Studying the Radial and Tangential Velocity Components of the Epithelization Healing Post Photorefractive Keratectomy Surgery of the Human Eye

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Abstract

Photorefractive keratectomy (PRK) is the refractive technique that began with a physical scraping of the epithelial layer of cornea subsequent by laser treatment. Post this procedure to about 48 hours the removed epithelial layer regenerated to protect the eye again. The regeneration process (called re-epithelization) started from the limbus of the cornea toward the central part of it. The re-epithelization mechanism consists of a change in cell density (mitosis) and cell concentration (migration) with a velocity in two directions: radial and tangential. In the present study, an estimation for both radial (responsible for the overlapped layers toward the outward direction of the cornea) and tangential components (contour shape wave from limbus to the center) has been done for the first time, not like the previous studies that always estimate the velocity values of the re-epithelization only. Results showed that the trend shape of both components agrees with the kinematic behaviour of the mitosis and migration, where the maximum cell density fluctuated toward the central part in exponential decay shape. For a healing diameter of 2mm, the maximum redial velocity was 16.85 µm/h, while the maximum tangential velocity was 55.48 µm/h. These two components give a speed of re-epithelization of 58 µm/h which agrees with the biological and practical healing speed measured of 60 µm/h. Estimating these two components will open the way to understand the relationship between the total epithelial layer required and the total healing time to control the medication period for the patient post-surgery.

Keywords: Re-epithelization, reaction – diffusion equation, PRK, speed of healing.

1. Introduction

Photorefractive Keratectomy (PRK) is the correction of the visual disturbance in refraction errors for nearsightedness, farsightedness, and astigmatism using some certain laser type. It was started earlier in the eightieth of the last century and approved to be used finally by the Food and Drug Administration (FDA) in 1996 [1].

Medically this type of surgical procedure has the following steps: physical removing of the first layer of the cornea called the epithelial as it is a protective and regenerative layer, followed by applying the treatment laser that related in its energy to the refractive error shape and value, and finally protects the cornea with bandage contact lens until the epithelia build back and protect the cornea again. The epithelial building back process is called the reepithelization, which started from the limbus toward the central part of the cornea of the human eye. This process has been studied in many research works, to estimate its speed, and the encouragement factors affecting it, and Sherratt and Murray were pioneers in this field.

In 1990 Sherratt and Murray [2] begun their work in mathematical modeling of the healing of an epidermal wound. The work presented the epidermal cell density, as a function of the wound radius of curvature and time, all which examined in the reaction–diffusion equation (RDE), which state:

Rate of increase of cell density, n	=	Cell migration	+	Mitotic generation	…(1)

In 1991 Sherratt and Murray [3] modified the simple RDE to a coupled equation, by including the concentration of mitosis. The differential equations are for cell density, and rate of change in chemical concentration of Epidermal Growth Factor (EGF). The mathematical model of wound healing becomes:

Rate of variation in cell density, n	=	Migration of cell	+	Mitotic generation	−	Natural loss	…(2a)

Rate of variation of chemical concentration, c	=	Diffusion of c	+	Production of c	−	Chemical decay	...(2b)

And in differential form:

$$\frac{\delta n}{\delta t} = D\nabla^2 n + s(c).n.\left(2 - \frac{n}{n_o}\right) - kn \qquad …(3a)$$

$$\frac{\delta c}{\delta t} = D_c\nabla^2 c + f(n) - \lambda c \qquad …(3b)$$

Where s(c), the logistic regression is a function of chemical concentration, k, D_c and λ are positive constants. $f(n)$ is a biological function. Equations (3) have been solved for different clinical applications. In ophthalmology, the corneal epithelial mapping attracted in the last five years the researchers, especially, after the presenting of the ocular coherence technology (OCT) system, which has the ability to measure and show the epithelial mapping [4].

Dale et al, [5] rewrite equations (3) considering the corneal epithelialization and solved them to find the speed of the process. The effect of concentration and density with the presence of EGF as a driving factor was considered. They proposed an analytical approximated solution verified by numerical scheme calculations. Their findings direct us to the truth that the EGF improves the healing rate or the speed of the traveling epithelial wave. The modified differential equations (based on equations (3) and customized for the epithelial corneal region) are:

$$\frac{\partial n}{\partial t} = \nabla.(D_n(c)\nabla n) + s(c)n\left(v - \frac{n}{n_o}\right) - kn \qquad (4a)$$

$$\frac{\partial c}{\partial t} = D_c\nabla^2 c + f(n) - h(c)n - \delta c \qquad (4b)$$

Where $D_n(c)$: is the cell diffusion coefficient, $h(c)$: cellular degradation, v, k, D_c and λ are positive constants.

