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Two dimensional finite element modelling for dynamic water diffusion through stratum corneum

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ABSTRACT

Solvents penetration through in vivo human stratum corneum (SC) has always been an interesting research area for trans-dermal drug delivery studies, and the importance of intercellular routes (diffuse in between corneocytes) and transcellular routes (diffuse through corneocytes) during diffusion is often debatable. In this paper, we have developed a two dimensional finite element model to simulate the dynamic water diffusion through the SC. It is based on the brick-and-mortar model, with brick represents corneocytes and mortar represents lipids, respectively. It simulates the dynamic water diffusion process through the SC from pre-defined initial conditions and boundary conditions. Although the simulation is based on water diffusions, the principles can also be applied to the diffusions of other topical applied substances. The simulation results show that both intercellular routes and transcellular routes are important for water diffusion. Although intercellular routes have higher flux rates, most of the water still diffuse through transcellular routes because of the high cross area ratio of corneocytes and lipids. The diffusion water flux, or trans-epidermal water loss (TEWL), is reversely proportional to corneocyte size, i.e. the larger the corneocyte size, the lower the TEWL, and vice versa. There is also an effect of the SC thickness, external air conditions and diffusion coefficients on the water diffusion through SC on the resulting TEWL.

1. Introduction

Water within stratum corneum (SC) plays a key role for stratum corneum's barrier function as well as its cosmetic properties (Forslind et al., 2007; Fluhr et al., 2005; Rawlings and Matss, 2005). Stratum corneum is dry outside and wet inside and there must exist a water concentration gradient. This water concentration gradient will cause water to diffuse from deeper part of stratum corneum toward stratum corneum surface, and forms the diffusion water flux, i.e. trans-epidermal water loss (TEWL). TEWL is an important index for trans-dermal drug delivery studies and there are many factors might affect the TEWL. The purpose of this study is to simulate the two dimensional dynamic water diffusion process through in vivo human stratum corneum based on the brick-and-mortar model (Forslind et al., 2007; Marquez-Lago et al., 2010; Mitragotri et al., 2011) using finite element methods, and to study the effects of intercellular routes and transcellular routes (William and Barry, 1992), as well as corneocyte size on water diffusions. The outcomes of the study will provide better understandings for trans-dermal drug delivery.

2. Materials and methods

The two dimensional water diffusion through in vivo stratum corneum can be described by following diffusion equations:

$$\begin{cases} \frac{\partial}{\partial x}\left(D\frac{\partial C}{\partial x}\right)+\frac{\partial}{\partial z}\left(D\frac{\partial C}{\partial z}\right)=\frac{\partial C}{\partial t} \quad 0\le z\le L_{SC}, \quad -\infty\le x\le\infty \\ C(x,z,0)=C_0 \quad \text{initial condition} \\ C(x,0,t)=C_0 \quad \text{SC}-\text{Air boundary condition} \\ C(x,L,t)=C_1 \quad \text{SC}-\text{Epidermis boundary condition} \\ C(r+,t)=C(r-,t) \quad \text{Corneocyte}-\text{Lipid boundary condition (continuity)} \end{cases} \tag{1}$$

where x is the lateral axis that is within the SC surface, z is the vertical axis that is going from the bottom of the SC ($z=0$) to the surface of the SC ($z=L_{SC}$), L_{SC} is the SC thickness, $C(x,z,t)$ is the SC water concentration at position (x, z) and time t, C_0 is the water concentration at the SC surface, C_1 is the water concentration at the bottom of SC, $C(r+,t)$ is the water concentration just outside a corneocyte, and $C(r-,t)$ is that just inside a corneocyte, D is the SC water diffusion coefficient which is the combination of water diffusion coefficient of corneocyte ($D_{\text{corneocyte}}$) and lipids (D_{lipid}). In this

