



Analysis on the Critical Issues of UV Light Induced Corneal Cross Linking

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Abstract: A dynamic model of UV light photoinitiated cross linking in corneal collagen is presented to analyze the critical issues involved in the procedure. These issues include the dynamics of the UV light penetration and the safety depth margin (z^*), the roles of the UV light intensity, concentration and extinction coefficient of the initiator. Analytic formulas are developed to show that z^* is a decreasing function of the extinction coefficient and the concentration of the initiator, but it is a nonlinearly increasing function of the light intensity and irradiation time. Our analytic formulas are used to analyze the measured data showing the dynamic feature of the light intensity. Finally, a new protocol is suggested based on our theoretical and experimental finding.

Keywords: UV cross linking, modeling, photoinitiation, corneal collagen, kinetic equation, medical devices

INTRODUCTION

The kinetics of UV light photoinitiated cross linking systems have been studied by many researchers which, however, are limited to the photo-polymerization for chemical engineering applications [1,2]. Much less efforts were performed for the medical applications such as for corneal cross linking. UV light induced corneal collagen cross linking (CXL) device is one of the important modern medical devices developed for vision related applications. It is clinically important for various medical deceases such as corneal keratoconus, corneal keratitis, corneal ectasia and corneal ulcers. It was also used to treat thin corneas which has higher rick in LASIK vision corrections. Other potential applications include the reduction of post-operation regress in vision corrections and correction of myopia. CXL devices use a UVA light source (at about 365 nm) and the administration of riboflavin (B2) solution pre-operatively and during the UV irradiation procedure. Although the CXL devices have been commercialized for many years, however, the basic dynamics of the procedures have not been fully explored theoretically. The distribution of B2 in corneal collagen have been reported [3-5] and a diffusion model was proposed for the B2 diffusion rate inside the corneal stroma collagen [6,7].

To the best of my knowledge, this paper presents the first in-depth analysis of cross linking in a corneal model. The critical issues of the CXL to be explored in this paper include the following:

- (a) the dynamics of the UV light penetration and the safety depth-margin for the CXL; where the time dependent light intensity caused by the initiator depletion will be measured to support our theory;
- (b) the roles of the UV light intensity, concentration and extinction coefficient of the initiator on the safety depth which is defined not only by the corneal thickness but also the UV light irradiation time;
- (c) based on the analysis developed in this paper, a suggested new clinical protocol which is safer than the current commercial protocol.

This paper will focus on the comprehensive analysis based on analytic formulas and provide new concepts relating to the above clinically important issues, whereas full analysis based on numerical simulation will be presented elsewhere [J.T. Lin and D. C. Cheng, to be published].

METHODS

We will first present the measured data showing the dynamics of the UV light intensity in the riboflavin solution. We will then present the theory to analyse the measured features. Analytic formulas will be developed to explore the clinical issues mentioned earlier.

A. Measurements

As shown in Fig. 1, the measured dynamic absorption spectrum of riboflavin (B2) solution (with diluted 0.005% initial concentration, filled inside a 10 mm width UV-transparent cubic tube) under a UVA light at 365 nm and intensity of 100 mW/cm^2 for 2 and 8 minutes. It shows that 33% increasing of light penetration after two minutes illumination of UV light. Figure 2 shows the measured transmitted UV light intensity (after a propagation length of 10 mm of the testing tube) versus time, where the increase of the UV light transmission is due to the depletion of the B2 photoinitiator concentration at an initial concentration of 0.005% (top curve) and 0.0075% (lower curve). These two initial photoinitiator concentrations are corresponding to an initial effective extinction coefficient $A(t=0)=2.35$ and 1.6 ($1/\text{cm}$), respectively, defined by a first order approximation $I(z,0) = I_0 \exp[-A(t)z]$, in which $A(t)$ in general is time dependent. We have also observed the color change (from dark to light) of the B2 solution after few minutes of UV light illumination. This also indicates the depletion of the photoinitiator after UV light irradiation. Further discussion will be shown later by our theory.