Equations (4) have been utilized as a starting point for the next research studies that deal with the re-epithelization of the corneal layer (see Figure (1)). Although these studies showed many aspects of interest but still no mentioned for the cell re-epithelization velocity directions. These directions (radial and tangential) consist of the move of layers from limbus to the center in contour shape and toward the outward of the cornea to fully protect it again. Estimating the velocity of each component alone needs more mathematical manipulation to predict the required time of full protection and manage the time of medication used during this period.
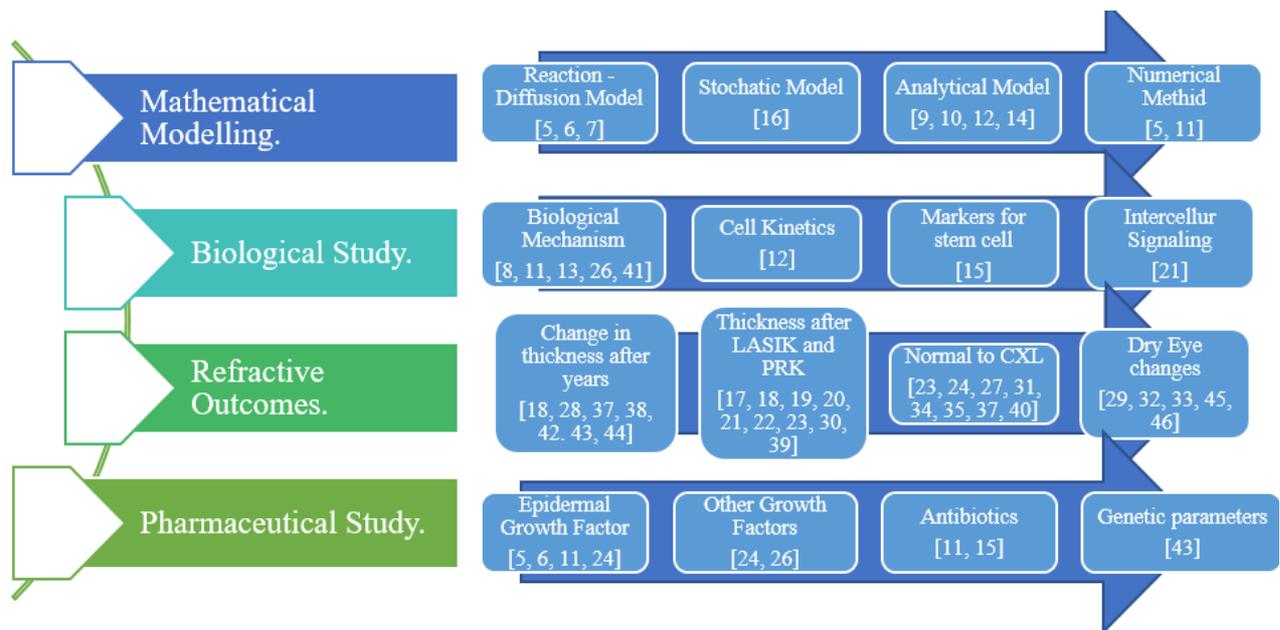
Fig. 1. Research studies regarding the Re-epithelization of cornea.

Four imperative disciplines (as shown above) were reflecting the interest of the researchers in studying the corneal re-epithelization process. These disciplines are:

a. **Mathematical Modelling.** The modeling here started by normalizing equations (4) with its boundary and initial conditions. Then found a semi exact solution after considering sets of assumptions and simplifications [5, 6 and 7]. The final resulted manipulation may require a computer numerical scheme [5 and 11]. Some solutions utilize wave theory to solve equations (4) [9, 10, 12, and 14].

b. **Biological Studies.** In such studies, the biological behaviour of the cell during the reepithelization has been considered. How to control the speed through certain corticosteroids and the expected time period for the healing process [8, 11, 13, 26, and 41]. Moreover, study the cell kinetics during the whole healing process and compare between simulation program and real pathogenesis case studies [12]. The possibility of including few markers and measure the triggering signal from the stem cell to realize the optimum healing shape and rate [15, 21].

c. **Refractive Outcomes.** For the patients with low refraction error, the PRK will be the treatment procedure (a safe surgery procedure). In such cases, the re-epithelization process will gain back the epithelial layer of about 50 µm which represents an extra power for the patient vision. During the healing period, the total thickness fluctuation and the visual outcomes

also [13-19, 24, 26, 33-35, 38-40]. Within the last few years after the invention of the epithelial mapping which described by the OCT system many ophthalmologists begun to use it as an indication for the corneal abnormality such as dryness and keratoconus [23, 24, 27, 29, 31, 32-36, 41, 45, and 46].

d. **Pharmaceutical Study.** Study the normal amount of the EGF during the healing process and the possibility of utilizing some sort of pharmaceutical components to improve the supplied amount to the stem cell [5, 6, 11, and 24]. Possibility of studying the α and γ – EGF and their converse role during the re-epithelization, with the impact of including antibodies [11, 15, 24 and 26]. Assessment of effective gene and recognize the possibility of gene control to control the final healing shape and rate [43].

2. Mathematical Model

The differential equations (4) have been utilized here, applying the non-dimensionalize model recommended by Dale [5], and using the following assumptions:

a. The thickness of the epithelium is littler than the required length of healing, so the model will be two-dimensional form.

b. By considering linear geometry of the wound healing or strip band form with long spatial domain length the equation will be solved in the semi-infinite domain of $-\infty \leq x <$

TZ (Treatment Zone), and the solution will be one dimensional toward the x – direction.

c. The original set of the axis is the wound boarder.

d. The cellular diffusion coefficient changes linearly with EGF concentration value (c).

The new differential form will be:

$$\frac{\partial n}{\partial t} = \frac{\partial}{\partial x}\left((\alpha c + \beta)\frac{\partial n}{\partial x}\right) + (\alpha_1 c + \beta_1)n(2 - n) - n \quad (5a)$$

$$\frac{\partial c}{\partial t} = D_c\frac{\partial^2 c}{\partial x^2} + \sigma(2 - 5n) - \frac{\mu nc}{(\hat{c}+c)} - \delta c \quad (5b)$$

Where the dimensionless parameters have the following values: $\alpha = 0.01$, $\beta = 0.1$, $\alpha_1 = 0.9$, $\beta_1 = 0.1$, $D_c = 25$, $\sigma = 4000$, $\mu = 1.37 \times 10^4$, $\hat{c} = 3.02$, $\delta = 110$ and the wound length or the TZ = 8 mm [4, 5, 6 and 7].

The initial and boundary conditions are biologically relevant to the surgical procedure or the PRK process. Figure (2) shows the center lines, wound center, epithelium boundary and the original point and axis.
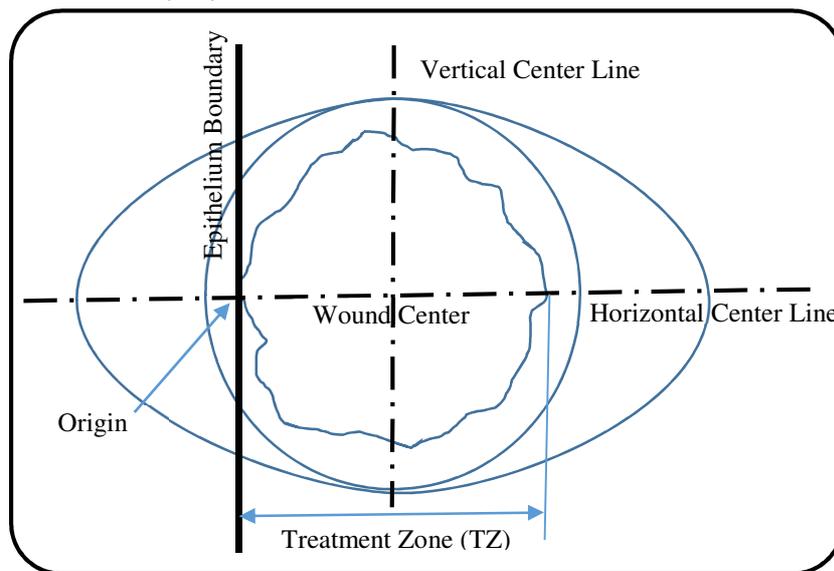
Fig. 2. Important notification on the human eye sketch.

