas (5). Isolated membranes of intact SC show a substantial barrier property. Moderately lipophilic drugs ($K_{oct/water} \leq 10^3$) of M.Wt. $\approx$ 300 show lag times for SC of thickness 10–15 μm of at least 5 h and permeabilities of $<10^{-4}$ cm/h (6). Various attempts have been made to relate this remarkable barrier property to the SC's heterogeneous morphology. All are variations of Maxwell's steady-state approximation for the dielectric behavior of a biphasic system (7). In the simplest cases, the corneocytes are described as impermeable blocks embedded in a permeable, homogeneous lipid phase, with the drug concentration satisfying Laplace's equation within the lipid (8,9). Alternatively, both lipid and corneocyte phases are considered permeable, with a partition coefficient at the phase boundaries (10,11). A refinement recognises the heterogeneity of the lipid phase by introducing a "hindrance coefficient" to characterise the hindered drug diffusion through a lipid bilayer compared with its free diffusion parallel to it (12). These steady-state approximations predict the flux of drug across a SC membrane for a given applied drug concentration gradient, and are undoubtedly adequate for evaluating the imprecise data obtained from SC permeation experiments.

Two of the current research efforts concerning SC are: i) to exploit transdermal delivery for a wider range of drugs than up until now possible; and ii) to determine how skin disorders can be related to disruption of the SC barrier. In both cases, an understanding of the diffusional pathway through the SC and the quantitative importance of SC morphology for its barrier function, is vital for success. This can only be achieved by seeking a non steady-state solution to the diffusion equation for the SC morphology. As this is not possible analytically, we have derived numerical solutions which describe how the SC's heterogeneous morphology maintains its barrier property. These solutions are not limited to predicting steady-state flux. They give the time-dependent drug concentration profiles within the heterogeneous SC, which illustrate for the first time the diffusional pathway within this membrane. The SC's barrier property is then quantified from the lag time and permeability. In this first paper we present the solution for the simplest, but frequently cited, representation of the SC, ie the biphasic "brick-and-mortar" geometry with a homogeneous lipid phase (9–11).

DESCRIPTION OF MODEL

Fig. 1 shows a transverse section of a model SC-membrane (to scale) having the "brick-and-mortar" arrangement of corneo-

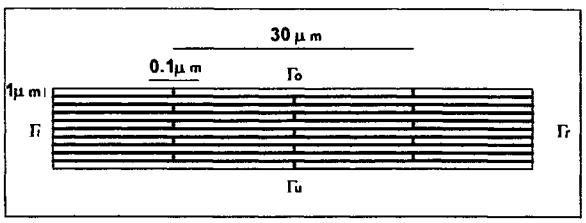

Fig. 1. The biphasic membrane Ω as a model for human stratum corneum shown to scale. Each corneocyte is 30 μm wide and 1 μm in height, and is surrounded by a homogeneous lipid layer of 0.05 μm. Ω is, therefore, 11 μm from Γ_u to Γ_o and each lipid channel is 0.1 μm wide. The sides Γ_l and Γ_r are insulated, and diffusion takes places from the bottom (Γ_u) to the top (Γ_o).

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cytes. We denote this bounded region "Ω". It contains 2 rectangular corneocytes within each of n = 10 parallel cell-layers, with the skin appendages (eg, sweat glands, hair follicles) being ignored. The dimensions within Ω are chosen to be realistic for abdominal human SC. Thus, each corneocyte has a width L = 30 μm and a height h = 1 μm, and is uniformly surrounded by a homogeneous lipid layer of thickness δ = 0.05 μm. The vertical alignment of the corneocytes is defined by an ordering parameter, ω(x), of periodicity x = (L + 2δ). The corneocytes are fully aligned when ω(0) = 0, and fully staggered (ie brick-and-mortar) when ω(1/2(L + 2δ)) = 0.5.

The drug concentration, $c_i(x,y,t)$, is given by:

$$-\mathrm{div}\{D_i(x, y)\nabla c_i(x, y, t)\} + \frac{\partial c_i(x, y, t)}{\partial t} = 0 \text{ in } \Omega \quad (1)$$

$$D_i(x, y) = \begin{cases} D_{lip}(x, y) \in \text{lipid} \\ D_{cor}(x, y) \in \text{corneocyte} \end{cases}$$

$$\frac{\partial c_i(x, y, t)}{\partial y} = 0 \quad \text{on} \quad \Gamma_l \cup \Gamma_r \quad \text{and} \quad c(x, \Gamma_u, t) = 1$$