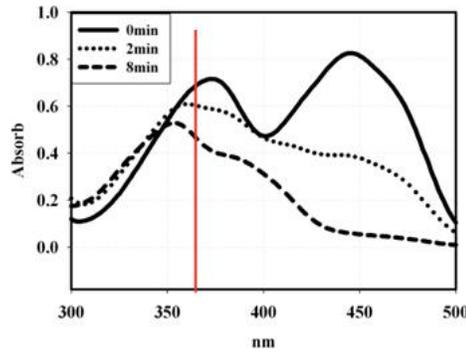


Fig. 1 The dynamic absorption spectrum of riboflavin solution (with 0.005% concentration, depth of 10 mm) under a UV light intensity of $I_0=100 \text{ mW/cm}^2$, initially (solid curve) and at 2 and 8 minutes (dotted and dashed curves). Also shown is the vertical line indicating the UV light wavelength at 365 nm.

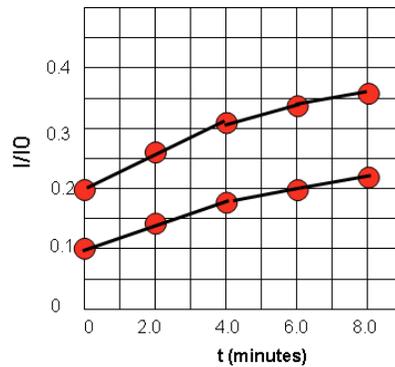


Fig. 2 The measured UV light intensity versus time showing the increase of the light transmission due to depletion of the photoinitiator concentration, where riboflavin initial concentration is 0.005% (top curve) and 0.0075% (lower curve).

B. Theory and Kinetic Equations

In order to analyse the above measured results, we will present the coupled kinetic equations for a simplified corneal model, where the B2 solution is assumed to be uniformly distributed inside the corneal collagen stroma (with the epithelial layer removed). A more realistic model having non-uniform B2 distribution requires extensive numerical calculations and will be presented elsewhere.

In a simplified one-dimensional corneal model system, the molar concentration of the un-reacted photoinitiator $C(z,t)$ and the UV light intensity $I(z,t)$ may be described by [1,2]

$$\frac{\partial C(z,t)}{\partial t} = -aI(z,t)C(z,t), \quad (1)$$

$$\frac{\partial I(z,t)}{\partial z} = -2.303[(\varepsilon_1 - \varepsilon_2)C(z,t) + \varepsilon_2 C_0 + \varepsilon_3]I, \quad (2)$$

where $C_0 = C(z, t = 0)$ is the initial value,; and $a = 83.6\lambda\phi\epsilon_1$, with ϕ being the quantum yield, λ being the light wavelength and ϵ_j ($j = 1, 2$) being the molar extinction coefficient of the initiator and the photolysis product, respectively. In a corneal system, we have included an additional extinction coefficient ϵ_3 for the UV absorption of the corneal collagen tissue (without B2 solution). In our calculations, the following units are used: $C(z, t)$ in mM, $I(z, t)$ in (mW/cm²), λ in cm, and ϵ_j ($j=1,2$) in (mM·cm)⁻¹ and ϵ_3 in cm⁻¹. The differential equation system should be solved with the initial conditions $C(z, 0) = C_0$ and boundary condition $I(0, t) = I_0$.

RESULTS AND DISCUSSIONS

A. Analytic Formulas

Equations (1) and (2) can be approximately solved for the first order of the light intensity using the zero-th order of the initiator concentration $C_{(0)}(t)$ as follows

$$I_{(1)}(z, t) = I_0 \exp\left\{-2.303\left[(\epsilon_1 - \epsilon_2)C_{(0)}(t) + \epsilon_2 C_0 + \epsilon_3\right]z\right\}, \quad (3.a)$$

$$C_{(0)}(t) = C_0 \exp(-aI_0 t). \quad (3.b)$$

Using the Taylor expansion of Eq. (3.c) $C_{(0)}(t) = C_0[1 - aI_0 t]$ in Eq. (3.a) and solving for Eq. (1) to obtain the first-order solution for the initiator concentration