The boundary and initial conditions for the solution will be described graphically as shown in Figure (3):
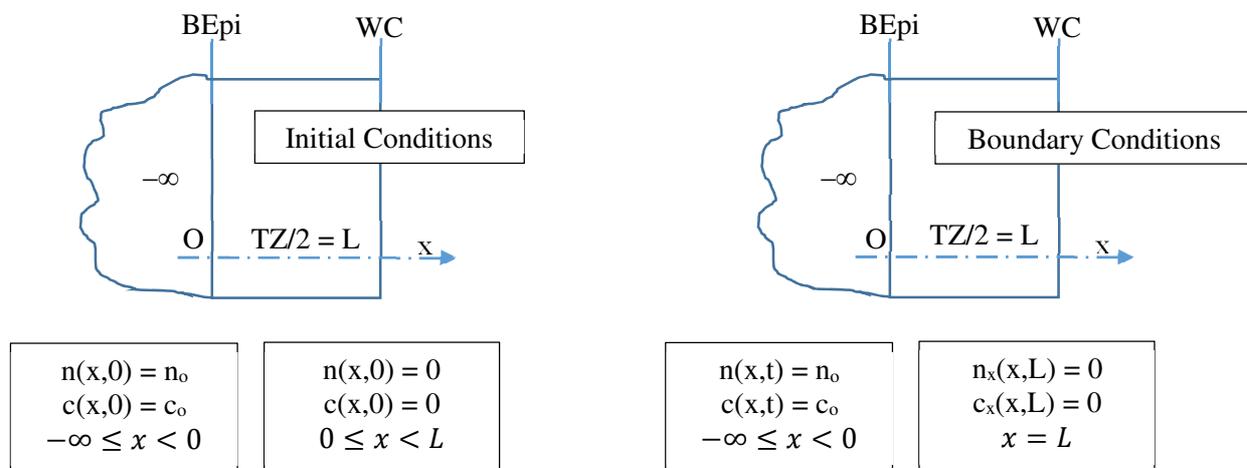
Fig. 3. Initial and Boundary Conditions selected. BEpi = Boundary of Epithelium, WC = Wound Center.

3. Proposed Solution

In the present work a solution for the final equations (5) has been suggested using the Finite Difference (FD) implicit method Crank Nicolson Scheme (CNS). The CNS has the following definitions for the independent variable u, first-order in time, second-order in direction (such as x) [16]:

$$\frac{u^{j+1} - u^j}{\Delta t} = \frac{1}{2}\left[F_i^{j+1}\left(x, t, u, \frac{\partial u}{\partial x}, \frac{\partial^2 u}{\partial x^2}\right) + F_i^j\left(x, t, u, \frac{\partial u}{\partial x}, \frac{\partial^2 u}{\partial x^2}\right)\right] \quad \ldots(6)$$

Each part of the differential equations (5) can be define according to the followings:

$$u = \frac{1}{2}\left(u_i^{j+1} + u_i^j\right) \quad \ldots(7a)$$

$\frac{\partial u}{\partial t} = \frac{u^{j+1} - u^j}{\Delta t}$ (1st order in time for the independent variable u) $\quad \ldots (7b)$

$$\frac{\partial u}{\partial x} = \frac{1}{4\Delta x}\left(u_{i+1}^{j+1} - u_{i-1}^{j+1} + u_{i+1}^j - u_{i-1}^j\right) \quad \ldots(7c)$$

$$\frac{\partial^2 u}{\partial x^2} = \frac{1}{2(\Delta x)^2}\left(\left(u_{i+1}^{j+1} - 2u_i^{j+1} + u_{i-1}^{j+1}\right) + \left(u_{i+1}^j - 2u_i^j + u_{i-1}^j\right)\right) \quad \ldots(7d)$$

The rearrangements and manipulation of the two differential equations, boundary and initial conditions will be done independently and then collect the final results as shown below:

a. One Dimensional Reaction Equation

From Equation (5a), rearrange the equation to be:

$$\frac{\partial n}{\partial t} = (\alpha c + \beta)\frac{\partial^2 n}{\partial x^2} + \alpha\frac{\partial n \partial c}{\partial x^2} + (\alpha_1 c + \beta_1)n(2 - n) - n \quad \ldots(8)$$

Equation (8) will be in CNS form:

$$\frac{n^{j+1} - n^j}{\Delta t} = \frac{1}{2(\Delta x)^2}\left[\alpha(c_i^{j+1} + c_i^j) + \beta\right]\left[(n_{i+1}^{j+1} + n_{i+1}^j) - 2(n_i^{j+1} + n_i^j) + (n_{i-1}^{j+1} - n_{i-1}^j)\right] + \frac{\alpha}{16(\Delta x)^2}\left[(n_{i+1}^{j+1} - n_{i-1}^{j+1} + n_{i+1}^j - n_{i-1}^j)(c_{i+1}^{j+1} - c_{i-1}^{j+1} + c_{i+1}^j - c_{i-1}^j)\right] + \left[n_i^{j+1} - n_i^j\right]\left[\frac{\alpha_1}{2}(c_i^{j+1} + c_i^j) + \beta_1\right]\left[1 - (n_i^{j+1} + n_i^j)\right] \quad \ldots(9)$$

b. One Dimensional Diffusion Equation:

From Equation (5b), the CNS form is:

$$\frac{c^{j+1} - c^j}{\Delta t} = \frac{D_c}{2(\Delta x)^2}\left[(c_{i+1}^{j+1} + c_i^{j+1}) - 2(c_i^{j+1} + c_i^j) + (c_{i-1}^{j+1} + c_{i-1}^j)\right] + \left[\sigma\left(2 - 5(n_i^{j+1} + n_i^j)\right)\right] - \frac{\mu(c_i^{j+1} + c_i^j)(n_i^{j+1} + n_i^j)}{\left(\hat{c} - (c_i^{j+1} + c_i^j)\right)} - \sigma(c_i^{j+1} + c_i^j) \quad ..(10)$$

Initial Conditions:

$$n_i^2 + n_i^1 = c_i^2 + c_i^1 = 0 \quad for\ 0 \leq x < L \ \ldots(11a)$$
$$n_i^0(x, 0) = n_o\ and\ c_i^0(x, 0) = c_o\ other\ than\ 0 \leq x < L \quad \ldots(11b)$$

Boundary Conditions:

$$n_i^0(x, 0) = n_o\ and\ c_i^0(x, 0) = c_o\ other\ than\ 0 \leq x < L \quad \ldots(12a)$$

For $n_x(L, t) = n_o$ and $c_x(L, t) = c_o$

$$n_{i+1}^{j+1} + n_{i+1}^j = n_i^{j+1} + n_i^j\ and\ c_{i+1}^{j+1} + c_{i+1}^j = c_i^{j+1} + c_i^j \quad \ldots(12b)$$

c. Speed of healing

Most of the studies regarding the speed of healing (U) started their modeling from the Fisher reaction-diffusion equation [2, 5, 10 and 20]. The traveling healing wave solution uses the analogy of the relative coordinate system to predict the final expected form, which may be expressed as [5]:

$$U = \frac{2}{\beta + D_c}\sqrt{\beta D_c\left[2D_c s\left(\frac{A+\sigma}{\delta}\right) - D_c - \delta\beta\right]} \quad \ldots(13)$$

Equation (13) has sets of constants that leads to a specific value of the healing speed of about 60 µm/h. The modification that has been added here to equation (13) is to suggest the shape of a solution that may analogy the trend of the solution in both of the cell density and concentration. This suggested analogy predicted from the mathematical interpolation of equations (9 and 10). The new modified shape of the healing speed (U) will be:

$$U_{mod} = \frac{2}{\beta + D_c}\sqrt{\beta D_c\left[2D_c s\left(\frac{A+\sigma}{\delta}\right) - D_c - \delta\beta\right]} \cdot e^{(n_{oo} + c_{oo})t}\sin(n_{oo} - c_{oo}) \quad \ldots(14)$$

Where n_{oo} and c_{oo} are the cell density and EGF concentration calculated from the above equations (9) and (10), as mentioned above for the state of constant speed of healing.

d. Velocity components (radial and tangential):

The flow velocity of the re-epithelization process is measured and estimated to be in a micro scale [2, 3 and 4]. The Reynold number, for this reason, is less than unity, and the flow could be considered as a creeping flow [43]. The description of the final equations for the two components velocity is:

$$u_r = -U\cos\theta\left(1 - \frac{3R}{2r} + \frac{R^3}{2r^3}\right) \quad \ldots(15a)$$

$$u_\theta = -U\sin\theta\left(1 - \frac{3R}{4r} + \frac{R^3}{4r^3}\right) \quad \ldots(15b)$$

Where the R and r, are the radius of curvature of the human cornea and new build-up layer thickness

or the epithelial during the healing (see Figure (4) for more details).
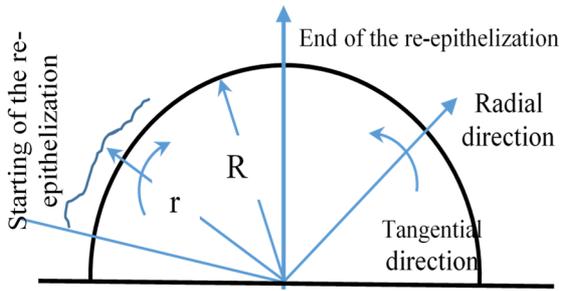
Fig. 4. Radial and tangential direction with the start and end of epithelization.

The final algorithm for the proposed solution discussed above from point (a) to point (f), can be summarized in the flowchart as shown in Figure (5).

Start

Define the constant of solution:
$\alpha = 0.01$, $\beta = 0.1$, $\alpha_1 = 0.9$, $\beta_1 = 0.1$, $D_c = 25$, $\sigma = 4000$, $\mu = 1.37 \times 10^4$, $\hat{c} = 3.02$, $\delta = 110$ and the wound length or the TZ = 8 mm.

Define the initial values: $n_i^o(x, o)$, $c_i^o(x, o)$

Define the Boundary values: $n_i^j(0, t)$, $c_i^j(0, t)$, $n_i^j(L, t)$, $c_i^j(L, t)$,

Solve Eq.(9) to find $n_i^{j+1}(x, t)$

Solve Eq.(10) to find $c_i^{j+1}(x, t)$

Change the time increment from 4h to 40h.

Use Eq.(14) to find the modified Healing Speed: U_{mod}

Use Eq.(15.a) to find the radial component Healing Speed: U_r

Use Eq.(15.a) find the tangent component Healing Speed: U_r

End

Fig. 5. Proposed solution, equations here are discussed above from point (a) to point (f).

4. Results

The numerical solution of reaction equation (9) and diffusion equation (10), with their initial and boundary conditions (11 and 12) have been done using the open-source scientific programming language Octave (version 4.4.1).

The solution of the above equations has been done after assuming the wound speed to be constant with a value of 60 µm/h [5]. In this step, both the cell density (n) and the variation in concentration (c) are evaluated from the limbus toward the center of the cornea. In the next step, an equation for the speed of the healing will be utilized to investigate the range and the shape of the wave speed of the healing process. This time the speed of healing will be examined with respect to the change of both n and c, which will decrease the total time period of the re-epithelization process (time of healing). After all the two components were assessed also based on the overall speed of healing.