$$c(x, \Gamma_o, t) = 0$$

$$c_i(x, y, 0) = 0$$

These equations describe the non steady-state diffusion of a drug through the heterogeneous model SC-membrane from the bottom (Γ_u in Fig. 1) to the top (Γ_o). Perfect sink conditions apply, ie the drug concentration is always unity at Γ_u and zero at Γ_o. The relative permeability of the corneocyte and lipid phases is given by the quotient D_{cor}/D_{lip}. This quotient governs the magnitude of the membrane's barrier property, since a barrier can only exist if $D_{cor}/D_{lip} < 1.0$, ie the corneocytes are less permeable than the lipid. A value for D_{cor} for drugs has never been determined, and estimations (10) are unreliable. Measurements of D_{lip} for drugs in a mixture of model SC-lipids are, however, available and give values of approx. 10^{-8} cm²/s (13). We assume this value for the homogeneous lipid phase in the model SC-membrane. Spontaneous partitioning of the drug occurs at the boundaries between lipid and corneocyte phases:

$$K_{cor/lip} \cdot c_{lip}(x, y, t)|_{n^-} = c_{cor}(x, y, t)|_{n^+} \quad (2)$$

where $K_{cor/lip}$ is the partition coefficient. At the phase boundaries the flux must be continuous:

$$D_{lip}\nabla c_{lip}(x, y, t)\cdot\vec{n} = D_{cor}\nabla c_{cor}(x, y, t)\cdot\vec{n} \quad (3)$$

As Eqs. 1–3 cannot be solved analytically in Ω, the problem was tackled numerically. The equations were first approximated in time by using an implicit Euler method, to leave an elliptic PDE in each time step. This was then approximated in 2-dimensional space by a fully-conservative finite volume method (14), giving a series of linear equations. A hierarchy of non-uniform rectangular grids (15) with varying mesh size was used to accommodate the highly anisotropic structure within Ω. The large discontinuity jumps in D at the lipid/corneocyte boundaries were accommodated by using a robust multigrid method (16), and the high aspect ratio of the corneocytes was compensated by anisotropic refinement (17). The result obtained was time-dependent drug concentration profiles within the heterogeneous model SC-membrane for values of D_{cor}/D_{lip} representing the spectrum of fully-permeable to highly impermeable corneocytes. The barrier property of the model SC-membrane was then characterised using the asymptotic lag time, τ_∞, and permeability P. The mass of drug, m(t), passing through Ω in the y-direction at Γ_o is given by Fick's First Law:

$$m(t) = -\int_0^t \int_{\Gamma_o} D(x, y)\nabla c_i(x, y, t)|_{y=\Gamma_o}\, dx\, dt \quad (4)$$

The drug permeation profile of m(t) versus t was calculated up to t = 50 000 h (ie at least 5000 lag times) to ensure steady state had been reached. The τ_∞[h] was determined by extrapolation back to m(t) = 0 and P [cm/s] was calculated from:

$$P = \{(\Delta m(t)/A\Delta t)|_{SS}\}/c(\Gamma_u, t).$$

RESULTS AND DISCUSSION

Drug Concentration Profiles Within the Heterogeneous SC-membrane

The permeability of the corneocytes within intact SC is unknown, with opinions varying between fully impermeable (8) and highly permeable (12). The heterogeneous model SC-membrane Ω shows that the shape and position of the drug concentration profiles are strongly dependent on corneocyte permeability, and also on the elapsed time. This is illustrated in Fig. 2a-c for the example of $K_{cor/lip}$ = 1 and fully-staggered corneocytes, ω(x) = 0.5. Note that the SC-membrane is not drawn to scale in Fig. 2, to enable the concentration profiles within the lipid to be clearly discernible. The contours of equal drug concentration were calculated at t/τ = 0.1, ie well before onset of steady-state. For D_{cor}/D_{lip} = 1, both corneocyte and lipid phases are equally permeable, and the model reduces to that of a homogeneous membrane (18). The result is parallel, horizontal contours which are continuous through both phases (trivial, therefore not shown). Reducing corneocyte permeability 1000-fold ($D_{cor}/D_{lip} = 10^{-3}$) results in non-symmetrical, wave-shaped contours across the membrane (Fig. 2a), whose amplitude increases from Γ_u to Γ_o. The wave peaks are centred alternately in the vertical lipid channels and the corneocytes. The drug is, therefore, evidently not confined to the intercellular lipid phase by reducing relative corneocyte permeability to 10^{-3}. This at first surprising result provides the key to understanding the available evidence of diffusional pathways within SC. Boddé et al. (19) visualised the permeation of $HgCl_2$ through excised SC-membranes and identified 'arc-shaped diffusion fronts' in corneocytes during early times. These are identical in shape to the wave peaks located within the corneocytes in Fig. 2a. Consider drug diffusion in the y-direction along the 1.1 μm vertical lipid channel between the 2 corneocytes of the first layer. The increasing drug concentration at the T-junction existing at the channel-end drives the drug in both x-directions along the adjoining horizontal lipid channels. The drug is, however, also driven in the y-direction through the centre of the overlying corneocyte in the second layer, resulting in the arc-shaped front seen in Fig. 2a and also in Boddé's study.