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paper, we assume that the water diffusion coefficient of corneocyte is linearly dependent on SC water concentration C, i.e.,

$$D_{\text{corneocyte}} = D_0 + \frac{D_1 - D_0}{C_1 - C_0} \times (C - C_0) \quad (2)$$

where D_0 and D_1 are the water diffusion coefficients of corneocyte at C_0 and C_1 water concentration, respectively. The values of D_0 and D_1 are estimated largely based on dry and wet SC water diffusion coefficients (Scheuplein, 1967). The water diffusion coefficient of lipids (D_{lipid}) is assumed 10 times higher than $D_{\text{corneocyte}}$. Based on this description, a 2D brick-and-mortar model was built to simulate in vivo human stratum corneum in order to have a better understanding on the effects of corneocyte size, stratum corneum thickness, external conditions and non-homogenous diffusion coefficients on TEWL, see Fig. 1. In this model, stratum corneum has two external boundaries, the SC – Air boundary and the SC – Epidermis boundary, it also has one internal boundary, the corneocytes and lipids boundary. We set the initial conditions and boundary conditions, use literature values for water diffusion coefficients of corneocytes and lipids (i.e. brick and mortar), and use finite element methods to simulate the dynamic water diffusion processes over a period of time within the stratum corneum.

Following values are used in the simulation:

Corneocyte size (40 μm × 1 μm), SC layers = 6

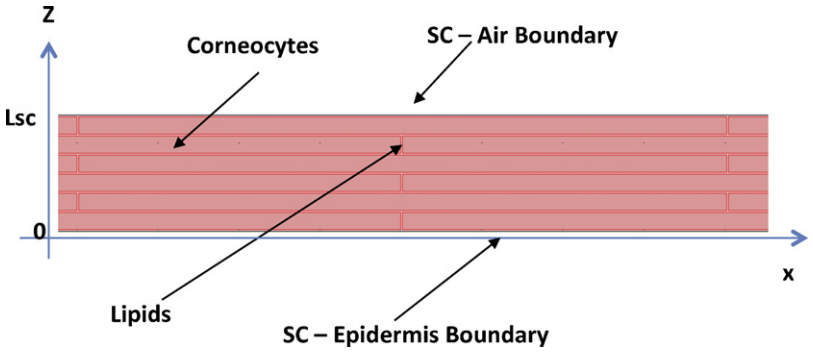

Fig. 1. 2D stratum corneum brick-and-mortar water diffusion model.

