Acta of Bioengineering and Biomechanics
Vol. 15, No. 2, 2013

Original paper
DOI: 10.5277/abb130207

Non-thermal plasmas induced electrostatic stress on corneocyte desquamation

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The advent of non-thermal plasma brought a breakthrough in exploring its clinical applications in dermatology to bolster tissue generation in the domain of plasma medicine. This study aimed to investigate the effect of non-thermal plasma on the corneocyte of the skin cells, in treating superficial skin diseases via the process of corneocyte desquamation, a probable mechanism for skin cell proliferation. The postulated brick and mortar arrangement of corneocytes in the stratum corneum was modeled consisting of three corneocytes and three corneodesmosomes in a simulation domain of 40.30×3.00 μm^2 using Maxwell 2D finite element analyzer. The corneocyte desquamation was quantified by the weakening of corneodesmosomes due to electrostatic pressure (~530 MV/m) on the corneodesmosome surface exceeding its tensile strength (~76 MPa). A mathematical model displaying a relationship between the plasma potential and the skin tensile strength is also presented in this investigation. The non-thermal plasma could emerge as a clean and dry therapy to treat superficial skin diseases. Our study propels investigating the interaction of non-thermal plasma with the wet tissue in the deeper layer (dermis) of the skin cells and also, the development of such instruments for a comprehensive skin treatment.

Key words: *corneocyte, stratum corneum, desquamation, proliferation, electrostatic, disruption*

1. Introduction

The skin is the evident body organ that is readily affected by chemical or environmental changes that lead to the outset of common skin diseases such as soap-induced xerosis, sunburn to skin cancer, as well as skin wrinkling and thickening, etc. The modern drugs such as peptides and proteins, etc., are generally administered orally and continuously for a specific period of time to cure these diseases. The oral administration of modern drugs is constraint, due to high metabolic activity in the gastro-intestinal tract and in the liver (first pass effect) [1]. Alternatively, the drugs might be administered through the epidermal route that has an advantage in terms of the limited metabolic activity in the skin compared to that in the liver and the possibility of achieving a continuous delivery profile. However, the drug administration through the transdermal route is restricted due to skin cells, specifically corneocytes that function as a protective barrier to any unwanted effects. In addition, there is another type of element or we can say a kind of drug element termed as gaseous plasma that can even invade the protective barrier and could bestow therapeutic effect to the mammalian cells.

Before dealing with details about non-thermal plasma treatment on skin cells, understanding the structure of corneocyte is prerequisite. The corneocyte constitutes the uppermost layer of the skin, and periodically shed and regenerated. These processes are called corneocyte desquamation and its proliferation, respectively, which are natural biological processes for a healthy skin and occur due to protease of corneodesmosomes. The corneocytes are bounded through each other via a link known as corneodesmosomes [2]. Such arrangement of corneocytes exist up to 20 μm depth in the superficial skin which is also known as stratum corneum, an up-

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Received: August 22th, 2012
Accepted for publication: February 13th, 2013

permost layer of epidermis [3]. The corneodesmosome can be affected by several contextual factors such as pH, water, or lights. The degradation of corneodesmosomes is known as a protease. Both exogenous and endogenous proteases are implicated in the cleavage of the corneodesmosome linkages [4]. The reasons for exogenous and endogenous proteases might be due to change in pH of the skin through the environmental or chemical exposure externally and morphological changes during cell proliferation internally, respectively. The acidic pH degrades the corneodesmosome, allowing its protease, and hence induces to desquamation [2]. However, the enzymatic degradation of the corneodesmosomes weakening the strong corneocyte–corneocyte interaction has also been demonstrated [5].

The gaseous plasma, which is electrically neutral and a collective mixture of free electrons, ions (cations and anions), neutral molecules, excited atoms, radicals and ultraviolet (UV) radiations, is meant as an ionized form of matter which can be produced as hot or cold (in other words, non-thermal) plasma. The non-thermal plasma maintains gas temperature close to room temperature and does not have detrimental effect on living tissues. Moreover, several experiments further rule out any effect of plasma resulting from UV and electric field [6]. Hence, the non-thermal plasma is used in biological applications. Having a potential in treating skin diseases [7], the non-thermal plasma can diffuse through the skin effectively and penetrates the smallest openings and hollow spaces instigating corneocyte desquamation. The non-thermal plasma therapy is a newly introduced technique in the medical domain to treat wound and skin burn, and even to destroy cancer cells [8]. One of the promising applications of non-thermal plasma is to treat rough and thickened skin that has aroused due to impaired corneocyte desquamation. However, the uncontrolled desquamation may lead to severe skin phenotype such as Netherton syndrome [9]. In this sense, a comprehensive investigation on the plasma-skin interaction in the corneocyte desquamation induced by non-thermal plasma will be crucial to prevent skin damage.

