A Mathematical Model of Corneal UV-A Absorption After Soaking With a Riboflavin Solution During Trans-epithelial Cross-linking

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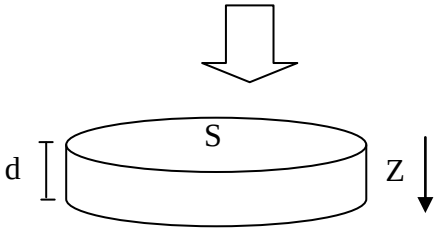
Purpose: a time-dependent mathematical model of UV-A absorption and of riboflavin consumption During cross-linking treatments, the intensity of the UV-A shaft that exits from the rear side of a treated cornea generally varies with time.
Therefore, a time-dependent mathematical model is necessary to describe cross-linking treatments.

Lambert-Beer's law

$$I(z,t) = I_R(z,t) + I_L(z,t) + I_C(z,t)$$



$$\frac{\partial I_R(z,t)}{\partial z} = -\varepsilon \cdot I(z,t) \cdot R_A(z,t)$$

$$\frac{\partial I_L(z,t)}{\partial z} = -\alpha \cdot I(z,t) \cdot R_L(z,t)$$

$$\frac{\partial I_C(z,t)}{\partial z} = -\beta \cdot I(z,t)$$

Wherein:

- $R_A(z,t)$: density of riboflavin available for cross-linking at the depth z in the corneal thickness at time t;
- $R_L(z,t)$: density of linked riboflavin because of cross-linking at the depth z in the corneal thickness at time t;
- $I(z,t)$: intensity of UV-A in the corneal thickness at the depth z at time t;
- ε: absorption coefficient of available riboflavin;
- β: absorption coefficient of cornea;
- α: absorption coefficient of linked riboflavin.

Mathematical model of UV-A absorption and riboflavin consumption

It is possible to demonstrate (Lambert-Beer's law) that intensity of UV-A in a cornea soaked with riboflavin is described by the following differential equation:

$$\frac{\partial I(z,t)}{\partial z} = -I(z,t) \cdot \left((\varepsilon - \alpha) \cdot R_A(z,t) + \alpha \cdot R_A(z,0) + \beta \right)$$

$$R_L(z,t) = R_A(z,0) - R_A(z,t)$$

Wherein:

- $R_A(z,t)$: density of riboflavin available for cross-linking at the depth z in the corneal thickness at time t;
- $R_L(z,t)$: density of linked riboflavin because of cross-linking at the depth z in the corneal thickness at time t;
- $I(z,t)$: intensity of UV-A in the corneal thickness at the depth z at time t;
- ε: absorption coefficient of available riboflavin;
- β: absorption coefficient of cornea;
- α: absorption coefficient of linked riboflavin.

And that the rate of consumption of riboflavin during a cross-linking treatment is:

$$\frac{\partial R_A(z,t)}{\partial t} = -\frac{\varepsilon \cdot p}{\gamma} \cdot I(z,t) \cdot R_A(z,t)$$

Being

$$\gamma = \frac{h \cdot c}{\lambda} \cdot \frac{A}{W_{mol}}$$

Wherein:

- ε: absorption coefficient of available riboflavin;
- W_{mol}: molecular weight of riboflavin;
- A: number of Avogadro (6.02214179·1023 mol^{-1});
- c: speed of the light in vacuum (299792458 m/s);
- S: cross-section of the treated cornea;
- H: Plank's constant (6.62606896 · 10^{-34} Js);
- λ: UV-A wavelength;
- p: probability that a photon succeeds in breaking a molecule of riboflavin.
- $hcA = 0.11314208\ J \cdot m \cdot mol^{-1}$

Simple case results

1) If the UV-A absorption of not treated cornea (β=0) and of linked riboflavin (α=0) may be neglected (superficial treatment),

$$E(d,t) - E(0,t) = \frac{\gamma}{p} \cdot \left(W_R(d,t) - W_R(d,0)\right)$$

Wherein:

- d: thickness of the treated cornea;
- $W_R(z,t)$: total weight of available riboflavin contained in the cornea between the null depth (0) and the depth z at time t;
- $E(z, t)$: energy crossing a generic section of the cornea at depth z and at time t.

First conclusion: The amount of riboflavin that is cross-linked depends on the total energy absorbed by the cornea and not on the power density of the source of UV-A, thus it is theoretically possible to carry out cross-linking treatments by increasing power and reducing exposure time proportionally, provided that a sufficient amount of riboflavin is in the cornea.

2) Intensity of the UV-A shaft exiting from the rear surface of the cornea is:

$$I(d,t) = I_0 \cdot \frac{\exp\left(-\varepsilon \frac{W_R(d,0)}{S}\right)\left[\exp\left(\frac{\varepsilon \cdot p}{\gamma} \cdot I_0 t\right)\right]}{\left[1 + \exp\left(-\varepsilon \frac{W_R(d,0)}{S}\right) \cdot \left(-1 + \exp\left(\frac{\varepsilon \cdot p}{\gamma} \cdot I_0 t\right)\right)\right]}$$

Wherein:

- $I(d,t)$: intensity at the rear surface of the cornea;
- I_0: intensity at the front surface of the cornea;
- $W_R(d,0)$: total amount of riboflavin absorbed by the cornea;
- S: corneal surface.

