Porous Medium Modeling of Combined Effects of Cell Migration and Anisotropicity of Stratum Corneum on Transdermal Drug Delivery

Arunn Narasimhan[1]
Professor
Heat Transfer and Thermal Power Laboratory,
Department of Mechanical Engineering,
Indian Institute of Technology Madras,
Chennai 600036, India
e-mail: arunn@iitm.ac.in

Ajith Joseph
Heat Transfer and Thermal Power Laboratory,
Department of Mechanical Engineering,
Indian Institute of Technology Madras,
Chennai 600036, India
e-mail: ajith.jsph@gmail.com

A numerical model for transdermal drug delivery (TDD) has been developed by treating skin as a composite, dynamic, porous medium. Governing unsteady mass transport equations in porous medium was solved for different cases for up to a period of drug-patch application of 10 hrs. The effects of cell migration and anisotropic diffusive properties of stratum corneum (SC) on TDD are analyzed. Each of the above factors and their combination are found to significantly affect TDD. The cell migration in SC decreases the predicted amount of drug considerably. Their combined effect in TDD helped in identifying four distinct regimes of pharmacological as well as engineering importance within the domain. [DOI: 10.1115/1.4030923]

Keywords: porous medium modeling, transient simulations, drug delivery, cell migration, dynamic porous medium

1 Introduction

TDD has been used through the ages for topical treatment of maladies by the application of creams, gels, and ointments. Its potential to replace oral drug delivery and hypodermic injections, however, is a more recent concept, driven by its advantages such as increased bioavailability, noninvasive administration, reduced daily dose, reduced deleterious side effects, continuous drug delivery, and stable plasma concentrations [1,2]. Medicated patches are now being increasingly used for the treatment of not just topical but also systemic maladies. Scopolamine patches for motion sickness and nicotine patches for tobacco de-addiction have been in use for years

Transdermal drugs for cardiovascular disease, Parkinson's disease, Alzheimer's disease, depression, attention deficit hyperactivity disorder, skin cancer, female sexual dysfunction, postmenopausal bone loss, and urinary incontinence are at various stages of clinical development [3]. Recently, rotigotine patches for Parkinson's disease and granisetron patches for chemo-induced emesis have been approved by U.S.-FDA. Such drugs are categorized as passive TDD systems. TDD systems are being considered for several maladies because of advantages such as ease of administration, capability of maintaining stable plasma concentrations over extended periods, and the possibility to transcend systemic and portal circulation. Some limitations of TDD include skin intolerance/allergy, especially during long-term application, and need for drug design/skin pretreatment that enables the drug to cross the skin barrier and variability of application site conditions [4]. Solutions to overcome the drawbacks include development of "active" drug delivery systems such as heat-assisted TDD, iontophoresis, and physical enhancement by microporation of the biological barrier (skin) prior to patch application. But such processes cannot be handled directly by the user without the assistance of an expert.

Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat pores, through the hair follicles and sebaceous glands, generally called the appendageal route, or by direct diffusion across the SC. The appendages comprise a fractional area for permeation of approximately 0.1% and their contribution to steady-state flux of most drugs is very small. This resulted in the majority of skin permeation enhancement techniques being focused on increasing transport across the SC. In order to optimize the properties of the diffusing drug and the pathway for drug delivery, it is essential to choose between the intercellular and transcellular routes of drug permeation within the SC. A molecule traversing via the transcellular route must partition into and diffuse through many lipid lamellae between each corneocytes. This series of partitioning into and diffusing across multiple hydrophilic and hydrophobic domains is unfavorable as it decreases the efficacy of most drugs. Hence, intercellular route is now considered to be the major pathway for permeation of most drugs across the SC.

Development of an effective TDD system warrants a deeper understanding of the factors that affect the absorption of the drug through the skin. Such factors include diffusivity of skin, concentration of drug in patch, depth of diffusion, period of application of patch, etc. [5]. There have been a few studies that analyze the effect of one or more of these factors on TDD [6–8]. Apart from the above parameters, an important, but largely ignored factor is natural "cell migration" within the skin. To understand the role of cell migration and other factors on drug availability during TDD, it is important to understand the structure of skin [9]. The skin consists of three distinct layers: the SC, epidermis, and dermis, which vary in their physiological and engineering properties. The outermost layer, the SC is made of dead cells called corneocytes. These corneocytes are cells excreted out from the body, which have reached the end of their lifespan and have migrated toward the surface to be periodically shed off. These cells are closely packed and arranged in a brick–mortar pattern [10] separated by a bilipid layer in SC. This tortuous diffusion layer consists of 10–15 layers of corneocytes and is nearly impermeable to any external pollutants and pathogens.

[1]Corresponding author.

Contributed by the Heat Transfer Division of ASME for publication in the JOURNAL OF HEAT TRANSFER. Manuscript received April 30, 2014; final manuscript received March 30, 2015; published online August 11, 2015. Assoc. Editor: Suman Chakraborty.

Corneocytes continually accumulate at the bottom of the SC. This addition of cells lifts the SC layer from its initial position. To maintain skin thickness, the SC sheds the older dead cells on the surface at the same rate as cell addition from the bottom. In about 10–15 days, the entire SC of a healthy skin is replenished with new cells. Since the addition and removal of corneocytes is a continuous process, SC can be assumed to a dynamic porous medium (a solid tissue matrix made of minute flow enabling pores) that slowly migrates outward without appreciable change in the thickness. This creates a virtual flow field, which impedes the drug diffusion process into the skin from the surface. Skin diseases such as psoriasis or eczema can alter this process of cell migration by increasing its rate by five to six times than the normal, thereby affecting the drug diffusion more adversely.