The current study aims to investigate the mechanism of corneocytes desquamation by numerical simulation of shining a non-thermal plasma beam, to treat thickened and rough skin without bringing any additional effect due to chemical changes to the superficial skin. The mechanism is still intriguing researchers to find an explicit explanation and is also discussed, and therein we focus our perspective and methodology behind the current proposition of skin treatment in the domain of plasma medicine. The development of electrostatic plasma potential is investigated utilizing the Gouy–Chapman–Grahame–Stern (GCGS) theoretical model that accounts to formulating a mathematical expression for the tensile strength of the skin.It is also noted that the sole word plasma should be referred to as non-thermal plasma wherever mentioned henceforth in this article.

2. Materials and methods

2.1. Simulation model

Investigation into the application of plasma to skin treatment has tremendously gained momentum ever since the United States Food and Drug Administration (USFDA) licensed plasma skin regeneration technology (PSR) for skin rejuvenation and for treatment of wrinkles in the year 2005 [7]. Subsequently, the researchers have extended plasma applications from blood coagulation; wound healing treatment, etc., to cancer treatment. We focus our studies on plasma–corneocyte interaction in the stratum corneum. Stratum corneum is relatively thin, i.e., extending up to a depth of approximately <100 μm, and belongs to the epidermis [10], an upper most layer of the skin. In contrast, the whole skin thickness comprising epidermis and dermis is about 2–4 mm in depth.

The plasma for biomedical application can be inexpensively produced at atmospheric pressure using helium gas, argon gas, and other mixtures, or even air by devices such as plasma needle, plasma torch, dielectric barrier discharge (DBD), etc. The devices, namely, Argon Plasma Coagulators (APC) [11], [12] and Plazon [13] were successfully clinically tested to tread blood coagulation and wound healing, respectively. The application of the plasma torch (Mircro-PlaSter β®), an argon plasma device, on the forearm of a patient has resulted in a distinct improvement of erythema and reduction of hepatogenic pruritis [14]. In most of the skin treatments mentioned above the depth of plasma penetration is only 2–3 mm, making the treatment method free of side effects [7]. Conclusively, the plasma torch fits in well for the treatment of common skin diseases and therefore it can readily be applied to study plasma–corneocyte interaction. Moreover, our study also propels instrumentation development researchers to design a device that could deliver plasma having even lesser penetration depth for skin surface treatment.

We have modeled the layered structure of corneocytes (brick and mortar) in the stratum corneum as postulated by Elias [15]. The geometric arrangement

of corneocytes is well estimated by Johnson et al. [16], which motivated many researchers to investigate the diffusion and transport of molecules through the epidermal route as one of the alternate methods of drug administration [17], [18]. Like real behavior, their plasma model can readily diffuse through the spatial arrangement of corneocytes and can adhere to the surface of corneodesmosomes intensely compared to any other surfaces. Their corneocyte model was mimicked such that the corneodesmosomes are modeled as elliptically shaped and the electric charge particles tend to accumulate in greater numbers at locations of greatest curvatures fundamentally than any other surfaces (corneocyte being rectangular in shape).

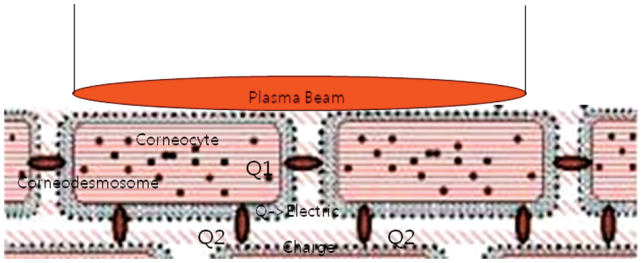

Fig. 1. Schematic of plasma beam interaction with corneocytes in the stratum corneum of the skin

Therefore, the deposited plasma will create higher electric field strength at the curve whose magnitude is larger. As far as the charge of plasma is considered, any plasma having greater number of positive or negative concentration could induce corneodesmosome degradation. A schematic of plasma beam interaction with corneocytes in the stratum corneum is shown in Fig. 1. The terms Q1 and Q2 represent the quantities of charge deposited on the horizontal and vertical corneodesmosomes, respectively.