The diffusional pathway within the SC-membrane can be discerned from the shape of the contours of equal drug concentration across the lipid and corneocyte phases. The position of a contour within each phase is determined by the balance between the ratio of the diffusivities, D_{cor}/D_{lip}, and the square

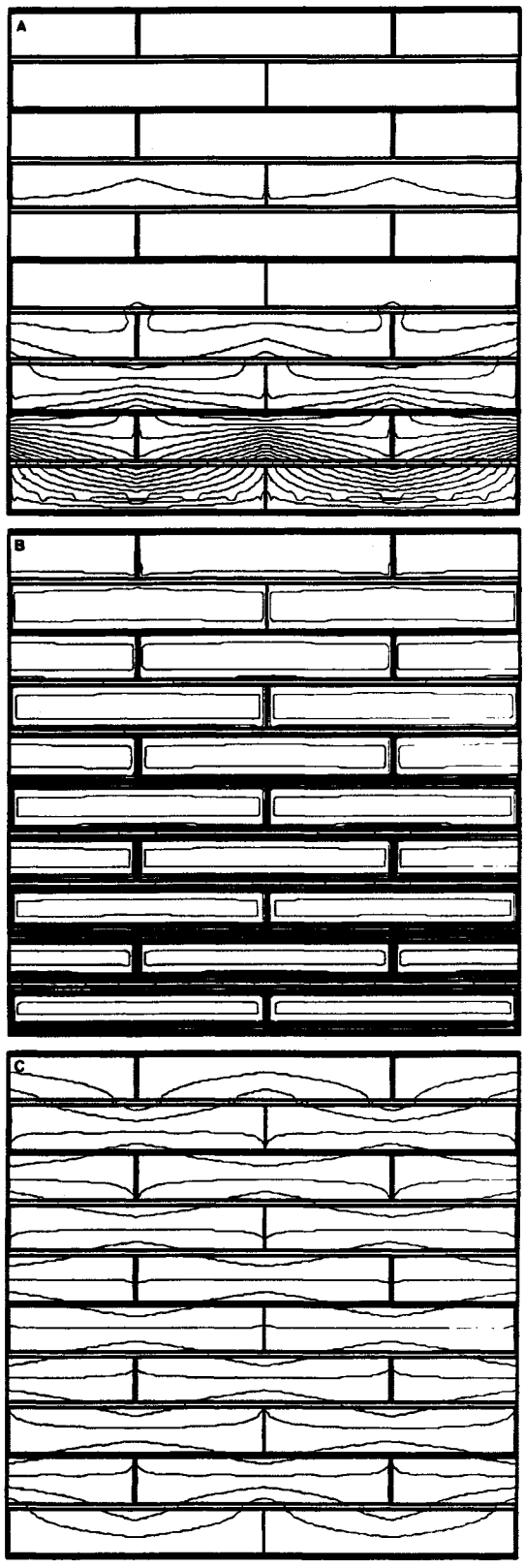

Fig. 2. Solute concentration profiles as functions of relative corneocyte permeability, D_{cor}/D_{lip} and elapsed time, t. The model SC-membrane is not drawn here to scale. a) $t/\tau = 0.1$ and $\epsilon = 10^{-3}$; b) $t/\tau = 0.1$ and $\epsilon = 10^{-6}$; c) $t/\tau = 10$ and $\epsilon = 10^{-3}$. In all cases 20 contours are shown at equally-spaced solute concentrations between $\Gamma_u = 1$ and $\Gamma_o = 0$. The concentration difference between any two adjacent contours is, therefore, $\Gamma_u/20 = 1/20$.

of the ratio of the pathlengths. The latter is equal to: $(l_{cor}/l_{lip})^2 = (1.1/31.2)^2 = 1/973$, since the corneocytes are 30 μm long and 1 μm deep, surrounded on each side by a 0.05 μm-thick lipid layer. In Fig. 2a the wave peaks in the lipid channels are only slightly further advanced than those in the corneocytes, since $D_{cor}/D_{lip} = 10^{-3}$ is comparable with $(l_{cor}/l_{lip})^2 = 1/973 \cong 10^{-3}$. By reducing relative corneocyte permeability to $D_{cor}/D_{lip} = 10^{-6}$ (Fig. 2b), closed contours are seen within each corneocyte. As the corneocytes are now 10^6 times less permeable than the lipid, the drug can circumnavigate the corneocyte intercellularly before it diffuses vertically through it. At this point, the ratio D_{cor}/D_{lip} of 10^{-6} is three orders of magnitude smaller than $(l_{cor}/l_{lip})^2$. The longer intercellular pathlength is more than accommodated by the smaller corneocyte permeability, producing a predominant intercellular diffusional pathway.