Cell density and Concentration

The change in cell density (n(x, t)) is a sign for cell migration, mitotic activity, and natural loss. This is what concerned in equation (2) and related specifically to the wound re-epithelization of the corneal tissue. Figure (6), shows the variation of cell density with regard to the direction of healing and time for the time period from 4 – 40 hours with ten steps changes.
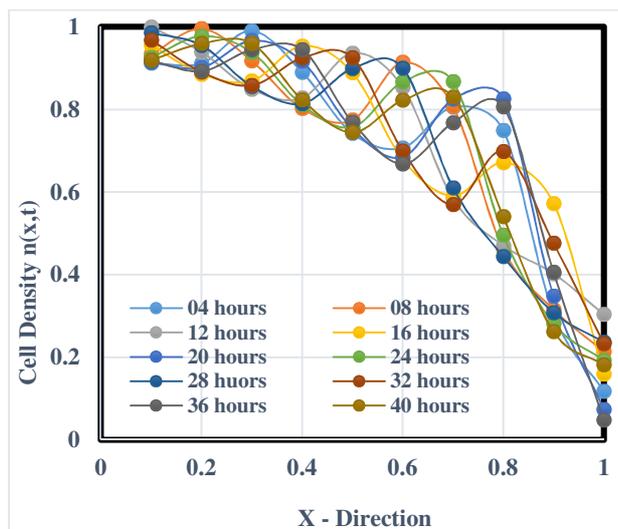
Fig. 6. Cell density for 10 steps of time with 4 hours per each, and through the length from the limbus to the center of healing (center of the eye).

The change in chemical concentration of EGF which represents the main drive for the proliferation for epithelial cell, Figure (7) shows the change in concentration c(x, t) for 40 hours.
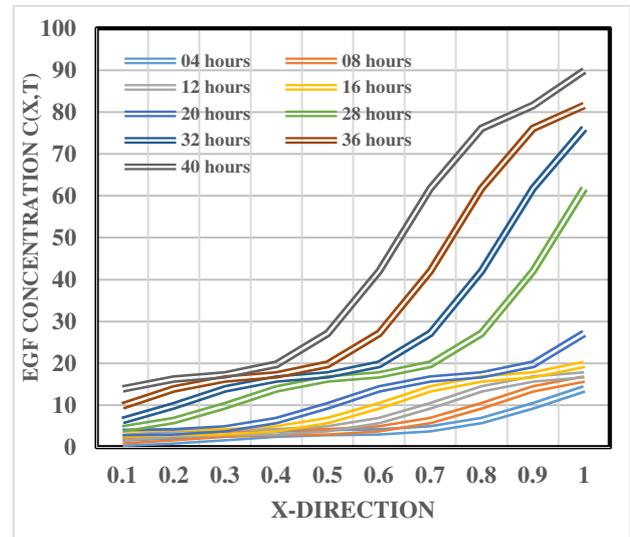
Fig. 7. Cell concentration for EGF for 10 steps of time with 4 hours per each, and through the length from the limbus to the center of the eye.

Speed of healing

Figure (8) shows the healing speed variation with respect to the EGF concentration with a time of healing variation from 4 – 40 hours.
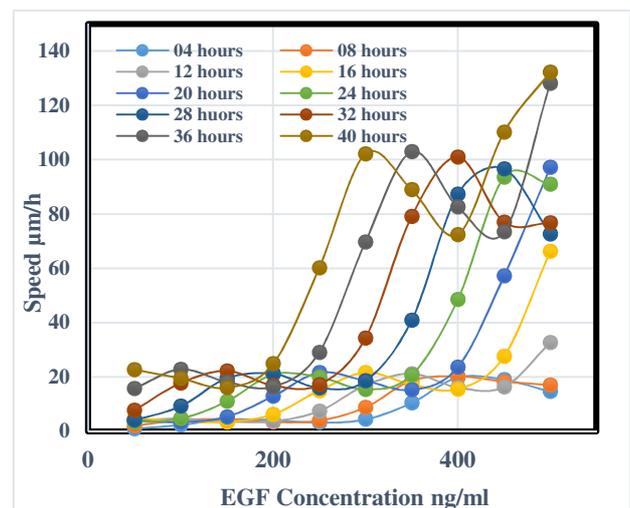
Fig. 8. Speed of healing to the EGF concentration for 10 steps of time.