In order to investigate the effect of plasma on the corneocyte degradation we have modeled the uppermost layer model of three corneocytes and three corneodesmosomes in a simulation domain of 40.30×3.00 μm^2, as depicted in Fig. 2. The dimensions of the corneocyte were: length ~40 μm and thickness ~ 0.8 μm. The corneocytes were covered by an envelope called corneocyte envelope (CE) with the thickness of 20 nm and a net surface area of 40.04×0.84 μm^2. The horizontal and vertical spacings (HS and VS, respectively) between the corneocytes (that are filled with the intercellular lipid matrix, also called mortar) were 75 nm [16]. This geometric arrangement intuited that the thickness of the corneodesmosome should be about 75 nm having an elongated shape with major radius up to 37.5 nm and minor radius up to 20 nm.

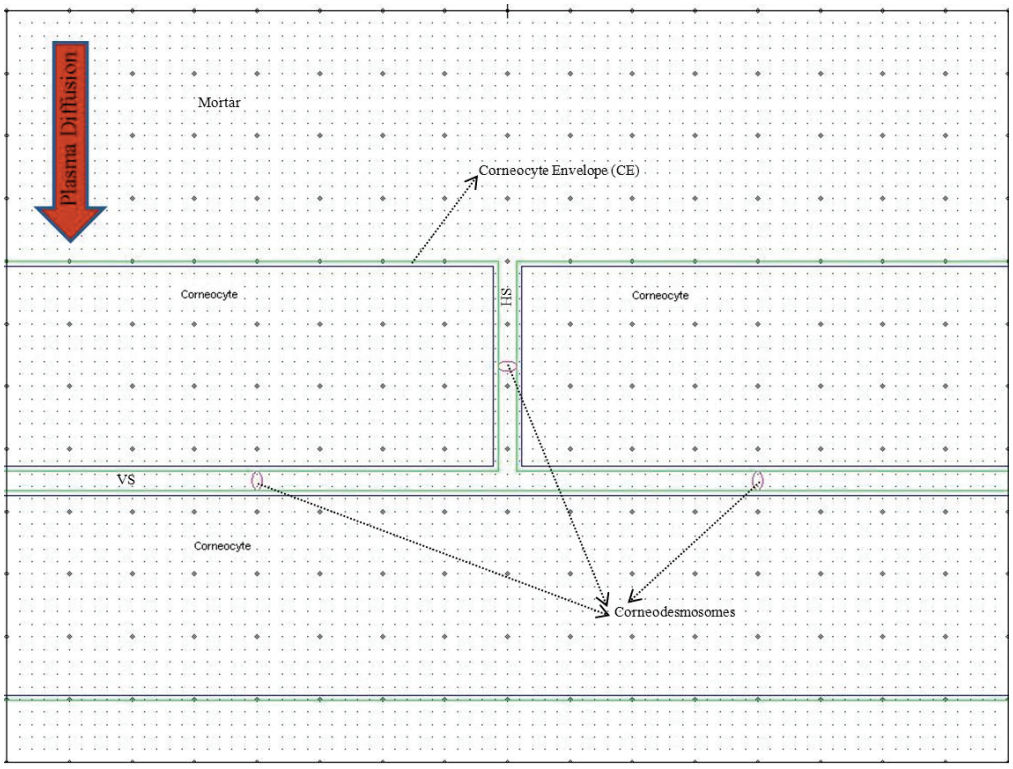

Fig. 2. The dimension of the corneocyte and corneodesmosome for a brick and mortar geometry

The geometric arrangement of the constituents of the stratum corneum also differs in terms of their di-

Table 1. Dielectric constant and conductance of the material used in the simulation

Material	Dielectric constant	Conductance (S/m)
Mortar	47	2.21
Corneocyte envelope	40	3.0
Corneocyte	35	5.0
Corneodesmosome	42	2.7

electric properties such as dielectric constant and conductivity. Gabriel et al. [19]–[21] and Yamamoto et al. [22] observed that the conductivity of the stratum corneum is exponentially related to the distance from the skin surface. The data (dielectric constant and conductance as shown in Table 1) used in the modeling to analyze the simulation results was taken from their investigations.