$$C_{(1)}(z, t) = C_0 \exp[-Q(z)F(t)] \quad (4.a)$$

$$Q(z) = \exp[-b'z] \quad (4.b)$$

$$F(t) = [\exp(bC_0 X) - 1]/(bC_0) \quad (4.c)$$

where $X = aI_0 t$, $b' = 2.3(\epsilon_1 C_0 + \epsilon_3)$ and $b = 2.3(\epsilon_1 - \epsilon_2)$.

Similarly, solving Eq. (2) using the Taylor expansion of Eq. (4.b), we obtain the second-order solution of the light intensity

$$I_{(2)}(z, t) = I_0 \exp[-b'z + (bC_0 / b')(1 - Q)F(t)] \quad (5)$$

It should be noted that the P(t) function is governed by three absorption factors, $\epsilon_1, \epsilon_2, \epsilon_3$ and the initial concentration. In general, it is nonlinearly proportional to the light intensity and the irradiation time (t).

For a more comprehensive model, one may define a dynamic extinction coefficient A(t). By the approximate expansion of (1-Q) to the first order of z, Eq. (5) is further simplified as

$$I(z, 0) = I_0 \exp[-A(t)z] \quad (6.a)$$

$$A(t) = [b' + bC_0 F(t)]. \quad (6.b)$$

For small X, Eq. (6) and shows a linear increasing function of time (t) at a given z, and this linear regime was shown by our measured data to be shown later. WE shall note that the dynamic extinction coefficient A(t) is a decreasing function of time, that is polymer medium becomes more transparent after the UV illumination, in consistent with our observed color change..

B. The Safety and Penetration Depth

Defining the initial normalized light intensity $I(z, t)/I_0$ (at t=0) drops to $1/e^2$, or 13.4%, as the safety depth (z^*) of the corneal thickness. We obtain from Eq. (6.a), $z^* = 2 / A(t)$.

Above equation shows that the safety depth is inverse proportional to the concentration and extinction coefficient of the riboflavin solution. It is also a nonlinearly increasing function of the light intensity and irradiation time, since $X = aI_0 t$. At t=0, F=0, we

easily obtain the initial safety depth given by $z^*(0) = 0.8684 / (\varepsilon_1 C_0 + \varepsilon_3)$ for a quantum yield of 0.2 and a UV light wavelength at 365 nm. It should be noted that the P function is governed by three absorption factors, $\varepsilon_1, \varepsilon_2, \varepsilon_3$ and the initial concentration. Moreover, the F(t) function, in general, is nonlinearly proportional to the light intensity and the irradiation time (t).

Given the molar extinction coefficient of riboflavin solution (at 365 nm) [7] $\varepsilon_1 = 204(\% \text{-cm})^{-1}$ or $8.16 (\text{mM-cm})^{-1}$ and the corneal stroma extinction coefficient [8] $\varepsilon_3 = 7.4 (1/\text{cm})$, and $\varepsilon_2 \ll \varepsilon_1$, the initial safety depth is calculated $z^*(0) = 312 \text{ um}$ for $C_0 = 2.5 \text{ mM}$ (or 0.1% w.v.). For a thin cornea, one requires a higher value $C_0 > 5.0 \text{ mM}$ (or 0.2%) in order to limit the UV light penetration depth to 180 um, initially. This initial penetration depth, however, is an increasing function of time, as shown by the function F(t). This feature is consistent with the measured data shown in Fig. 2 which is further analyzed as follows.

Equations (5) and (6) provide the dynamic UV intensity which, at a given depth z, is proportional to the irradiation time (t) and is inverse proportional to the concentration and extinction coefficient of the riboflavin solution as shown by Eq. (6.a). The measured data of Fig. 2 shows the linear regime of Eq. (6.b) and also the dependence of C_0 .