Figure (9) shows the comparison between the first 4 hours with respect to the 12, 20, 28 and 36 hours.
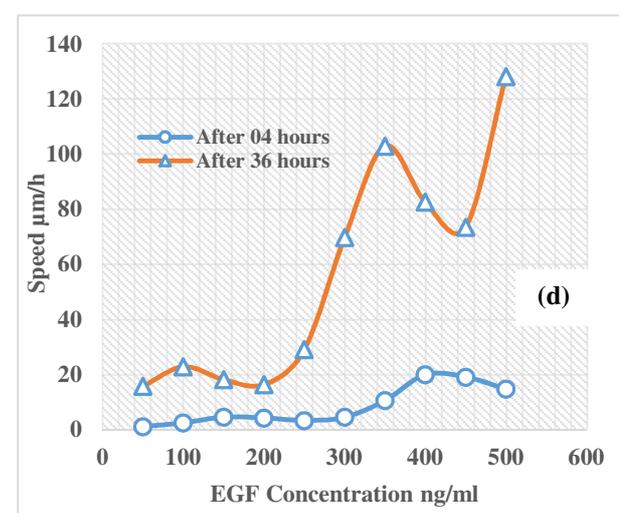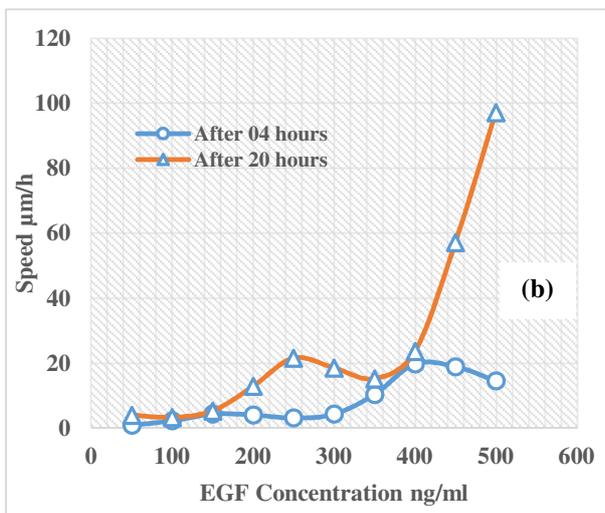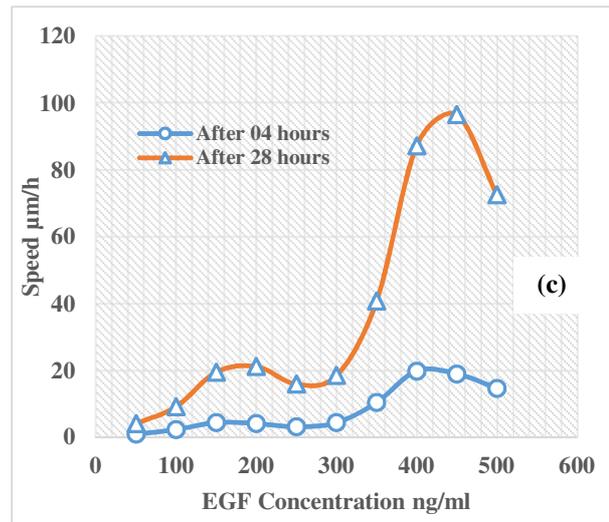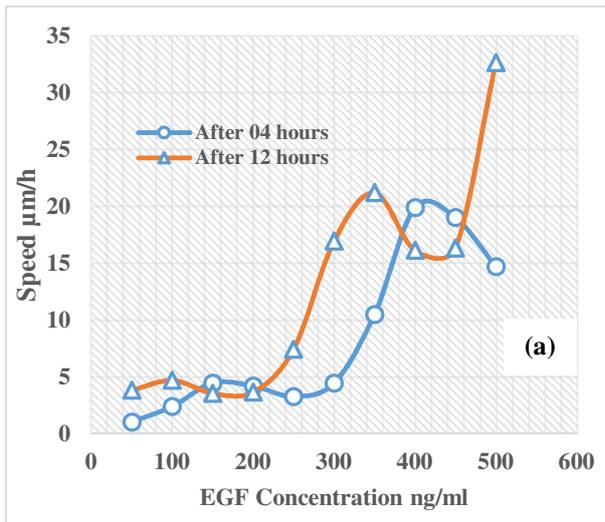
Fig. 9. Speed of healing with respect to the cell concentration of EGF for 4 steps: (a) 12 h, (b) 20h, (c) 28h and (d) 36h compared with 4 hours.

The radial component of the velocity described in equation (15a) shown in figure (10) below.
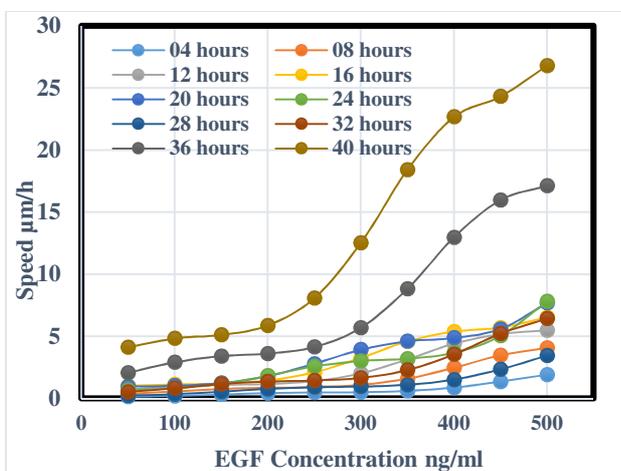
Fig. 10. Radial speed of healing w.r.t the EGF concentration for 10 steps of time.

Figure (11) shows the comparison between the first 4 hours with respect to the 12, 20, 28 and 36 hours.
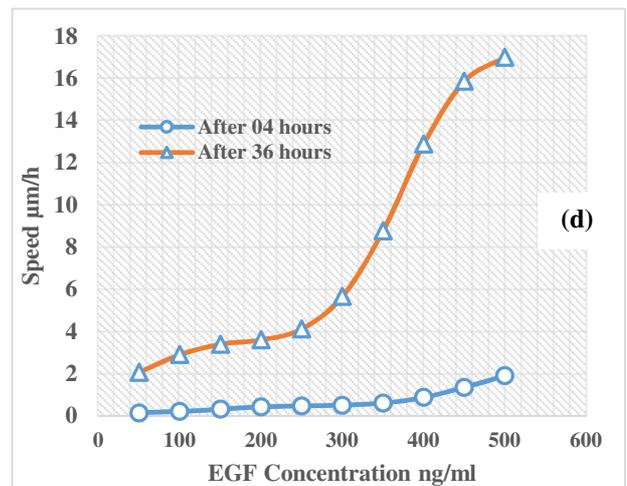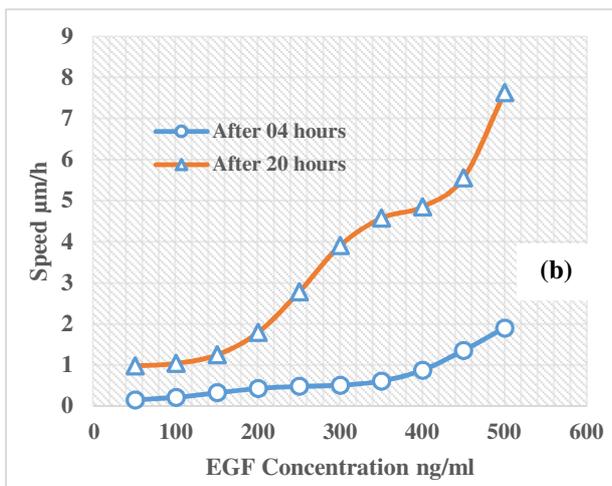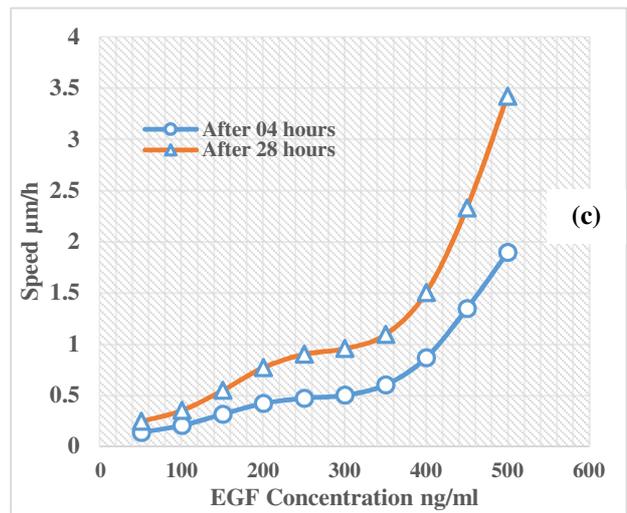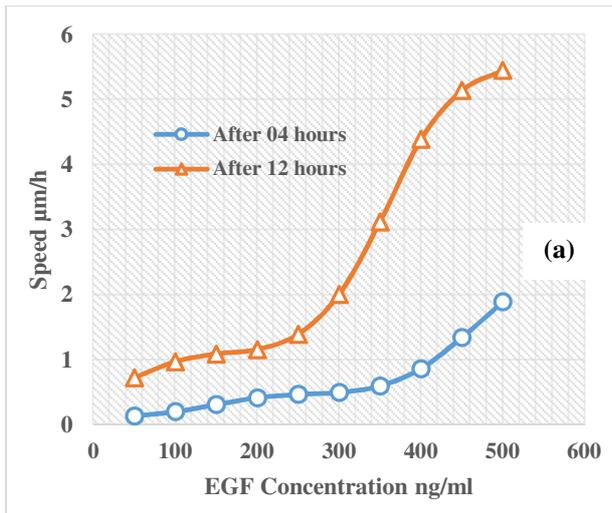
Fig. 11. Radial speed of healing with respect the cell concentration of EGF for 4 steps: (a) 12h, (b) 20h, (c) 28h and (d) 36h compared with 4 hours.