2.2. Mathematical model

The diffusion of plasma into the stratum corneum and accumulation of surface charge density, σ (C/m^2) on the surface of cornedesmosome develop a plasma potential, $\Phi(V)$ across it. In order to estimate the charge density we first need to calculate the surface area of the corneodesmosome. Since we have considered an ellipsoid type corneodesmosome in this investigation, the surface area of the ellipsoid S can be expressed as [23]

$$S = 4\pi\left[\frac{(ab)^p + (ac)^p + (bc)^p}{3}\right]^{1/p}, \qquad (1)$$

where p = 1.6075 and a, b and c are the three semi-axes. In a two dimensional condition and in the limit when $c \ll a$, b, the approximated surface area of the corneodesmosome becomes

$$S = 2\pi ab \qquad (2)$$

and a and b are the major and minor radii of the corneodesmosome. Therefore, the expression of surface charge density in turn can be expressed as

$$\sigma = \frac{Q}{S}, \qquad (3)$$

and Q is the total charge on the surface of the corneodesmosome. The dimension of the embedded corneodesmosome in the brick and mortar arrangements of the corneocytes is in nanometer scale and in this scenario it can be considered as a nanoparticle. And, the stability can be quantified in terms of potential that can be estimated via the Gouy–Chapman–Graham–Stern (GCGS) zeta potential model [24]. The zeta potential could be considered as analogous to plasma potential due to the fact that charge build-up on the surface of corneodesmosome is only due to the external plasma ions which are negated in the absence of it. Therefore, the nonlinear relationship between Φ and σ can be written as

$$\Phi = \frac{\sigma\lambda_D}{\varepsilon r}\exp\left[-\frac{r}{\lambda_D}\right], \qquad (4)$$

where r, ε and λ_D are the interaction length, dielectric constant and Debye length of the corneodesmosome in the stratum corneum, respectively.

When a cell is subjected to an external electric field, an electrostatic potential $\Phi(V)$ develops on the surface of the cell causing the rupture of the membrane when the outward electrostatic stress exceeds its tensile strength. The electric potential required to rupture a membrane of radius R (μm) and its thickness Δ (μm, $\ll a_0$, R) with a hemispherical irregularity of radius a_0 (μm, $\ll a_0 R$) can be written as [25], [26]

$$\Phi \geq 0.2\sqrt{a_0 R}\,\sqrt{\Delta / R}\,F_t^{1/2}, \qquad (5)$$

where F_t is the tensile strength of the membrane in dyne/cm^2. Also, for a spherical cell without spherical irregularity, a_0 can be replaced by R in equation (5); and the condition for rupture of the membrane can be deduced as

$$\Phi \geq 0.2\sqrt{\Delta R}\,F_t^{1/2}. \qquad (6)$$

In our mathematical analysis, we have considered corneodesmosome as a part of a spherical cell with thickness and radius of curvature, and the modeling of such dimensions are explained in the discussion section. Moreover, in the present situation plasma potential is equivalent to the electrostatic potential, thus, equating equation (4) and equation (6) gives a mathematical expression for estimating the tensile strength of the corneodesmosome

$$F_t \frac{25}{\Delta R}\left(\frac{Q\lambda_D}{S\varepsilon}\right)^2\left(\frac{\exp[-r/\lambda_D]}{r}\right)^2. \qquad (7)$$

We have used mathematica version 8.0 to manipulate the parameters in equation (7) to estimate the tensile strength of the corneodesmosome, and for the parameters Q = 30 nC, λ_D = 7 nm, r = 30 nm, ε = 38.58, S = 4.71 × 10^{-15} m^2 and $\alpha = \Delta \times R$ = 0.0924, the manipulated value comes out to be, F_t = 7.67 × 10^7 dynes/(cm^2) ≈ 76 MPa, which is equivalent to the tensile strength of the skin [27]. The accumulation of a total charge of about 30 nC in theoretical calculation

for the corneodesmosome degradation is verified through the finite element simulation. Inferentially, the variation in the value of α will cause change in the value of σ and the other parameters providing a necessary condition for the corneodesmosome rupture. We have discussed it by considering two cases in the discussion section. Therefore, the mathematical expression expressed by equation (7) presents a mathematical model for corroborating a relationship between the skin tensile strength and the plasma charge density of the analyzed phenomena.