Another interesting property of SC is the anisotropy of its diffusivity. The effective diffusivity of SC in the lateral direction (direction parallel to the skin surface) is almost double that in the transverse direction. The lower transverse diffusivity is a result of the highly tortuous intercellular lipid paths, through which the drug must diffuse from the surface to reach the epidermis; the effective distance a drug has to travel in the transverse direction is more than double the thickness of SC. In the lateral direction, on the other hand, the path is almost linear, which makes diffusion easier than in transverse direction [11]. When modeled as a porous medium, these anisotropies can be accounted for in the direction dependent effective diffusivities of the corresponding layers.

Dermis, the innermost layer, contains blood capillaries that extend into the deeper subcutaneous tissue. Drug which diffuses through the intercellular path of SC and epidermis finally reaches the blood capillaries, where it is absorbed into the circulatory system. The blood flow rate through the capillary bed in the dermis is dependent on the physical and mental conditions of the individual. During physical exertion or when exposed to high temperatures, blood flow is maximum and when at rest or in cold environments, it is minimum. Some of the previous works in this field were able to quantify the effects of blood flow [12–14]. But most of them were aimed on active mode of TDD. Many models of the skin have been developed in the past decade [15–17] taking into account the complex geometrical structure of the corneocytes in SC.

In the present study, we propose a novel model for passive mode of TDD. The concept of dynamic porous medium has been introduced to make the model realistic in terms of the biological processes, particularly cell migration, and anisotropic diffusive nature of SC. The composite porous medium modeling done for the entire domain also considers the effect of tortuous diffusion paths through the layers of the skin. Blood flow in the capillary bed within dermis has been modeled as Darcy flow. The study reveals that the modeling of TDD to investigate the effects of anisotropicity and upward cell migration not only shed light in pharmacological aspects of TDD but also helped in identifying some key regions within a dynamic/moving porous anisotropic medium when diffusion happens through it.

2 Mathematical Modeling

Numerical analysis was done with two-dimensional as well as three-dimensional models. Cross-sectional view of the computational domain used is shown in Fig. 1. The schematic is not to scale, as the ratio of depth to length of the skin (265×10^{-6} m: 15×10^{-2} m) is very small. The gray arrow marks indicate the blood flow in dermis region. Dotted arrow marks show the direction and location of application of the patch. Here, x is the lateral and y is the transverse direction.

The domain consists of three distinct layers which represent SC, epidermis, and dermis. All these layers were assumed to be porous with a porosity ranging from 0.1 to 0.9. Diffusivity values are 1×10^{-14} m^2/s, 1×10^{-12} m^2/s, and 1×10^{-10} m^2/s for SC, epidermis, and dermis, respectively [18,19]. In the porous medium modeling of the SC, to take into account of the tortuous diffusion paths, its lateral diffusivity is taken as double that of the above given transverse diffusivity. Epidermis and dermis were treated as isotropic porous media with identical diffusive properties in the transverse and lateral directions. The thickness of the skin and the size of the transdermal patch was selected based on the biological and pharmacological data available [20,21]. The cell migration velocities are taken as 1×10^{-11} m/s and 6×10^{-11} m/s for normal and diseased conditions of skin, respectively. They are calculated from the fact that it takes an average time of 12.5 days for a layer of SC cells to migrate from the bottom to the top of SC across its thickness.

The equations governing the diffusion through the porous medium are

In SC

$$\varepsilon \frac{\partial C}{\partial t} + \nabla(Cv) = \nabla \cdot (D_i \nabla C) \tag{1}$$

where the effective diffusivity is taken according to

$$D = \varepsilon \tau D_F \tag{2}$$

C represents the concentration of drug. v represents the virtual velocity field considered for taking into account of the cell migration in SC. ε is the porosity of the skin layers. τ denotes the tortuosity factor of the porous medium. D_F is the diffusivity of the fluid phase filling the porous media. D_i denotes the direction dependent diffusivity of drug in SC. The effective diffusivities of each layer in the porous medium model were calculated such that the value accounts for the macroscopic effects of the tortuosity and porosity on diffusion.

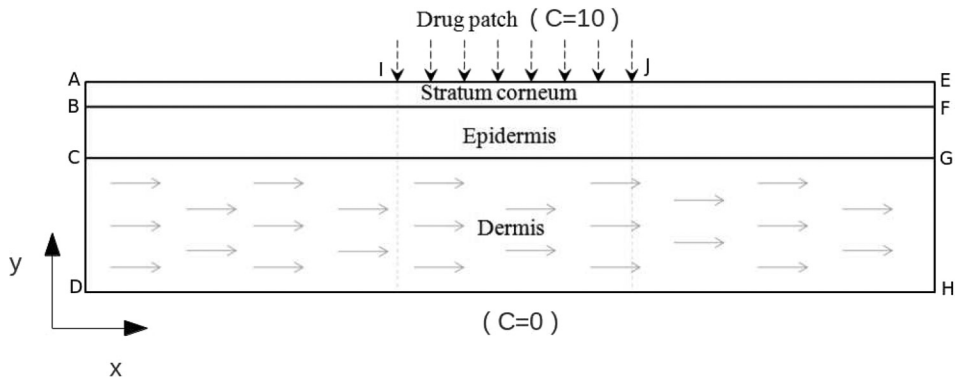

Fig. 1 Representative computational domain

In epidermis

$$\varepsilon \frac{\partial C}{\partial t} = \nabla \cdot (D \nabla C) \tag{3}$$

In dermis

$$\varepsilon \frac{\partial C}{\partial t} + \nabla (Cu) = \nabla \cdot (D \nabla C) \tag{4}$$

Here, u represents the steady Darcy flow velocity of blood inside dermis.