Second conclusion: the intensity of the UV-A shaft exiting from the rear surface does not depend on how riboflavin is distributed in the cornea.

It is not mandatory to use a **constant** UV-A source.

3) Intensity of the UV-A source exiting from the rear surface of the cornea is constant if the intensity of the UV-A source is progressively reduced:

$$I(0,t) = I_S \cdot \frac{\exp\left(\varepsilon \cdot \frac{W_R(d,0)}{S}\right)\exp\left(\frac{\varepsilon \cdot p}{\gamma} \cdot I_S t\right)}{\left[1+\exp\left(\varepsilon \cdot \frac{W_R(d,0)}{S}\right)\cdot\left(\exp\left(\frac{\varepsilon \cdot p}{\gamma} \cdot I_S t\right)-1\right)\right]}$$

Wherein:

- I_S: constant intensity at the rear surface of the cornea;
- $I(0,t)$: intensity on the front surface of the cornea;
- $W_R(d,0)$: total amount of riboflavin absorbed by the cornea;
- S: corneal surface.

If I_S is a safe UV-A intensity for the eye, the cross-linking treatment will be safe for patients even without continuously administering riboflavin during the treatment.

Third conclusion: It is possible to realize intrinsically safe cross-linking equipment that, using an electronically controlled power stage, generate UV-A shafts of intensity modulated according to the above equation.

Exemplary graphs (simulations)

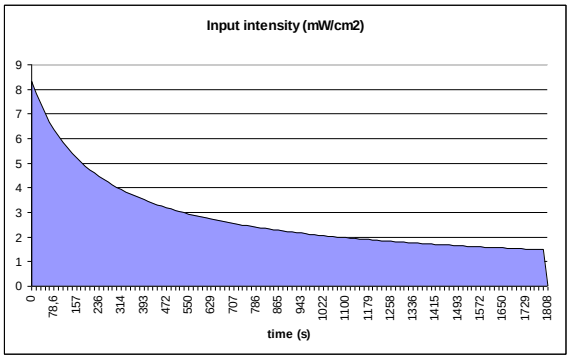


Fig. 1: Input intensity

Fig.2: Available riboflavin

Wherein I_s=0.3 mW/cm^2

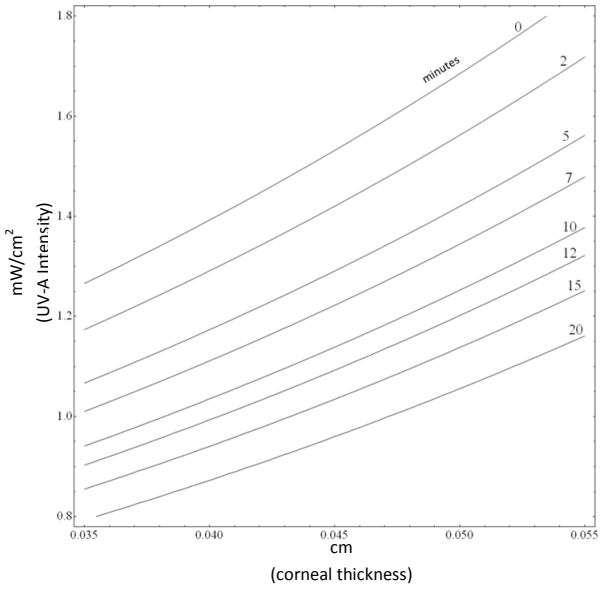


Fig.3: Mathematical model

This graph is a product of the mathematical model. The effects of the treatment of cross-linking are : UV-A intensity – irradiation time – corneal thickness – riboflavin consumption rate dependent (intensity-dependent and not energy-dependent). To avoid, however, that patients can be subject to excessive doses of UV-A, it is necessary to fix the irradiation time and intensity of the source as a function of corneal thickness, using the graph (CUSTOM FAST CXL) and not the law of Bunsen-Roscoe, respecting, always the limit output of 0.3 mW / cm^2, beyond which the endothelium would be irremediably damaged. This graph allows to determine, depending on the thickness corneal expressed in micrometers, the source intensity UV-A and the irradiation time of a cornea soaked with riboflavin plus vitamin E TPGS and washed with BSS. It identifies the corresponding curve on the chart: the abscissa and the ordinate, the points belonging to this curve, represent respectively corneal thickness and intensity of the UV-A source.

Conclusions

The amount of riboflavin that is cross-linked depends on the total energy absorbed by the cornea and not on the power density of the source of UV-A, thus it is theoretically possible to carry out cross-linking treatments by increasing power and reducing exposure time proportionally, provided that a sufficient amount of riboflavin is in the cornea.

The intensity of the UV-A shaft exiting from the rear surface does not depend on how riboflavin is distributed in the cornea.

It is possible to realize intrinsically safe cross-linking equipment that, using an electronically controlled power stage for adjusting the power density of UV-A, generate UV-A shafts of time-modulated intensity.

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