All evidence of a predominant intercellular pathway disappears in the steady-state, eg after ten lag times ($t/\tau = 10$). For completely permeable corneocytes ($D_{cor}/D_{lip} = 1$), an analytical solution to Laplace's equation can be obtained which has the form for a homogeneous membrane: $c(y) = y - \Gamma_o/(\Gamma_u - \Gamma_o)$. This equation describes parallel, horizontal contours of equal drug concentration across the SC-membrane (trivial, therefore not shown). These change gradually to wave-shaped contours as the corneocytes become less permeable. Fig. 2c shows the example of $D_{cor}/D_{lip} = 10^{-3}$, where symmetrical waves extend across the SC-membrane to a depth of no more than one cell-layer. A reduction in corneocyte permeability thus produces a decrease in the rate of advance of the contours through the SC-membrane (clearly visible on video). It does not lead in the steady-state to a purely intercellular diffusional pathway. During the steady-state phase the SC behaves, therefore, as a homogeneous membrane. This is the theoretical basis for the common observation that permeation experiments using excised human SC can be evaluated using Fick's First Law by using diffusivities corrected by a factor for pathlength and area.

Importance of Relative Corneocyte Permeability and Corneocyte Alignment

The barrier property of the SC-membrane is unequivocally defined by the combination of lag time, τ, and permeability, P. We show first that the model SC-membrane gives realistic values for both. For $D_{cor}/D_{lip} = 1$, the corneocytes are fully permeable. Consequently, τ_∞ in Fig. 3a is only 20 s and independent of corneocyte alignment within the SC-membrane described by ω(x). The analytical solution for this homogeneous membrane (18) gives the relation: $\tau_\infty = l^2/6D$. Setting $D = D_{lip} = 10^{-8}$ cm²/s [13] and $\ell = 11$ μm (the thickness of the model SC-membrane) gives 20 s, confirming exactly the numerical result. In Fig. 3b the P for $D_{cor}/D_{lip} = 1$ is 9.1×10^{-6} cm/s, which is also exactly that obtained for a homogeneous membrane using Fick's First Law. It is also independent of corneocyte alignment, ω(x).

A decrease in relative corneocyte permeability reduces D_{cor}/D_{lip} below unity and a heterogeneous membrane results. Consequently τ_∞ increases (Fig. 3a) and P decreases (Fig. 3b) for all corneocyte alignments. Each converges to an ω(x)-dependent limit as the corneocytes approach impermeability and $D_{cor}/D_{lip} \rightarrow 0$. For fully-staggered corneocytes (ie, $\omega(x) = 0.5$), τ_∞ converges to approx. 11 h and P to approx. 4×10^{-9} cm/s, which, therefore, represent the maximum barrier possible for the

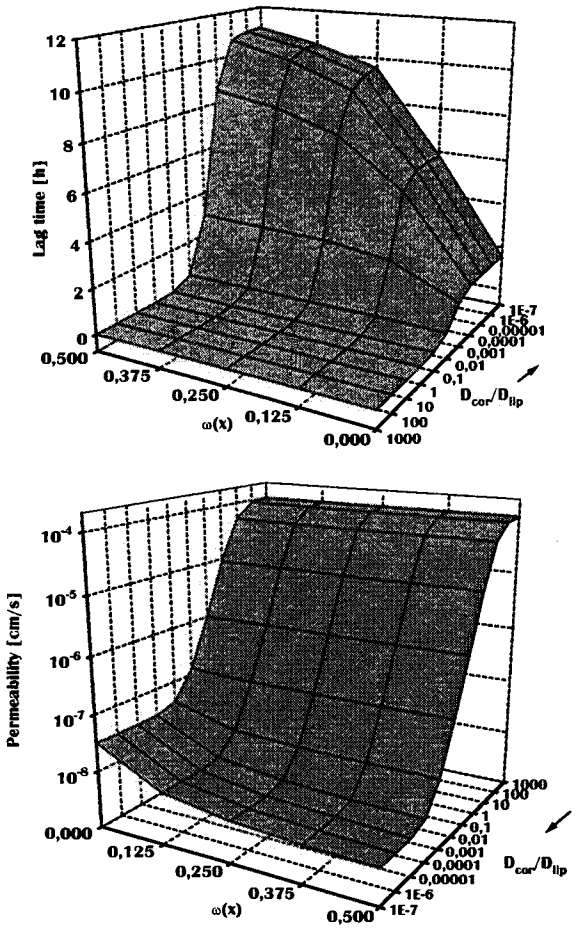

Fig. 3. Influence of relative corneocyte permeability (D_{cor}/D_{lip}) and corneocyte alignment ($\omega(x)$) on barrier property. a) Lag time, τ_∞; b) permeability, P. To maintain pictorial clarity both the x and y axes run in different directions in the two figures. D_{cor}/D_{lip} and P are shown on $\log_{10}$ axes.