To further demonstrate the dynamic feature of I(z,t), we solved the coupled equations (1) and (2) numerically by finite element method. Figure 3 shows the numerical results of the normalized UV light intensity, $I(t,z)/I_0$, versus z for various irradiation time of 0, 10, 20, 30 and 60 seconds. These curves may be easily realized by our analytic Eq. (5) which indicates that I(z,t) is an exponentially decaying function of Pz, but it is an increasing function of time, or X, caused by the depletion of C(z,t), referring to Eq. (3.a) and (3.b). Also shown in Fig. 3 is the horizontal straight line for $I(z,t)/I_0 = 0.135$ (or $1/e^2$), in which the crossing point among the horizontal line and the intensity curves defines the safety depth (z^*) at various time. These crossing points move toward the corneal depth when time goes as predicted by our analytic formula, Eq. (7). The safety depth is an increasing function of time. This indicates that a larger safety margin is needed after the UV light irradiation than its initial value (at t=0). Therefore, more caution is needed when the procedure is close to the complete depletion of the photoinitiator and the UV light becomes more transparent in the B2 solution.

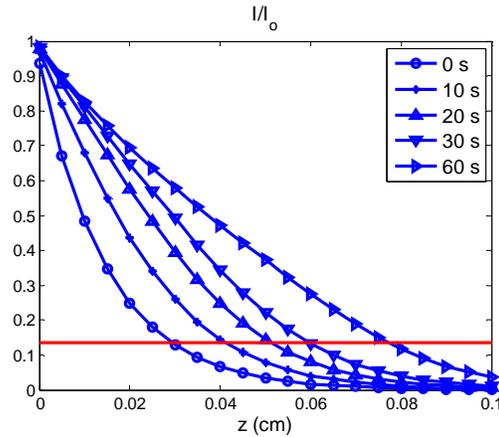


Fig. 3 the numerical results of the normalized UV light intensity, $I(t,z)/I_0$, versus z for various irradiation time of 0, 10, 20, 30 and 60 seconds for $I_0 = 10 (\text{mW/cm}^2)$ and $C_0 = 2.5 \text{ mM}$. Also shown is the straight line for $I(z,t)/I_0 = 0.135$ which defines the safety depth (z^*) at various time.

C. The New Protocol

We have observed the color change (from dark to light) of riboflavin solution after few minutes of UV light illumination in a laboratory test. Our analytic formula, Eq. (4) shows the initiator depletion (or the crosslinking process) starts from the corneal surface (at $z=0$) and gradually moves toward the stroma volume. Eq. (4) also shows that faster crosslinking process, defined by the rate of initiator depletion, may be achieved by a higher initial UV light intensity, which on the other hand also results a higher risk at a given initiator concentration. The safety depth defined by Eq. (7) also indicates that higher initial B2 concentration is required to protect thinner corneas, particularly under a high intensity light.

Based on our theoretical finding and the measured dynamic features, the following new protocol for CXL is suggested.

- (a) Pre-operation, as commonly suggested, apply the riboflavin solution (RS) on the cornea (having epithelia removed first) every 5 minutes for about 5 times; wait for longer time if needs to make sure the enough diffusion of the RS into the stroma;

- (b) use BSS to wash out the extra amount of RS left on the corneal surface
- (c) apply UV light for about 30-120 seconds (depending on light intensity ranging 10 to 60 mW/cm²);
- (d) reapply RS and waiting for 1-2 minutes for its diffusion into the corneal stroma before reapplying the UV light;
- (e) repeat (b) to (d) for 3-5 times, depending on the light intensity used, until a total dose of 5.4 J/cm² is achieved.

D. Special Notes for CXL

Our theory developed in this paper as shown by Eqs. (3) to (7) indicates that safety and effectiveness (or CXL procedure speed) are actually two competing factors which must be optimized. Special notes are summarized as follows.