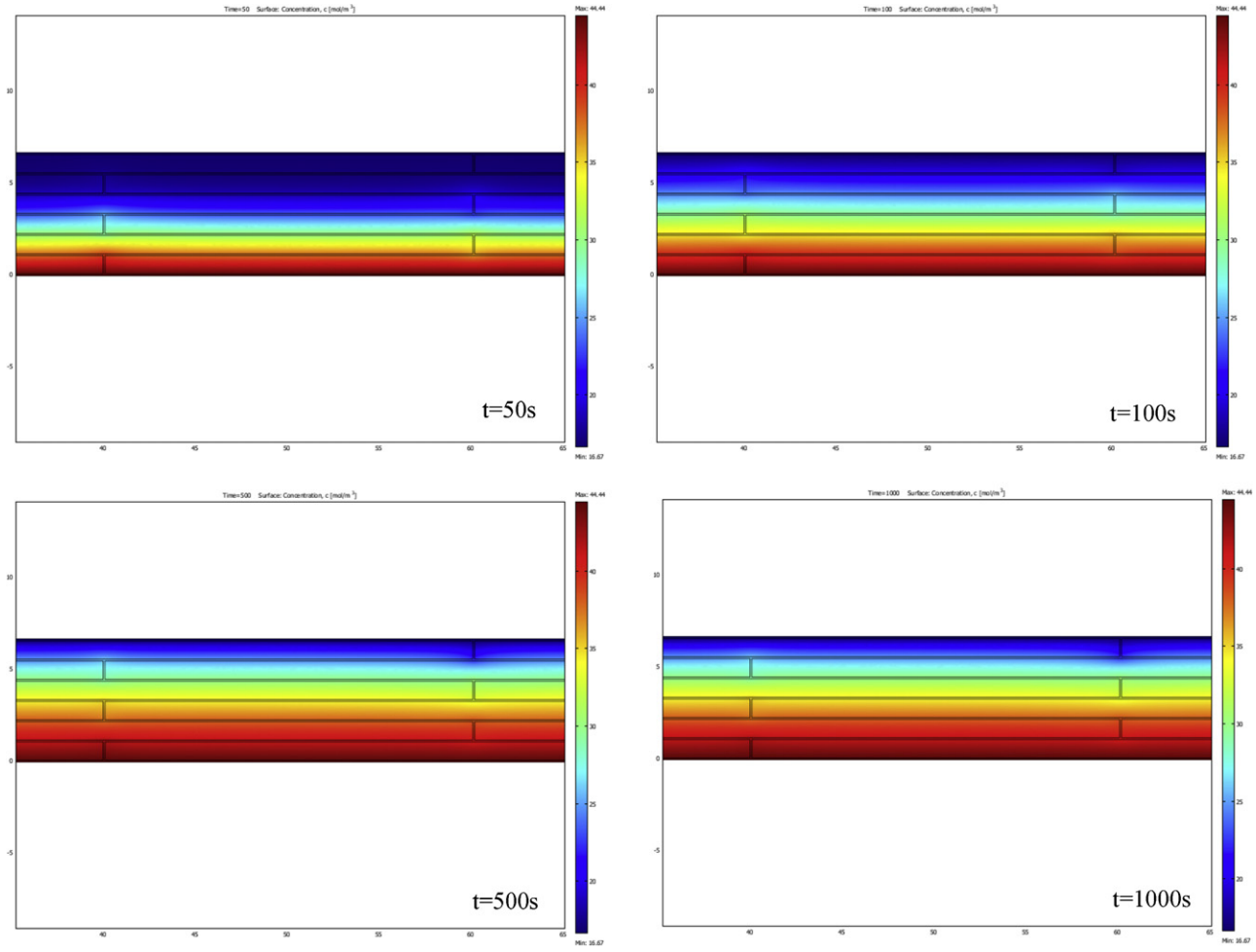

Fig. 2. Water concentration distributions within stratum corneum at different times (t = 50, 100, 500 and 1000 s).