Total area of human body covered by skin is almost 1.74 m^2. It is known that almost 8.5% of total cardiac output (which is 5–6 l/min in resting condition) is circulated as dermal blood flow. This can increase by seven to eight times during physical exertion or in hyperthermia [22]. It is assumed that this dermal flow is same in magnitude everywhere in the body. An average velocity field of 28.571×10^{-3} m/s inside the dermis under a patch of size 5 cm × 5 cm was taken based on the above data. This velocity was taken as the direct solution of the macroscopic Darcy momentum equation represented by

$$u = -\frac{K}{\mu} \nabla P \tag{5}$$

Porous medium continuity equation solved within dermis is

$$\nabla \cdot (\rho u) = 0 \tag{6}$$

Here, K is the macroscopic permeability of blood through the porous structure of dermis. It is well established in porous medium theory [23] that this macroscopic value accounts for the microscopic pore variation of interstitial velocities, as the LHS of Eq. (5) also is the macroscopic Darcy velocity. The μ and ρ represent the dynamic viscosity and density of blood, respectively, and were taken according to the available literature [21].

2.1 Boundary and Initial Conditions. The different boundary conditions used are explained in Table 1. Labeling of different boundaries has done according to what is shown in Fig. 1. A constant concentration condition of $C = 10$ mol/m^3 was used at the top surface of the stratum corneum where the drug patch is applied. It has been taken $C = 0$ mol/m^3 at bottom surface of dermis, which is considered as a perfect sink for the transdermally delivered drug. All the interfaces between different layers of skin are assumed to provide smooth concentration continuity, without any jump.

At the interface between epidermis and dermis

$$J = D \frac{\partial C}{\partial y}|_{x,t} \tag{7}$$

Here, J is the diffusive flux crossing the boundary separating dermis and epidermis.

Table 1 Boundary conditions

Boundary name	Boundary condition	Nature of boundary
A-B, B-C, E-F, F-G, A-I, J-E	$D\frac{\partial C}{\partial n} = 0$	Impermeable wall
C-D	$u = 28.571 \times 10^{-3}$ m/s	Darcy velocity inlet
G-H	$u = 28.571 \times 10^{-3}$ m/s	Darcy velocity outlet
I-J	$C = 10$ mol/m^3	Constant concentration patch
D-H	$C = 0$ mol/m^3	Perfect sink
B-F	$C_{epi} = C_{SC}$	Concentration no-jump
C-G	$J = D\frac{\partial C}{\partial y}$	Flux equivalence

Velocity inlet and velocity outlet were imposed, respectively, at extreme left and extreme right of dermis. All the other boundaries were made impermeable and had the following condition:

$$D \frac{\partial C}{\partial n} = 0 \tag{8}$$

Here, n represents the direction perpendicular to the boundary specified. The initial condition in the domain applicable to all the three layers is $C = 0$.

2.2 Numerical Procedure. A commercially available software, COMSOL, was used to solve the discretized governing equations by finite-element method. Implicit time stepping, which uses the backward differentiation formula, was used to numerically solve the equations. The fully coupled attribute feature was attached to time nodes and a direct linear solver was used. The convergence was checked using residues in the conservation of mass and species. A convergence criterion of 1×10^{-6} was imposed for all the equations. Calculations were performed with and without cell migration in SC. Simulations were also performed incorporating the anisotropy of SC.

2.3 Grid and Domain Independence Study. The model used for the analysis was checked for domain and grid independence. Grid independence study is conducted for skin with cell migration and anisotropic SC. The computational domain was discretized using quadrilateral elements with fine grid close to patch and interface between different layers. The size of the extended domain used for this test is 50% of the patch. The grid within the domain is varied as shown in Table 2.

The predicted drug concentration at the interface between SC and epidermis at $t = 1000$ s was used to check the grid independence test. Between the grids 569,000 and 826,000 the percentage deviation in the drug concentration was found to be only 0.047. The grid of 569,000 elements in domain was selected as the optimum grid size.

For the domain independence study, the size of the extended domain on both sides of the patched skin was set equal and the total size was varied as 50%, 100%, and 200% of the patch size, as shown in Table 3. The grid just under the patch was the same as the optimum grid obtained in the grid independence study. The percentage difference of drug concentration between 200% and 100% extension was only 0.006. Thus, an extension of 100% size of the patch was selected as the optimum domain size. The final converged domain consisted of 569,000 cells and an extended domain of two times the width of patch and is shown in Fig. 2.

Table 2 Grid independence study

Number of cells	Concentration of drug	Percentage deviation between successive concentrations
105,000	0.311685	3.352
198,000	0.322496	2.811
288,000	0.331825	1.143
569,000	0.335665	0.047
826,000	0.335823	

Table 3 Domain independence study

Size of extended domain (%)	Concentration of drug	Percentage deviation between successive concentrations
50	0.33428	0.402
100	0.33581	0.006
200	0.33583	

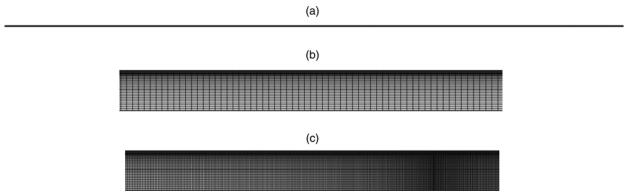

Fig. 2 Computational grid showing (*a*) entire domain, (*b*) mesh refinement near to patch, and (*c*) mesh refinement near to patch edge