- (a) It should be emphasized that after the administration of the riboflavin solution (RS) and prior to the UV light irradiation, one shall use BSS to wash out the extra amount of RS left on the corneal surface which may block the UV light and reduce the effective light penetrating to the RS diffused corneal stroma. As shown by Eq. (3) or (5), the light intensity is a strong decreasing function of the RS concentration, therefore, extra RS on the corneal surface may reduce significantly the useful UV light inside the stroma. The commonly used protocol ignoring the steps of BSS washing has largely reduced the effectiveness of the CXL, even the irradiation time is as long as 30 minutes, where only the last few minutes (after the corneal surface extra RS is depleted) is effective, although longer time may assist the RS diffusion.
- (b) As shown by Eq. (7) for the safety depth, certain amount, about 15%, of RS concentration inside the stroma (about 50-100 μ m depth) shall be kept during the CXL procedure in order to protect the endothelium. Therefore, over irradiation time causing a complete depletion of the RS initiator should be avoided, as shown by Fig. 3 the light intensity is an increasing function of time when the RS initiator is depleted gradually. The UV light intensity (or fluence) of 10 to 80 mW/cm² is suggested for fast procedure while keeping the safety margin which also requires a high RS initial concentration, say >0.25 mM.
- (c) For safe and effective CXL, I propose a progressive-mode, where a progressive decreasing light intensity is used to compensate the increasing risk to the endothelia due to the increasing light penetration (resulting from the RS depletion) during the procedure.
- (d) The current new generation commercial CXL devices, keeping the same dose of light energy 5.4 J/cm², have used an intensity of 30 to 60 mW/cm² to replace the old model using 3 mW/cm² in order to speed up the procedure from 30 minutes to 1.5 to 3.0 minutes. However the risk factor resulted from the dynamic increasing light intensity (due to the initiator depletion) has been ignored, other than the requirement of a corneal thickness of 400 μ m. Our new finding shown by Eq. (7) indicates that one should not deplete the B2 solution too much in order to keep the safety margin, specially when one uses a high UV intensity, say larger than 30 mW/cm².

CONCLUSION

We have presented a comprehensive modeling for the kinetic of UV light photoinitiated corneal cross linking. Our analytic formula, Eq. (4) shows the initiator depletion (or the crosslinking process) starts from the corneal surface (at $z=0$) and gradually moves toward the stroma volume. Eq. (4) also shows that faster crosslinking process, defined by the rate of initiator depletion, may be achieved by a higher initial UV light intensity, which on the other hand also results a higher risk at a given initiator concentration. The safety depth defined by Eq. (7) also indicates that higher initial B2 concentration is required to protect thinner corneas, particularly under a high intensity light. Moreover, the safety depth shall be defined not only by the corneal thickness but also the UV light irradiation time. Based on our finding, both in theory and measured data, we are able to suggest a new protocol for CXL which is fast and safe. It is critical that the irradiation time should be limited as shown by Eq. (7) and not to deplete the B2 solution too much in order to keep the safety margin, specially when one uses a high UV intensity and a low B@ initial concentration. Analysis and numerical simulation for another important parameter, the cross linking time, defined by the 87% depletion of the initiator are in progress. Moreover, a more realistic corneal model with an actual B2 distribution inside the stroma will be presented elsewhere.

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BIOGRAPHY



Jui-Teng Lin received his Ph.D in Chemical Physics from the University of Rochester in 1980. He is currently the Chairman and CEO of New Vision, Inc. (Taiwan) and a visiting Professor at He Medical University (China). He was a visiting Professor at the National Chiao-tung University and National Taiwan University (2007-2010), a faculty at CREOL,UCF(1986-1991) and founder and CEO of two US Nasdaq listed companies (1991-2004). He holds over 50 international patents and is the inventor of LASIK procedure (US Pat, 1991) using flying-spot scanning laser currently used in all major eye hospitals worldwide. Lin has published over 50 book chapters and 60 SCI journal papers. His achievements include WHO's WHO in Leading American Executives (1993), Model of oversea Chinese Young Entrepreneur (1997), Chair and/or co-chair in SPIE Conferences. Prof. Lin is a Fellow of American Society of Laser Medicine and Surgery ASLMS).