3. Results

The application of plasma on the skin induces the charging of the corneodesmosomes by an amount Q1 and Q2 creating a region of high electric field at the curvatures. The charging of the corneodesmosomes continues until homogeneity is attained and hence equal charging up of the corneodesmosomes has been considered. The electrostatic field strengths of the three corneodesmosomes in a brick and mortar

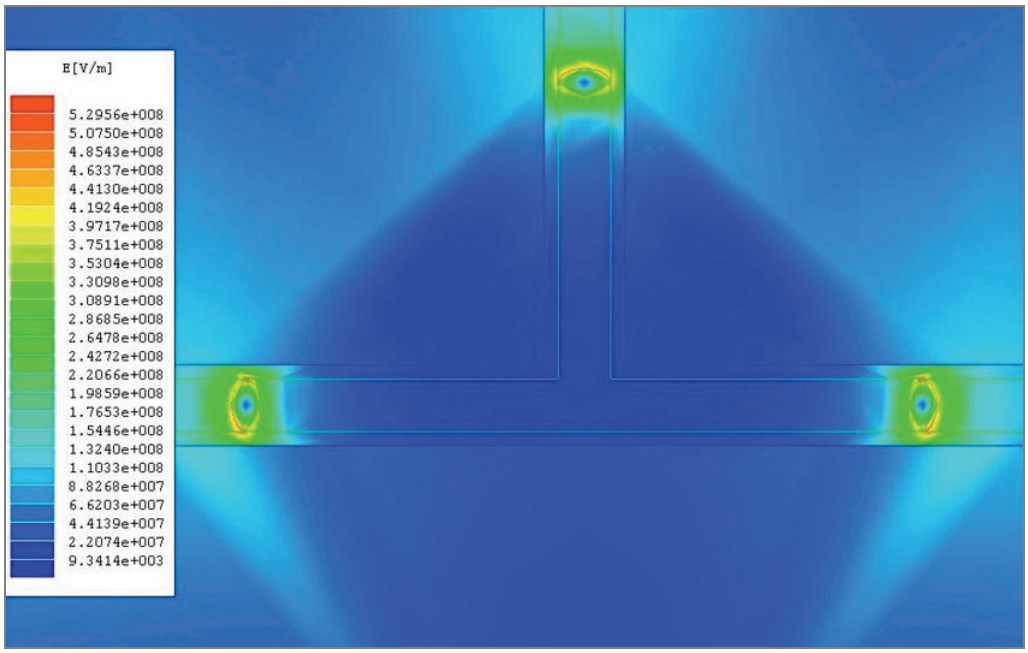

Fig. 3. The electrostatic field strengths of the three corneodesmosomes in a brick and mortar arrangement

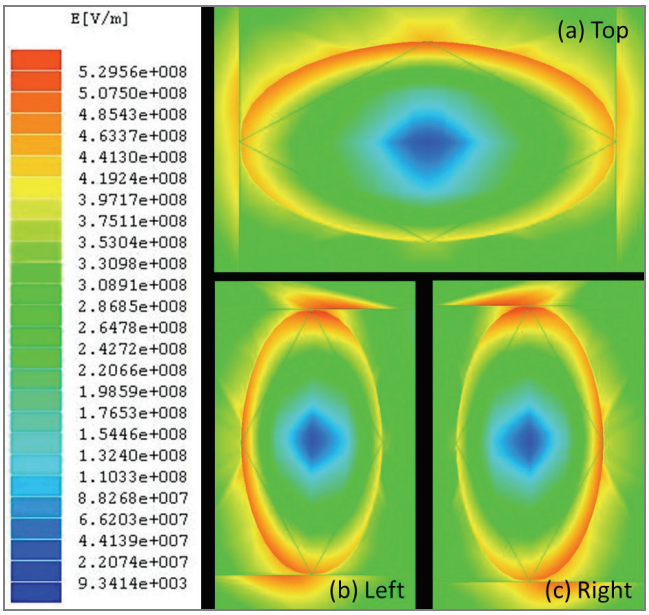

Fig. 4. The zoomed images of the top (a), bottom left (b), and bottom right (c) corneodesmosomes

arrangement are shown in Fig. 3. It was observed that the opposite corneodesmosome surfaces experience higher electric field strengths compared to the one close to the plasma source. The reason of this phenomenon is the repulsive nature of the charges. Figure 4 demonstrates the zoomed images of the top (a), bottom left (b), and bottom right (c) corneodesmosomes.