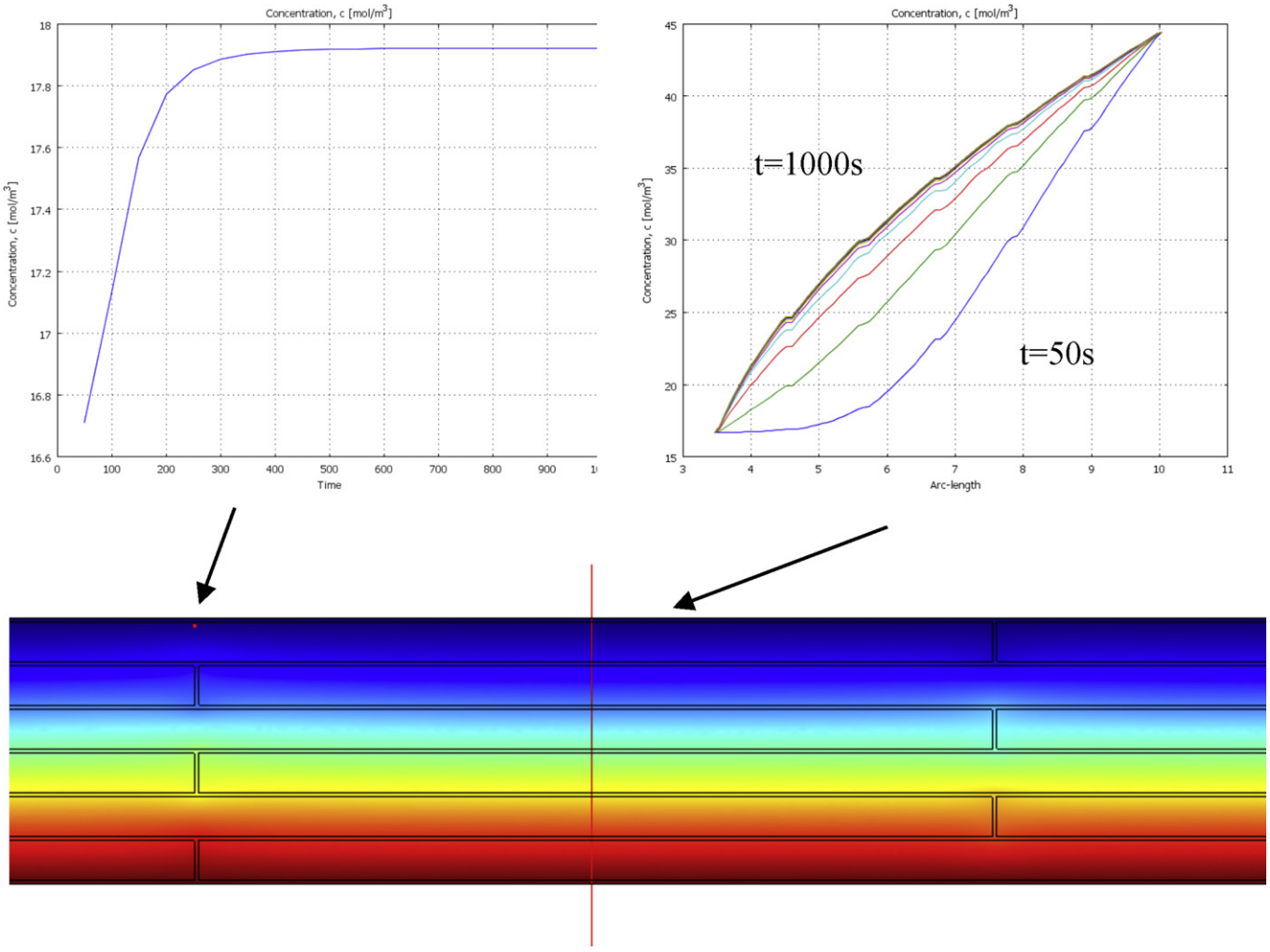

Fig. 3. The time dependent concentration curve at a point near the SC surface (top left), and the cross section plot of water concentration levels (top right) at different times.