The tangential component of the velocity described in equation (15b) shown in figure (12) below.

Figure (13) shows the comparison between the first 4 hours to the 12, 20, 28 and 36 h.
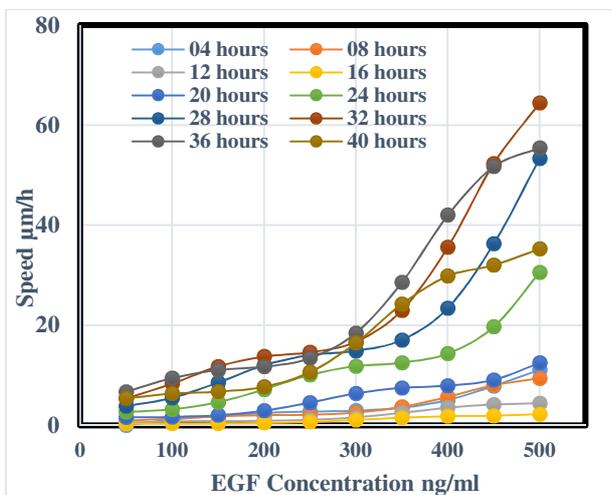
Fig. 12. Tangential speed of healing to the EGF concentration for 10 steps of time.
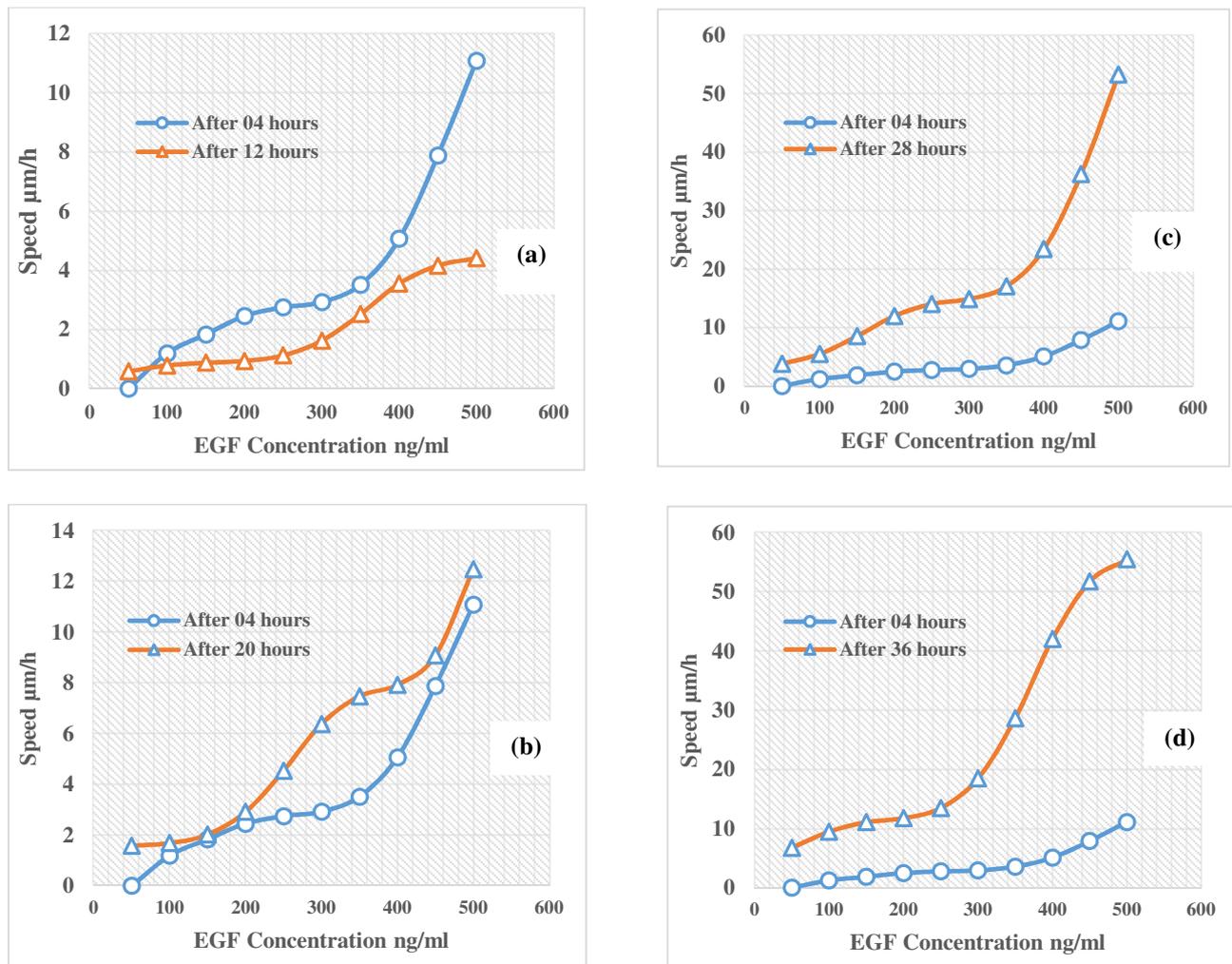
Fig. 13. Tangential speed of healing with respect to the cell concentration of EGF for 4 steps: (a) 12h, (b) 20h, (c) 28h and (d) 36h compared with 4 hours.