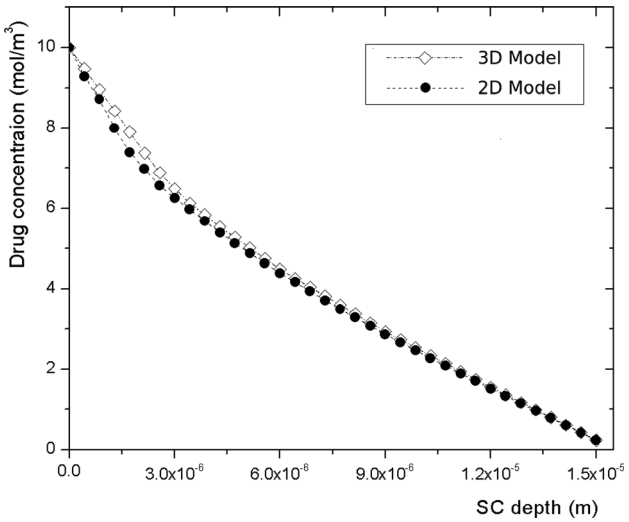

Fig. 3 Comparison of 3D and 2D modeling of TDD; concentration profiles within SC at $t = 10{,}000$ s

A 3D model is also analyzed. The face mesh of the 3D model was set identical to the converged 2D model. The differences in results between the 2D and 3D models are very small, as shown in Fig. 3. The figure shows the concentration profiles of the transdermal drug within SC after 2.8 hrs of patch application. The patch edge was chosen for comparison, since this is the site where the 2D and 3D results could vary because of the possible edge effect that is seen in 2D models.

2.4 Model Validation. The results of concentration distribution of transdermal drug within SC from the present model were validated against experimental results reported by Alberti et al. [24]. The experiment has been simulated using the present model with the same initial concentration of drug terbinafine (TBF) as used in the in vivo tests. Figure 4 shows the excellent agreement in distribution of TBF obtained from present model with the experimental data. The model overpredicts the concentration by about 20% near 0.25 depth of SC. This could be because of the 2D model used in this study and the possible absorption of TBF within the SC. The underprediction seen in concentration at a depth of 0.4–0.6 of SC could be a result of viable epidermal tissues present in the vicinity of SC that could increase its effective diffusivity.

3 Results and Discussion

Numerical analysis was conducted for different periods of application of the patch with and without considering the effect of cell migration in SC. Figure 5 shows the variation of drug concentration with depth of skin when the effect of cell migration is not considered. It can be inferred that a steady state is reached around $t = 1000$ s as the concentration curves overlap. The abrupt change seen in the slope of the curve at a depth of 1.5×10^{-5} m is due to the large difference in diffusivity values of the drug in SC and epidermis.

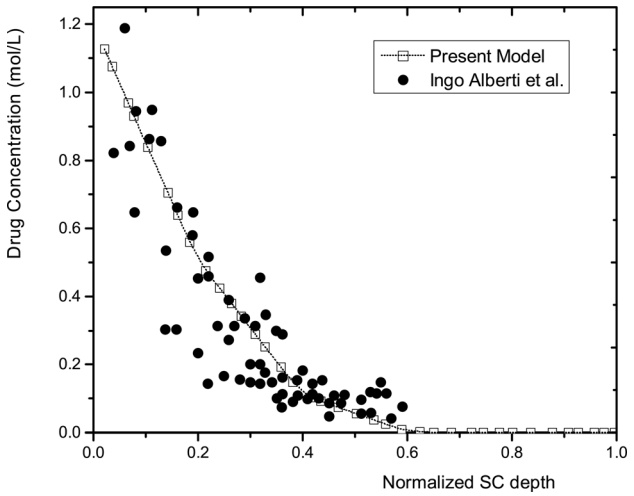

Fig. 4 Validation of present model with Alberti et al. [24]; TBF concentration within SC after 2 hrs of application

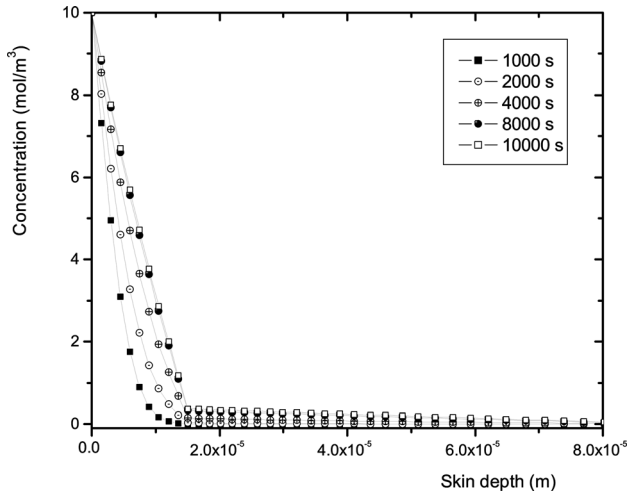

Fig. 5 Drug concentration profiles along the depth of skin at center of application of patch for different periods of application when there is no cell migration in SC

3.1 Effect of Cell Migration in SC. Figure 6 shows the steady-state concentration profiles along the depth of the skin at the center of application of patch with and without the cell migration. It can be seen that when there is cell migration, the concentration does not reach the levels obtained when there is no migration of cells. The migrating cells set up a virtual velocity field in a direction opposite to the direction of drug diffusion, thus impeding its motion. This effect is more in SC as this is the site of cell migration. It can be seen from the graph that the effect of cell migration in SC decreases the concentration levels of drug in epidermis, too.