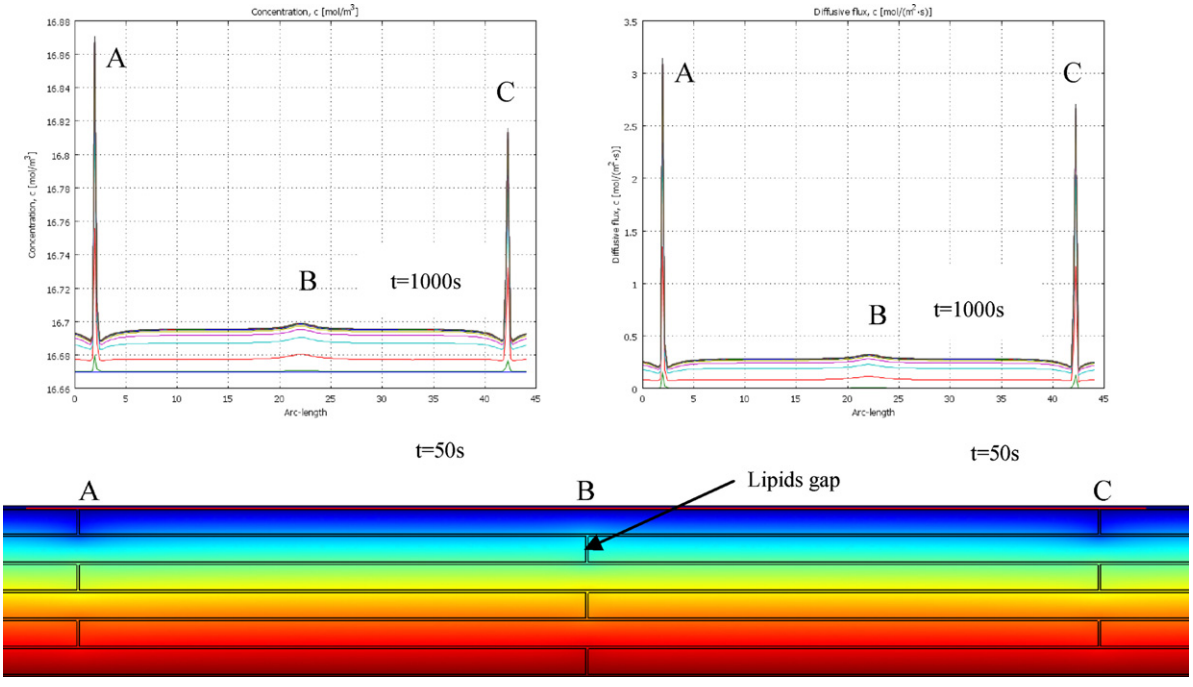

Fig. 4. The cross section plot of water concentration levels (top left) and corresponding water flux (top right), near the surface of the SC – Air boundary layer (bottom) at different times.

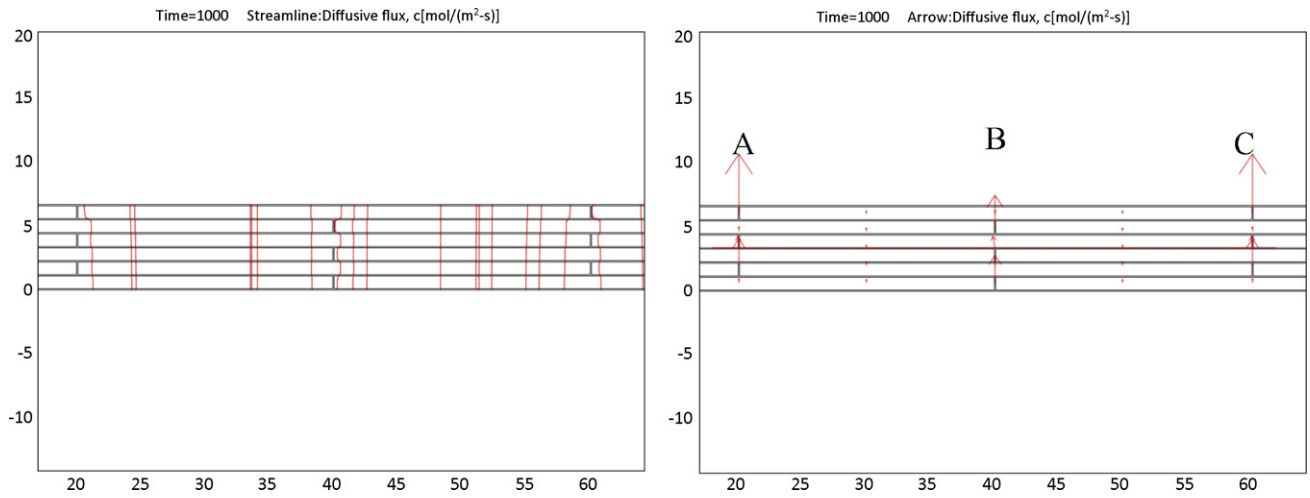

Fig. 5. The streamline (left) and directional arrow (right) of water diffusive flux at a cross section of stratum corneum at the time of 1000 s.

The thickness of the lipid layer = 0.1 μm (Wang et al., 2006)
$D_{\text{corneocyte}} = D_0 + \frac{D_1 - D_0}{C_1 - C_0} \times (C - C_0)$,
$D_0 = 2.5 \times 10^{-14}$ m²/s, $D_1 = 10^{-13}$ m²/s, $D_{\text{lipid}} = 1 \times 10^{-12}$ m²/s,
C_0 = 30% or 16.67 mol/m³, C_1 = 80% or 44.44 mol/m³.
Time range = 0–1000 s.