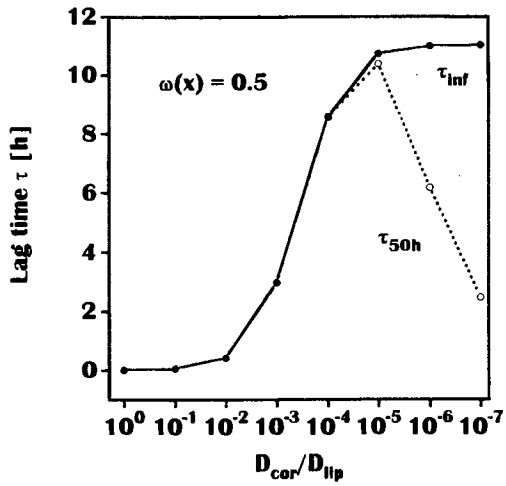

Fig. 4. Illustration of discontinuity in lag time calculated numerically in the limit of fully-impermeable corneocytes, $D_{cor}/D_{lip} \to 0$. τ_∞ was calculated from the plot of m(t) versus t obtained over 50 000 h (5000 lag times). τ_{50h} was calculated from the same plot over only 50 h (5 lag times).

model SC-membrane. This limiting case of fully impermeable corneocytes can be approximated by diffusion through a one-dimensional pore of pathlength ℓ_{lip} and cross-sectional area A_{lip} within an otherwise impermeable block (8). The analytical solution to this case for $\ell_{lip} = 11$ μm gives a P of 2.3×10^{-9} cm/s, which is acceptably close to the numerical result obtained in the limit as $D_{cor}/D_{lip} \to 0$. The lag time for fully impermeable corneocytes is obtained analytically from: $\tau = \ell_{lip}^2/6D = 146^2$ [μm²]/6 · 10^{-8} [cm²/s] = approx. 1 h, compared with 11 h for the numerical solution (cf. Fig. 3a). The reason for this discrepancy is the different limits taken for the numerical and analytical calculations. The analytical result is calculated from $\lim_{t\to\infty} m(t)$ for $D_{cor}/D_{lip} = 0$, whereas the numerical one is calculated from the double limit

$$\lim_{D_{cor}/D_{lip}\to 0} \; (\lim_{t\to\infty} m(t, D_{cor}/D_{lip}))$$

Consequently, the value calculated numerically for the lag time depends on the time over which m(t) is examined. This effect is illustrated in Fig. 4, where both τ_∞ and τ_{50h} (lag time calculated over 50 h only) are plotted versus D_{cor}/D_{lip} for the case of fully-staggered corneocytes. The value for τ_{50h} increases with decreasing corneocyte permeability, as seen for τ_∞, but reaches a maximum at $D_{cor}/D_{lip} = 10^{-5}$, and then falls back to converge to 1 h in the limit $D_{cor}/D_{lip} \to 0$.

How do these theoretical values for τ_∞ and P calculated from the model SC-membrane compare with experimental values obtained using excised SC membranes? τ and P for moderately-lipophilic drugs ($K_{oct/water} \leq 10^3$) of M.Wt. ≈ 300 vary greatly and depend on membrane thickness, but are generally ≥5 h (20) and $<10^{-4}$ cm/h (6), respectively, for human SC. A comparison with Figs. 3a&b illustrates the importance of relative corneocyte permeability and corneocyte alignment for the SC's barrier function. Thus, Fig. 3a shows that a τ_∞ of 5 h or more can only be reached if $\omega(x) \geq 0.125$ and $D_{lip}/D_{cor} < 10^{-3}$. A highly-staggered arrangement of corneocytes is therefore necessary, and the corneocytes must be at least 1000 times less permeable than the lipid phase. A typical experimental P of $<10^{-4}$ cm/h ($\approx 10^{-8} - 10^{-7}$ cm/s) is predicted in Fig. 3a at the same values of corneocyte permeability ($D_{cor}/D_{lip} < 10^{-3}$) and alignment ($\omega(x) \geq 0.125$) where realistic lag times occur. This at-first satisfying result is, however, puzzling, since the model SC-membrane does not include partitioning of drug at its outer side, ie at Γ_u. P is calculated using the drug concentration in the outermost membrane layer, $c(x, \Gamma_o, t)$. Experimentally, however, P is determined using the drug concentration in a perfectly-stirred donor solution adjacent to the SC's outer surface. These two concentrations will differ if spontaneous drug partitioning into the SC occurs from the donor, which should cause P to be underestimated in the model SC-membrane by a factor equivalent to the SC/donor partition coefficient, Yet the model SC-membrane predicts accurately values of P of $10^{-8} - 10^{-7}$ cm/s without regard to partitioning at the outer surface.