5. Discussion

Figure (6) showed the fluctuation in the cell density amount for the direction from the limbus to the center of the eye, for different time of healing started from 4h postoperatively to 40h. The behaviour here agrees with the wave theory and also satisfy the clinical evidence that the stem cells will kinetically increase the mitotic generation activity, which increases the number of cells ready for migration at the first instant after surgery. This motivated kinetic activity will be decreased exponentially reaching the new cells to the center of the cornea. For each instant of time (4h) a wave started from limbus toward the center with fluctuation period and depression rate different from one to another.

Figure (7) the cell concentration behaviour started the first 4h with about flat change building up to increase the concentration near the center of the eye within time.

After 40h the concentration level will reach the maximum required protection [5, 7, and 11]. It is evident from Figure (9) that the increase in the EGF concentration level will increase the healing speed. Biologically this is often due to an increase in the diffusion of the produced cell. This increase would happen after the wave of healing reaches close to the center of the corneal surface. The predicted speed of healing would alter from 14.690, 32.649, 97.208, 96.658, and 128.150 µm/h for the 4, 12, 20, 28, 36 hours' time of healing.

The average of the ten steps maximum speed of healing is 72.872 µm/h, whereas the average of the means of the ten steps of times is 62.516 µm/h witch agrees with the biological and practical findings [2, 5, 10 and 20]. This leads to a practical sense that the speed of healing or diffusion rate both are compensated with respect to the position and time to recover the effect reepithelization of the surface of the cornea [17, 23, 29, and 30].

6. Conclusions

The overall healing process of epithelial post-PRK surgery has many biological and chemical effective parameters. These parameters all together affect the cells mitotic and migration, that physically represented by the speed of re-epithelization. To understand the mechanism of healing two components of velocity of re-epithelization have been estimated and compared with the biological finding.

During the 40 hours of the study, the maximum radial velocity reaches about 16.85 µm/h in the healing diameter of 2mm, whereas the maximum tangential velocity was about 55.48 µm/h in the same healing diameter. These two components give a speed of re-epithelization of 58 µm/h which agrees with the biological and practical healing speed of 60 µm/h. Furthermore, we need more mathematical manipulation and prediction tools (such as artificial intelligence [47] and safety criteria [48] to check the predicted values) that finally we could estimate the required healing process per each patient after considering the other refractive error values.

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دراسة مكونات السرعة الشعاعية والمماسية لشفاء النسيج الطلائي بعد جراحة اصلاح قرنية العين البشرية

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الخلاصة

انفصال القرنية بالانكسار الضوئي (PRK) هي احدى تقنيات تصحيح الاخطاء الانكسارية والتي تبتدأ بازالة الطبقة الطلائية الامامية لقرنية العين البشرية ثم يستخدم الليزر كعلاج تصحيحي. بعد هذا الإجراء بفترة 48 ساعة تقريبًا ، تجديد الطبقة الطلائية الامامية التي إزيلت مسبقا لتعاود حماية حماية العين البشرية من جديد. تبتدأ عملية التجديد هذه (والتي تسمى عملية إعادة بناء النسيج الطلائي) من طرف القرنية باتجاه الجزء المركزي منها. وتكون آلية إعادة تكوين هذا النسيج من خلال تغيير في كثافة الخلايا (بالانقسام) وزيادة تركيزها (وتسمى بالهجرة) بسرعة في اتجاهين: شعاعي وعرضي.

في هذه الدراسة ، تم تقدير قيمة مركبات السرعة لاعادة نمو الطبقة الطلائية لكلا من المركبة الشعاعية (وهي المسؤولة عن الطبقات المتداخلة بالاتجاه الخارجي للقرنية) والمركبة العرضية (موجية الشكل من الاطراف باتجاه المركز) لاول مرة، على عكس الدراسات السابقة التي تقدر دائمًا قيم سرعة إعادة النمو فقط.

أظهرت النتائج أن شكل الاتجاه لكلا المكونين يتفق مع السلوك الحركي للانقسام والهجرة ، حيث تتقلب كثافة الخلية القصوى نحو الجزء المركزي في شكل الاضمحلال الأسي. لقطر علاج يبلغ 2 ملم ، كانت أقصى سرعة لإعادة البناء هي 16,85 ميكرومتر /ساعة، بينما كانت السرعة العرضية القصوى 55,48 ميكرومتر /ساعة. يعطي هذان المكونان سرعة إعادة تكوين النسيج الطلائي 58 ميكرومتر /ساعة والتي تتوافق مع سرعة الشفاء البيولوجية والعملية التي تبلغ 60 ميكرومتر /ساعة. يؤدي تقدير هذين المكونين إلى فتح الطريق لفهم العلاقة بين الطبقة الطلائية الكلية المطلوبة ووقت الشفاء الكلي للتحكم في فترة العلاج للمريض بعد الجراحة.