3. Results and discussion

Fig. 2 shows the 2D water dynamic distributions within SC at different times. In the beginning, water concentration is much higher in lipids, due to the relatively high diffusion coefficients of lipids, but as time goes on, the difference between water concentration in lipids and that in corneocytes is getting smaller.

Fig. 3 shows the time dependent concentration curves at a point near the SC surface and a cross section plot, from the SC – Epidermis boundary to the SC – Air boundary, of water concentration distributions at different times. The time dependent concentration curve results show that it takes about 500 s to reach steady state. The cross section plot results show that there is a discontinuity between water concentration distribution within corneocytes and lipids, due to the high diffusion coefficient differences. But this discontinuity tends to become smaller as time goes on. The water concentration distribution across the SC is also curved, not linear, due to the water dependent diffusion coefficient of corneocytes used in the simulation. This result generally agrees well with our previous one dimensional water diffusion studies (Xiao, 1998; Cui, 2005; Xiao and Imhof, 1998).

Fig. 4 shows the cross section plots of water concentration levels and corresponding water flux near the surface of the SC – Air boundary layer at different times. Again, the results show that water diffusion flux is much higher at the intercellular points (A and C) than the corneocyte surfaces. But it is interesting to point out that at the point B, which is in the middle of a corneocyte surface, the water concentration and water diffusion flux are also higher than the other points along the corneocyte surface. This is likely due to the lipids gap underneath, which has much higher water concentration and water diffusion flux. The result suggests that the high water flux in lipids layer will influence the water diffusion through adjacent corneocytes.

By integrating the area underneath flux curve, we can also estimate how much water diffuse through transcellular routes, and how much through intercellular routes. The results show that, at this cross section, the ratio of the amount of water diffuse through transcellular routes and intercellular routes is about 10:7 at time t = 50 s and 10:3 at time t = 1000 s. Therefore, although lipids has much higher water diffusion coefficient, the total amount of water diffuse through transcellular routes is still larger than that through intercellular routes, largely due to the high corneocytes to lipids cross area ratio.

Fig. 5 shows the streamline and directional arrow plots of water diffusive flux through stratum corneum. The streamline results suggest that although water tries to go through between corneocytes during diffusion through stratum corneum, water cannot completely avoid diffusion through corneocytes due to the geometry of corneocytes and multilayer nature of stratum corneum. In other words, according to diffusion law, no water can go through stratum completely through intercellular routes. The directional arrow plot results again suggest that the lipids gap will influence the diffusion within the adjacent corneocyte, and will result in higher flux.

Imhof et al. (2009) showed that, according to Fick's first law, the water diffusion through stratum corneum in steady state can be modeled similarly as current flow in an electrical circuit (Wheldon and Monteith, 1980) using the concept of diffusion resistance. If we assume that the basic building unit of the stratum corneum is just a corneocyte and some surrounding lipids, see Fig. 6 (left), then its diffusion resistance can be represented as Fig. 6 (right) and Eq. (3).

$$\begin{cases} R = \dfrac{R1 * R2}{R1 + R2} + R3 \\ \text{where } R1 = \dfrac{Hc}{D_{\text{corneocyte}}} \times \dfrac{Li + Lc}{Lc},\ R2 = \dfrac{Hc}{D_{\text{lipids}}} \times \dfrac{Li + Lc}{Li},\ R3 = \dfrac{Li}{D_{\text{lipids}}} \end{cases} \quad (3)$$

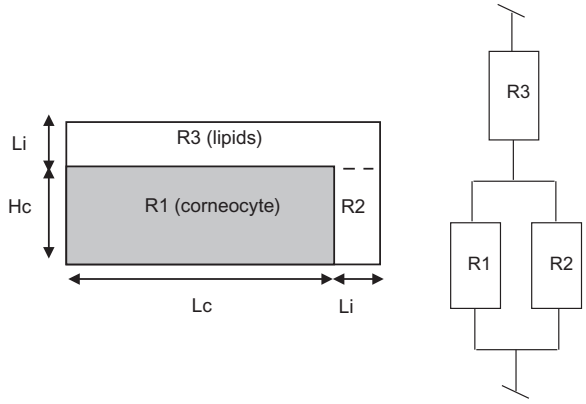

Fig. 6. Schematic representation of the SC basic building unit (left) and its equivalent electrical diagram (right), where *Lc* is the length of corneocyte, *Hc* is the thickness of corneocyte, *Li* is the size of lipids gap.