Figures 7 and 8 also show similar effects of cell migration on the concentration profiles in SC. Although the concentration distribution seems similar in both cases, the contour corresponding to 0.42 mol/m^3 is slightly pulled back into the SC by the migrating cells. Concentration profiles within the SC and epidermis are compressed by the velocity field created by the cell migration. This effect of compression in transverse direction against the diffusion of drug causes the profiles to expand in the lateral direction away from the patch edge. An increase of 11% in lateral spread of drug

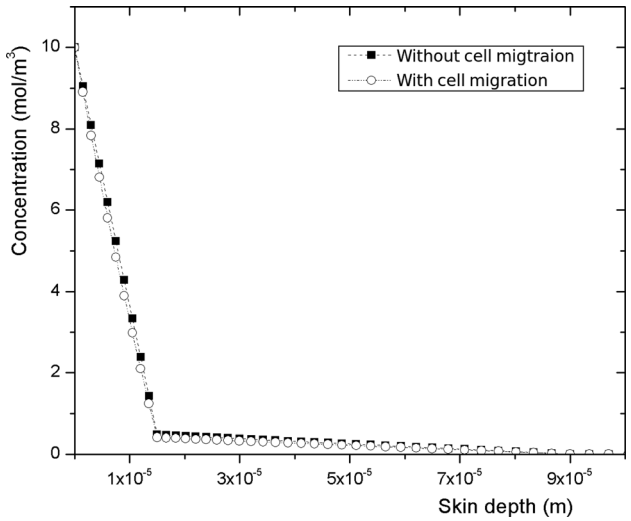

Fig. 6 Comparison of drug concentration profiles along the depth of skin at center of application of patch at steady state with and without cell migration in SC

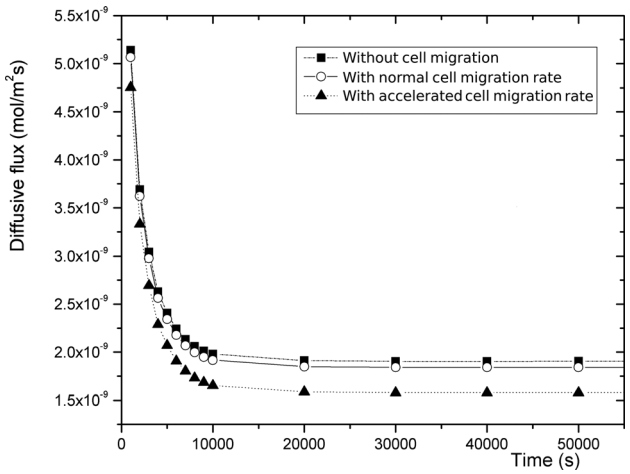

Fig. 9 Comparison of effect cell migration rate on amount of drug absorbed

when there is cell migration can be observed on comparing Figs. 7 and 8, which indicates the contribution of cell migration to increase the anisotropy of diffusivity of SC.

The decrease in concentration levels within SC owing to cell migration resistance was reflected in flux absorbed into skin also. It decreased the average flux crossing the patch–skin boundary by up to 20%. The decrease in amount of drug absorbed for different cases can be quantified from Fig. 9. It shows the difference in flux absorbed into skin between different cases, which considered cell migration and one without considering cell migration. All curves maintain a constant difference throughout the period of application of the patch. It can thus be inferred that the total amount of drug delivered over a period of time would decrease significantly when there is cell migration in SC.

The effect of cell migration on TDD in diseased conditions of skin, such as psoriasis or eczema, was also examined (Fig. 9). In such cases, the cell migration gets accelerated and can occur five to six times faster than normal [25]. In such cases, the efficacy of transdermal patches would be considerably low than for a normal skin. While designing a TDD module, this has to be taken into account for compensating the possible decrease in the overall dosage of the drug. Possible corrective measures include increasing the drug concentration in the patch, increasing the diffusive properties of skin artificially by application of heat, etc., and increasing the duration of patch usage or combinations of these approaches [14,26]. But there are pharmacological problems associated with keeping the concentration of drug beyond a particular safe limit within the body. Similarly increasing the duration of a lower concentration patch decreases the drug concentration in blood stream with time and can fall below the required levels. As there is only a narrow window of "working therapeutic concentration" for most of the drugs [27,28], it is important to keep the concentration of drug in a patch within this range. So, it can be inferred that the effect of cell migration has to be considered while designing a transdermal patch depending upon the conditions of skin, which can alter the normal cell migration.

3.2 Effect of Anisotropic Diffusive Nature of SC. Figures 10 and 11 show the increased lateral spread of the drug within skin layers when the SC is assumed to be anisotropic. The anisotropic nature of SC causes the drug to spread more around the area of application within SC. Comparing Figs. 8 and 11, it can be seen that the lateral spread of the drug in anisotropic SC is almost double that in isotropic SC.