If the relative corneocyte permeability, D_{cor}/D_{lip}, is higher than 10^{-2}, both lag time (Fig. 3a) and permeability (Fig. 3b) are independent of the corneocyte alignment, $\omega(x)$. Even fully-aligned corneocytes ($\omega(x) = 0$) do not produce a weaker barrier than fully-staggered ones ($\omega(x) = 0.5$). As corneocyte permeability is reduced to below 10^{-3}, their alignment assumes, however, more influence on τ_∞ and P. As to be expected, the smallest

τ_∞ and largest P are now found for fully-aligned corneocytes where the intercellular pathlength is the shortest possible and the lag time never exceeds approx. 1.5 h (Fig. 3a). In the range $0.25 < \omega(x) \leq 0.5$, τ_∞ and P remain, however, insensitive to corneocyte alignment (Figs. 3a&b). Here there is rapid convergence to the longest lag time and smallest permeability at $\omega(x) = 0.5$ (fully-staggered corneocytes). Substantial deviation from the fully-staggered corneocyte alignment can, therefore, be tolerated in the SC-membrane without greatly reducing its barrier property. Only if $\omega(x)$ is reduced to below 0.25 will lag time be substantially reduced and permeability increased (Fig. 3a& b). The high aspect ratio of the corneocytes is, therefore, vital for maintaining the maximum possible barrier within the SC whilst accommodating natural variation in corneocyte alignment.

Importance of Partitioning Between Corneocytes and Lipid

Previous steady-state calculations for the brick-and-mortar geometry (10,11) predict an inverse, linear relation between permeability and corneocyte/lipid partition coefficient, $K_{cor/lip}$. The more lipophilic the drug is, the greater its predicted permeability (10). The non steady-state solution predicts a more complex influence of $K_{cor/lip}$ on τ_∞ and P, which strongly depends on the relative corneocyte permeability, D_{cor}/D_{lip}. We consider only the fully-staggered corneocyte alignment, $\omega(x) = 0.5$. Take, firstly, the case that drug partitioning into the corneocytes is favored (ie $K_{cor/lip}$ in Eq. 2 is >1). The result is a strong dependence of both τ_∞ and P on relative corneocyte permeability. Reducing the latter thus causes a sharp increase in lag time (Fig. 5a), which for $K_{cor/lip} = 100$ reaches approx. 10^3 h in the limit of fully-impermeable corneocytes. These prolonged lag times arise because, although lipid/corneocyte partitioning according to Eq. 2 is spontaneous, the subsequent rate of drug diffusion within the corneocyte depends on corneocyte permeability. The smaller D_{cor}/D_{lip} is, the slower the drug diffuses through the corneocytes and the longer it takes for a steady-state to be established. The formation of a drug "depot" within the corneocytes requires, therefore, both a hydrophilic drug and low corneocyte permeability. Reducing corneocyte permeability causes also a parallel, sharp decrease in P when drug partitioning into the corneocytes is favored ($K_{cor/lip} > 1$). This converges, independent of $K_{cor/lip}$, to the limit of approx. 4×10^{-9} cm/s for fully impermeable corneocytes already observed in Fig. 3b as being the smallest permeability possible in the model SC-membrane.

If drug partitioning into the lipid phase is favored (ie $K_{cor/lip} < 1$), the corneocyte permeability looses its influence over lag time or permeability. For highly lipophilic drugs having $K_{cor/lip} << 1$, the lag time does not exceed 1 h (Fig. 5a) and P reaches its lower limit of approx. 4×10^{-9} cm/s (Fig. 5b). This combination of extremely short lag time and very low permeability must, therefore, be a characteristic of highly lipophilic permeants which do not partition into the corneocytes from the lipid phase. The result in Fig. 5b proves that a decrease in corneocyte/lipid partitioning (ie, increasing drug lipophilicity) will always reduce permeability. Decreasing $K_{cor/lip}$ concentrates the drug within the lipid channels and reduces the diffusional area within the SC-membrane. P must then decrease accordingly, despite the greater drug concentration gradient