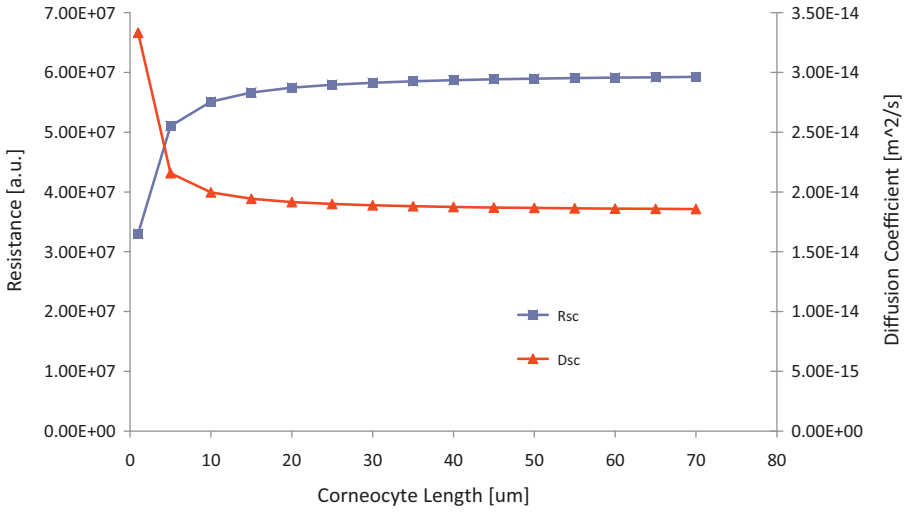

Fig. 7. The SC diffusion resistance and corresponding diffusion coefficient at different corneocyte sizes.

The total diffusion resistance of stratum corneum (R_{SC}) can be calculated as a collection of this building unit's diffusion resistance, and the diffusion coefficient of stratum corneum (D_{SC}) can be calculated as

$$D_{SC} = \frac{L_{SC}}{R_{SC}} \tag{4}$$

where L_{SC} is the total thickness of stratum corneum.

Fig. 7 shows the SC diffusion resistance and the corresponding diffusion coefficient at different corneocyte sizes (*Lc*). The SC water diffusion resistance increases as corneocyte size increases, while the SC water diffusion coefficient decreases as corneocyte size increases. As a result, the SC water diffusion flux will also decrease as corneocyte size increases. Machado et al. (2009) have also observed a similar trend in their study.

Similarly, we can also study the effects of other parameters such as SC thickness, the SC – Epidermis boundary water concentration levels and the SC – Air boundary water concentration levels. In the future, we would also like to investigate the anisotropic nature of water diffusion within lipids (Wang et al., 2006; Johnson et al., 1996), which will no doubt affect the water concentration profiles and flux profiles within SC.

4. Conclusions

Finite element simulation is a powerful tool for studying dynamic water diffusion processes within the stratum corneum based on the brick-and-mortar model. The simulation results show that, it takes about 500 s to reach a steady state, and according to diffusion theory, no water can penetrate through SC solely through intercellular routes, water has to penetrate through corneocytes at some points during the journey. Both intercellular routes and transcellular routes are important for water diffusion through the SC, however, the majority amount of water still diffuses through transcellular routes due to the high corneocyte to lipids cross area ratio. The high water concentration and water flux in lipids layer will influence the water diffusion through the adjacent corneocytes.

We have also developed a simple steady state diffusion model to study the effect of corneocyte size, the results show that the SC water diffusion resistance increases as corneocyte size increases, while the SC water diffusion coefficient decreases as corneocyte size increases. As a result, water diffusion flux, i.e. TEWL, is found inversely proportional to corneocyte size.

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