Since there is a considerable spread of drug with transdermal patches, the effective area of action is larger than the actual patch area. This could be useful in designing new types of transdermal

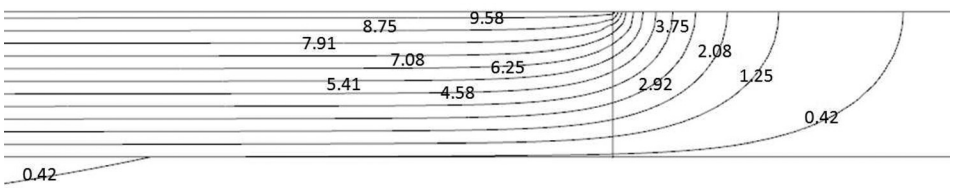

Fig. 7 Contours of drug concentration in SC near patch edge without considering cell migration at $t = 1000$ s

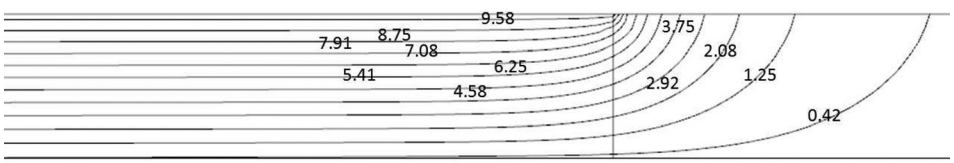

Fig. 8 Contours of drug concentration in SC near patch edge considering cell migration at $t = 1000$ s

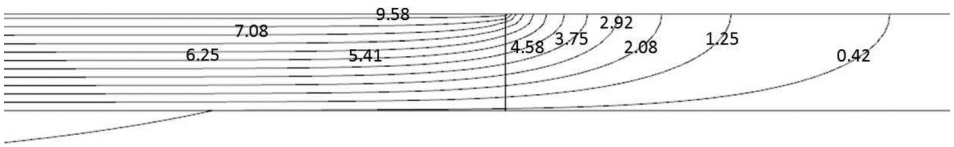

Fig. 10 Drug concentration in anisotropic SC, near patch edge when there is no cell migration at $t = 1000$ s

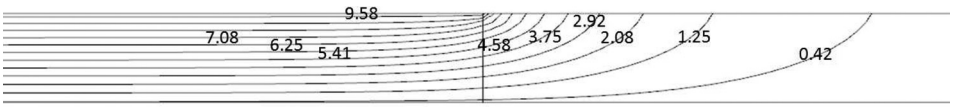

Fig. 11 Drug concentration in anisotropic SC, near patch edge when there is cell migration at $t = 1000$ s

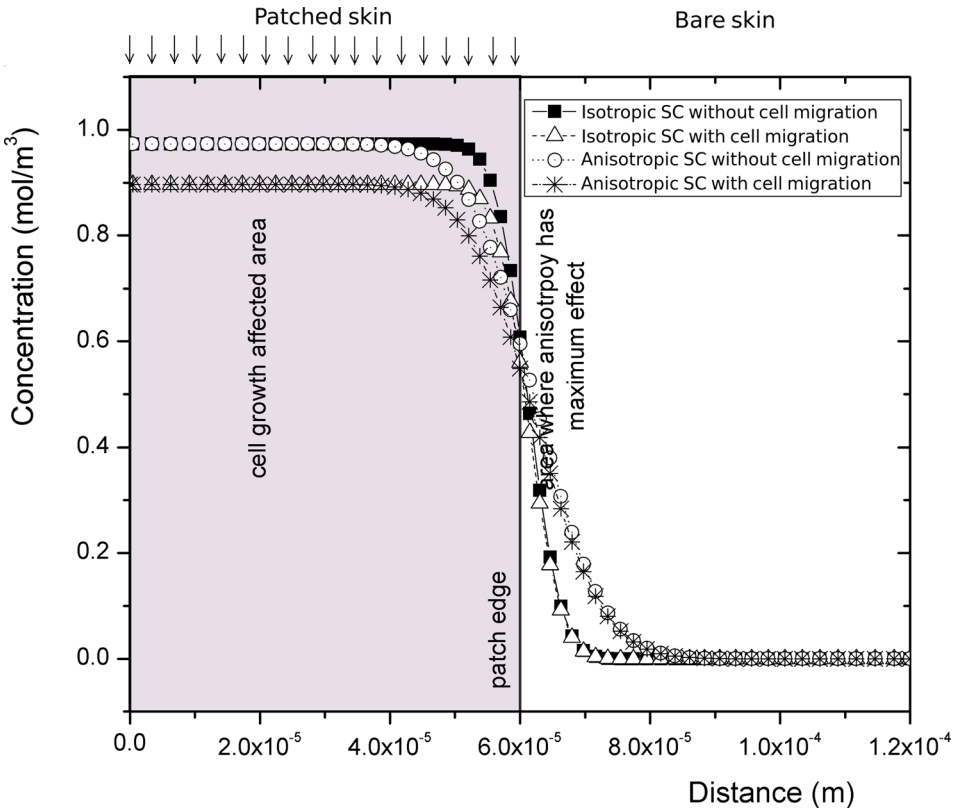

Fig. 12 Combined effect of anisotropy and cell migration at patch edge at mid depth of SC

patches that allow a narrow drug-free space between the skin and drug secreting patches. This drug-free space can be utilized for keeping agents which prevent skin irritation and allergies associated with the specific drug used in the patch. This is important as the skin tolerability issues such as skin irritation, allergies, and local edema on prolonged usage of patches occur in 20–50% of patients [29,30]. Appropriate remedies like use of moisturizers and topical corticosteroids are needed for 2–7% of patients who suffer from such complications.

The drug concentration profiles for anisotropic SC, as seen in Fig. 11, show a pattern very similar to that of isotropic SC in Fig. 8. But the combined effect of increased lateral spread of the drug and cell migration toward the patch in SC flattens the profiles near the patch edge. The effect of cell migration in anisotropic SC can be seen by comparing Figs. 10 and 11. The slopes of the curves in Fig. 11 are less than those in the curves of Fig. 10. The opposing migration of cells prevents the concentration profiles from crossing the SC–epidermis boundary. The same effect is also seen in isotropic SC, but the increase in lateral spread in isotropic SC is smaller than that in anisotropic SC.