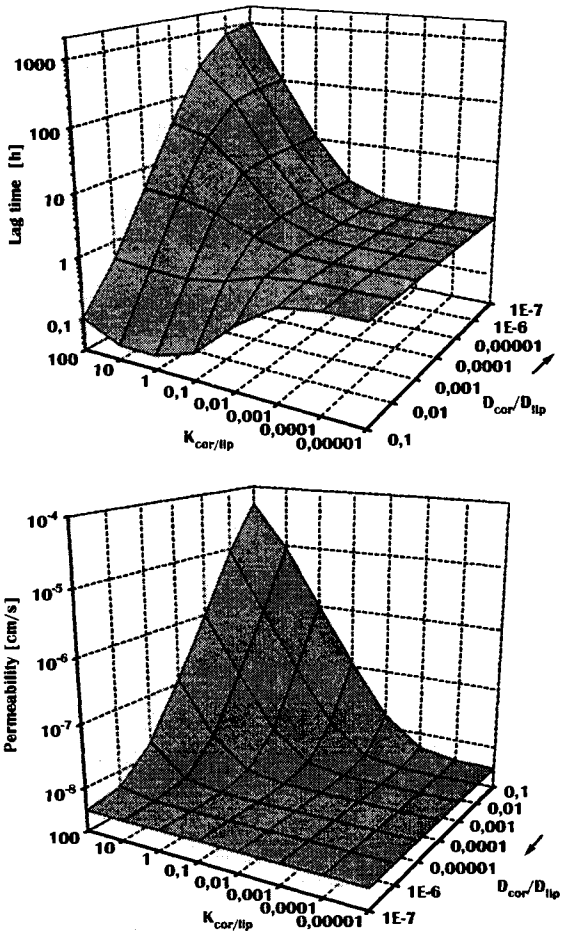

Fig. 5. Influence of corneocyte/lipid partition coefficient ($K_{cor/lip}$) on barrier property for various corneocyte permeabilities (D_{cor}/D_{lip}). a) Lag time, τ_∞; b) permeability, P. To maintain pictorial clarity the y axis runs in different directions in the two figures. All axes are $\log_{10}$.

within the lipid. This effect is most pronounced for permeable corneocytes ($D_{cor}/D_{lip} \geq 10^{-3}$) and disappears for impermeable one ($D_{cor}/D_{lip} \leq 10^{-5}$) where $K_{cor/lip}$ becomes irrelevant (Fig. 5b). The corneocyte/lipid partition coefficient within the SC-membrane exerts, therefore, a fundamentally different influence than does the SC/donor partition coefficient, $K_{SC/don}$, defined at the outermost SC layer, Γ_u. An increase in $K_{SC/don}$ (ie increasing lipophilicity) will always increase permeability, owing to the larger concentration gradient across the SC.

CONCLUSIONS

The model SC-membrane is the solution to the non steady-state diffusion equation for the brick-and-mortar structure. It predicts, from purely morphological principles, lag times and permeabilities that are in remarkable agreement with experimental values obtained using excised human SC. The analysis of the factors corneocyte alignment, corneocyte/lipid partitioning and relative corneocyte permeability presented here leads to 3 conclusions.

1. The elongated, flattened corneocyte shape renders lag time and permeability insensitive to large changes in corneocyte alignment. A lateral corneocyte displacement of 50% of its width, for example, reduces the lag time at most by 15% and

increases the permeability at most by 30% (cf Figs. 3a&b). This is a striking example of the effectiveness of the SC's brick-and-mortar geometry as a barrier.

2. Corneocyte/lipid partitioning within the SC is fundamentally different to SC/donor partitioning at the SC's surface. Increasing drug lipophilicity reduces its uptake into the corneocytes, causing lag time and permeability to decrease. Highly lipophilic drugs will have the unusual combination of very short lag times and very small permeabilities.

3. The long lag times and small permeabilities found experimentally for moderately-lipophilic drugs require both a highly-staggered corneocyte geometry and highly impermeable corneocytes.

There is ample microscopic evidence to demonstrate that corneocytes have—at least when viewed two-dimensionally—an apparently staggered, interlocking geometry (21). It is questionable, however, if corneocytes could be 1000 times less permeable than the lipid phase. Although they comprise >80% of densely-packed fibrills of α-keratin, highly cross-linked via disulphide bridges (22), they take up large amounts of water from a contiguous aqueous donor solution. Our efforts to measure D_{cor} directly using thin slices of hydrated horse hoof failed, owing to the presence of macroscopic pores within the α-keratin. Low corneocyte permeability could be a consequence of the "durable lipid envelope"-monolayer of N-(omega-hydroxyacyl)-sphingosin bound covalently to the outer corneocyte wall (23). There is indeed evidence to suggest that a barrier to protons exists in the outermost corneocyte wall (24). An alternative explanation reasons that corneocytes appear impermeable as a consequence of anisotropic drug diffusivities within a *heterogeneous* lipid phase. Drug molecules of the size and lipophilic character referred to here diffuse through a lipid bilayer slower than they diffuse parallel to it. Thus the value of $D_{cor}/D_{lip} \leq 10^{-3}$ predicted here could just be a consequence of a ratio of transverse to lateral diffusivities of $\ll 1$ within the lipid phase. The solution for this SC-membrane with heterogeneous lipid phase will be presented in due course.