4. Discussion

It is intriguing to examine the amount of electric field strengths developed on the corneodesmosome surfaces in their different locations, since the exact location of corneodesmosomes is experimentally unknown. Therefore, we estimated the electric field strengths when the bottom corneodesmosomes intra-separation was varied from 0.16 to 37.90 μm, keeping the position of the top corneodesmosomes fixed. They mutually exerted electric field strengths of ~597.68–541.12 MV/m and an average field strengths ~556.218 MV/m on the surfaces. It was observed that the corneodesmosomes exhibited an individual charging effect but a limitation on their separation. The separation helps in mutual charging and hence their far end separation is negated. Thus, a homogeneous electric field strength development at the corneodesmosome surfaces is achieved when bottom left and right corneodesmosomes are separated at a distance of 0.96 μm. The maximum electric field strength developed at this separation is about 530 MV/m which is quite provokable in corneodesmosomes desquamation, although lesser than the average electric field strengths. We have also investigated the quantity of charge that should build up at the corneodesmosome surfaces. Therefore, we have seen the effect of charges in the range of micro-Coulomb to femto-Coulomb producing electric field strengths ~530 TV/m–530 kV/m on the corneodesmosomes surfaces and such observation is shown in Table 2. Consequently, the optimum charging should be of the order of 30 nano-Coulombs to harness the plasma aided skin treatment.

Table 2. Charge build-up and electric field strength development on the corneodesmosomes surfaces

Charge on corneodesmosome (Coulomb)	Electric field intensity (V/m)
30 mC	529.56×10^{12}
30 μC	529.56×10^{9}
30 nC	529.56×10^{6}
30 fC	529.56×10^{3}

Furthermore, how this induced 530 MV/m electric field strengths could boost corneodesmosomes degradation is plausibly explained by investigating the tensile strengths of the skin. If the electric field strength at the corneodesmosomes surfaces exceeds its tensile strength, then the corneodesmosomes could be broken. The tensile strength of an idealized biological cell and cell dimension is related by a mathematical expression as depicted by equation (7). In order to employ the above mathematical relation, we model the corneodesmosome curvature as part of an idealized cell having radius of curvature R and thickness Δ. So, we have simulated through our modeling to determine its thickness and radius as shown in Table 3. The simulated data reveals that we can consider the corneodesmosome thickness to be ~0.040 μm and its radius of curvature ~≤ 1 μm that would induce a maximum electric field intensity of the order of 345 MV/m. However, if the corneodesmosome thickness is approximately 0.075 μm, the maximum electric field intensity induced is of the order of 472 MV/m. In this condition, the induced electric field strength of approximately 530 MV/m can potentially weaken the corneodesmosome and hence its rupture following desquamation. On the other hand, if the radius of curvature is ≥ 1 μm, say 1.5 μm, the maximum electric field strength induced is of the order of 427 MV/m for 0.04 μm thickness; which is still less than the maximum field intensity of ~530 MV/m, so that our analysis is still valid. However, if the corneodesmosome thickness is ~0.075 μm, the induced electric field intensity will be ~ 584 MV/m where no weakening of the corneo-

Table 3. Simulated data for corneodesmosome thickness Δ and radius R to estimate the theoretical values of electric field strengths

Δ (μm)	Φ (V)	Radius of curvature (μm)
0.075	337.639	0.5
0.04	246.577	
0.03	213.542	
0.02	174.356	
0.075	413.521	0.75
0.04	301.993	
0.03	261.534	
0.02	213.542	
0.075	472.694	0.98
0.04	345.207	
0.03	298.958	
0.02	244.098	
0.075	584.808	1.5
0.04	427.083	
0.03	369.865	
0.02	301.993	

desmosome could be inferred. Eventually, we can set a parameter, such as corneodesmosome radius less than 1 μm and its thickness of the order of 0.04 μm to corroborate our simulations results.

In conclusion, the non-thermal plasma has a significant influence on treating skin diseases and hence clinical tests proved its applicability as the non-thermal plasma can efficiently diffuse through the transdermal route. We investigated the effect of plasma to treat superficial skin diseases through the process of corneocyte desquamation and its proliferation via the process of corneodesmosomes degradation. The degradation mechanism is due to the homogeneous and equal charging up of corneodesmosomes inducing the development of electrostatic electric field strengths exceeding its tensile strengths. The maximum electric field strength induced on the surface of the corneodesmosome in the superficial layer of the stratum corneum is of the order of 530 MV/m, which is sufficient to overcome the skin tensile strengths. Furthermore, the current investigation also motivates to investigate the effect of non-thermal plasma in the deeper layer of stratum corneum which is usually wet and has a different cell physiology. In this situation, the non-thermal plasma might behave differently and could provide a better understanding and mechanism of plasma–biological cell interaction.

Acknowledgements

This work was supported by research grants from the Catholic University of Daegu in 2013.

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