3.3 Combined Effect of Anisotropic Diffusive Nature of SC and Cell Migration. Figure 12 depicts the concentration profile plotted along an imaginary line, which lies at half the depth of SC right bellow the patch edge. This line bisects a vertical drop line through patch edge as shown. The left side of the patch edge line comes directly under the transdermal patch and is shaded in gray. The diffusion of the drug toward the blood stream occurs below this area. To the right of the patch edge line is the bare skin that is exposed to the air. In both areas, there is cell migration and the SC is treated as anisotropic with diffusivity value in the lateral direction being twice as much as in the vertical/transverse direction. The concentration profiles for four different cases as indicated in legend are shown in the figure.

It can be seen that in the left of the patch edge line, profiles of the anisotropic and isotropic cases with cell migration in SC

merge. Similarly, the curves for isotropic and anisotropic cases without cell migration overlap. Thus, in this region, the drug diffusion is not affected by the anisotropic nature of SC but only by cell migration.

In the area to the right of the patch edge line, the profiles show that the anisotropic nature makes a difference, particularly near the patch edge. Between patch edge, where all the curves merge and the splitting point of the initial pairs, both anisotropy of SC and cell migration show similar effects on the distribution of drug within the SC. Since this is a region with no distinct curve pairs, this region is affected with both anisotropic nature of SC and cell migration in SC.

As we move further right of the patch edge line, two pairs are formed again. Here, the curves become independent of cell migration. In the case of anisotropic SC, lateral diffusion of drug predominates over the transverse direction. Since there is very little diffusion of drug in transverse direction, the cell migration, which occurs in the transverse direction, has no effect on drug diffusion.

With increasing distance from the patch edge line to the right, all curves merge to result in near zero value of drug concentration as this region is well beyond the limits of diffusion. Thus, it can be seen that between the pair splitting point and limit point of diffusion, drug diffusion is largely affected by the anisotropic nature of SC and is independent of the effects of cell migration.

4 Conclusion

This study models TDD by treating the human skin as a composite, dynamic, porous medium. The transient numerical study explains the effect of two major factors, viz., cell migration and anisotropic diffusivity of SC on drug diffusivity, and hence, efficiency of the TDD process.

It was observed that cell migration in the SC layer adjacent to the drug patch has a significant effect on drug diffusion. The virtual flow field created by the cell migration can change the drug concentration field within the skin. A maximum reduction of 20% in average flux crossing the skin surface was observed.

It was observed that the decrease in quantity of drug absorbed from the drug patch because of the cell migration at any particular time is independent of the time elapsed from the start of patch application. This can lead to a large decrease in the total amount of drug absorbed into the body over a period of time. This effect could be dominant when the transdermal patches are applied for prolonged periods of time.

Another interesting effect of cell migration is that it increases the anisotropic diffusive nature of SC by slowing down the diffusion of drug in transverse direction. It increases the lateral spread of drug in SC by 11%.

When the SC is treated as a layer with anisotropic diffusivity, there is a huge increase of 104% in the lateral spread of the drug. Therefore, it may be practical to apply multiple disconnected patches of the drug rather than one large patch to minimize side effects such as allergies.

Four distinct regimes inside the SC are identified from the results of drug diffusion in anisotropic SC with cell migration.

- The region directly under the drug-patch is affected only by cell migration and is independent of the effects of anisotropic nature of SC.
- The region between the patch edge and cell migration affected region is affected almost equally by the cell migration and anisotropic nature of SC.
- The region just beyond the patch edge is affected only by the anisotropic nature of SC and not by cell migration.
- The region further away from the patch edge is unaffected by cell migration and anisotropic nature of SC, because it falls beyond the diffusion limit of the drug.

These identified regimes inside the SC during TDD are of high pharmacological and engineering importance as they suggest methods to enhance the passive diffusion through skin modeled as dynamic porous media.

Nomenclature

C = concentration of drug (mol/m^3)
D = effective diffusion coefficient (m^2/s)
D_F = diffusion coefficient in fluid phase (m^2/s)
D_i = direction dependent diffusion coefficient (m^2/s)
J = diffusive flux (mol/m^2 s)
P = pressure (Pa)
SC = stratum corneum
t = time (s)
TDD = transdermal drug delivery
v = velocity component in direction perpendicular to that of the skin surface (m/s)
x, t = at constant depth and time
ε = porosity
μ = dynamic viscosity (Pa·s)
τ = tortuosity factor