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REFERENCES

1. F. de Haan, H. Boddé, W. de Bruijn, L. Ginsel, and H. Junginger. Visualising drug transport across stratum corneum: cryotechniques, vapour fixation, autoradiography. *Int. J. Pharm.* **56**:75–86, 1989.
2. M. Lampe, A. Burlinghame, J. Whitney, M. Williams, B. Brown, E. Roitman, and P. Elias. Humans stratum corneum lipids: characterisation and regional variation. *J. Lipid Res,* **24**:120–130, 1983.
3. P. Elias. Epidermal barrier function: intercellular lamellar lipid structures, origin, composition and metabolism. *J. Cont. Rel,* **15**:199–208, 1991.
4. J. Bouwstra, M. de Vries, G. Gooris, W. Bras, J. Brussee, and M. Ponec. Thermodynamic and structural aspects of the skin barrier. *J. Cont. Rel,* **15**:227–236, 1991.
5. B. Forslind. A domain mosaic model of the skin barrier. *Acta Derm. Venerol,* **74**:1–6, 1993.
6. T. Degim, J. Hadgraft, and W. Pugh, *Prod. Int. Sym. Cont. Rel. Bio. Mater.,* **22**:652, 1995.
7. C. Maxwell. Treatise on Electricity and Magnetism. Oxford University Press, London. I:365, 1873.
8. W. Albery and J. Hadgraft. Percutaneous absorption: in vivo experiments. *J. Pharm. Pharmacol.* **31**:140–147, 1978.
9. R. Lange-Lieckfeld and G. Lee. Use of a model lipid matrix to demonstrate the dependence of the stratum corneum's barrier properties on its internal geometry. *J. Cont. Rel.* **20**:183–194, 1992.
10. A. Michaels, S. Chandrasekaran, and J. Shaw. Drug permeation through human skin: theory and in vitro experimental measurement. *AIChE J.* **21**:985–996, 1975.
11. K. Tojo. Brick model for drug transport across stratum corneum, *J. Pharm. Sci.* **76**:889–891, 1987.
12. D. Edwards and R. Langer. A linear theory of transdermal transport phenomena. *J. Pharm. Sci,* **83**:1315–1334, 1994.
13. R. Lieckfeld, J. Villalaín, J. Gómes-Fernándes, and G. Lee. Diffusivity and structural polymorphism in some model stratum corneum lipid systems. *Biochim. Biophys. Acta.* **1151**:182–188, 1993.
14. W. Hackbusch. On first and second order base schemes. *Computing* **41**:277–296, 1989.
15. W. Hackbusch. Multi-grid Methods and Applications. Springer, Berlin, 1985.
16. G. Wittum. On the robustness of ILU-smoothing. SIAM, *J. Sci. Stat. Comp.* **10**:699–717, 1989.
17. P. Bastian and G. Wittum. Adaptivity and robustness. *In:* Adaptive Methods-Algorithms, Theory and Applications. Hackbusch, W., and Wittum, G. eds. NNFM, Braunschweig, 1994.
18. J. Crank. The Mathematics of Diffusion. Oxford University Press, London, 49–53, 1975.
19. H. Boddé, I. van den Brink, H. Koerten, and F. de Haan. Visualisation of in vitro percutaneous penetration of mercuric chloride; transport through intercellular space versus cellular uptake through desmosomes. *J. Cont. Rel.* **15**:227–236, 1991.
20. B. Barry. Dermatological Formulations, Marcel Dekker, New York, 1983.
21. M. Fartasch and M. Ponec. Improved barrier structure formation in air-exposed human keratinocyte culture systems. *J. Invest. Dermatol.* **102**:366–374, 1994.
22. S. Teng. Correlation of specific keratins with different types of epithelial differentiation: monoclonal antibody studies. Cell **30**:361–363, 1982.
23. D. Swartzendruber, P. Werz, K. Madison, and D. Downing. Evidence that the corneocyte has a chemically bound lipid envelope. *J. Invest. Dermatol.* **88**:709–713, 1987.
24. K. Packer and T. Sellwood. Proton magnetic resonance studies of hydrated stratum corneum. *J. Chem. Soc. Faraday II.* **74**:1592–1605, 1978.