References

[1] Scheuplein, R. J., 1967, "Mechanism of Percutaneous Absorption," J. Invest. Dermatol., **48**(1), pp. 79–88.
[2] Hadgraft, J., and Guy, R. H., 1989, *Transdermal Drug Delivery: Developmental Issues and Research Initiatives*, Vol. 35, Marcel Dekker, New York.
[3] Waters, C., 2013, "The Development of the Rotigotine Transdermal Patch: A Historical Perspective," Neurol. Clin., **31**(Suppl. 3), pp. S37–S50.
[4] Wohlrab, J., Kreft, B., and Tamke, B., 2011, "Skin Tolerability of Transdermal Patches," Expert Opin. Drug Delivery, **8**(7), pp. 939–948.
[5] Barry, B., 2001, "Novel Mechanisms and Devices to Enable Successful Transdermal Drug Delivery," Eur. J. Pharm. Sci., **14**(2), pp. 101–114.
[6] Kretsos, K., Miller, M. A., Zamora-Estrada, G., and Kasting, G. B., 2008, "Partitioning, Diffusivity and Clearance of Skin Permeants in Mammalian Dermis," Int. J. Pharm., **346**(1–2), pp. 64–79.
[7] Khalil, E., Kretsos, K., and Kasting, G., 2006, "Glucose Partition Coefficient and Diffusivity in the Lower Skin Layers," Pharm. Res., **23**(6), pp. 1227–1234.
[8] Frederick Frasch, H., 2002, "A Random Walk Model of Skin Permeation," Risk Anal., **22**(2), pp. 265–276.
[9] Montagna, W., 1974, *The Structure and Function of Skin 3E*, Academic Press, New York.
[10] Heisig, M., Lieckfeldt, R., Wittum, G., Mazurkevich, G., and Lee, G., 1996, "Non Steady-State Descriptions of Drug Permeation Through Stratum Corneum. I. The Biphasic Brick-and-Mortar Model," Pharm. Res., **13**(3), pp. 421–426.
[11] Park, J.-H., Choi, S.-O., Seo, S., Choy, Y. B., and Prausnitz, M. R., 2010, "A Microneedle Roller for Transdermal Drug Delivery," Eur. J. Pharm. Biopharm., **76**(2), pp. 282–289.
[12] Petersen, K. K., Rousing, M. L., Jensen, C., Arendt-Nielsen, L., and Gazerani, P., 2011, "Effect of Local Controlled Heat on Transdermal Delivery of Nicotine," Int. J. Physiol., Pathophysiol. Pharmacol., **3**(3), pp. 236–242.
[13] Cross, S. E., and Roberts, M. S., 1995, "Importance of Dermal Blood Supply and Epidermis on the Transdermal Iontophoretic Delivery of Monovalent Cations," J. Pharm. Sci., **84**(5), pp. 584–592.
[14] Hadgraft, J., 1999, "Passive Enhancement Strategies in Topical and Transdermal Drug Delivery," Int. J. Pharm., **184**(1), pp. 1–6.
[15] Kalia, Y. N., and Guy, R. H., 2001, "Modeling Transdermal Drug Release," Adv. Drug Delivery Rev., **48**(2), pp. 159–172.
[16] Iordanskii, A. L., Feldstein, M. M., Markin, V. S., Hadgraft, J., and Plate, N. A., 2000, "Modeling of the Drug Delivery From a Hydrophilic Transdermal Therapeutic System Across Polymer Membrane," Eur. J. Pharm. Biopharm., **49**(3), pp. 287–293.
[17] Manitz, R., Lucht, W., Strehmel, K., Weiner, R., and Neubert, R., 1998, "On Mathematical Modeling of Dermal and Transdermal Drug Delivery," J. Pharm. Sci., **87**(7), pp. 873–879.
[18] Rim, J. E., Pinsky, P. M., and van Osdol, W. W., 2009, "Multiscale Modeling Framework of Transdermal Drug Delivery," Ann. Biomed. Eng., **37**(6), pp. 1217–1229.
[19] Lv, Y., Liu, J., Gao, Y., and Xu, B., 2006, "Modeling of Transdermal Drug Delivery With a Microneedle Array," J. Micromech. Microeng., **16**(11), pp. 2492–2501.
[20] Mehdizadeh, A., Toliate, T., Rouini, M. R., Abashzadeh, S., and Dorkoosh, F., 2004, "Design and In Vitro Evaluation of New Drug-in-Adhesive Formulations of Fentanyl Transdermal Patches," Acta Pharm., **54**(4), pp. 301–317.
[21] Hadgraft, J., and Guy, R. H., 2010, *Transdermal Drug Delivery*, 2nd ed., Vol. 123, Informa Healthcare, London.
[22] Filer, C., Allen, G., Brown, T., Fowles, S., Hollis, F., Mort, E., Prince, W., and Ramji, J., 1994, "Metabolic and Pharmacokinetic Studies Following Oral Administration of ^{14}C-Famciclovir to Healthy Subjects," Xenobiotica, **24**(4), pp. 357–368.

[23] Narasimhan, A., 2013, *Essentials of Heat and Fluid Flow in Porous Media*, ANE Books, New Delhi, India.
[24] Alberti, I., Kalia, Y. N., Naik, A., Bonny, J.-D., and Guy, R. H., 2001, "In Vivo Assessment of Enhanced Topical Delivery of Terbinafine to Human Stratum Corneum," J. Controlled Release, **71**(3), pp. 319–327.
[25] Lowes, M. A., Bowcock, A. M., and Krueger, J. G., 2007, "Pathogenesis and Therapy of Psoriasis," Nature, **445**(7130), pp. 866–873.
[26] Benson, H. A., 2005, "Transdermal Drug Delivery: Penetration Enhancement Techniques," Curr. Drug Delivery, **2**(1), pp. 23–33.
[27] Kramer, C., and Tawney, M., 1998, "A Fatal Overdose of Transdermally Administered Fentanyl," J. Am. Osteopath. Assoc., **98**(7), pp. 385–386.
[28] Tanner, T., and Marks, R., 2008, "Delivering Drugs by the Transdermal Route: Review and Comment," Skin Res. Technol., **14**(3), pp. 249–260.
[29] Ale, I., Lachapelle, J.-M., and Maibach, H., 2009, "Skin Tolerability Associated With Transdermal Drug Delivery Systems: An Overview," Adv. Ther., **26**(10), pp. 920–935.
[30] Zhai, H., and Maibach, H. I., 2001, "Skin Occlusion and Irritant and Allergic Contact Dermatitis: An Overview," Contact Dermatitis, **44**(4), pp. 201–206.