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Analysis of the application of the Generalized Monod kinetics model to describe the Human Corneal Oxygen-Consumption Rate During Soft Contact Lens Wear

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Conflicts of interest

The authors have no conflicts of interest to declare.

ABSTRACT

This work is an analysis of the application of the generalized Monod kinetics model describing human corneal oxygen consumption during soft contact lens wear to models previously used by Chhabra et al (2009) and Larrea et al (2009). We use oxygen tension from *in vivo* estimations provided by Bonanno [Bonanno *et al* 2002, and Bonanno *et al* 2013]. We consider four hydrogel and six silicone hydrogel lenses. The cornea is considered a single homogeneous layer, with constant oxygen permeability regardless of the type of lens worn. Our calculations yield different values for the maximum oxygen consumption rate $Q_{c,max}$, whith differents oxygen tensions (high and low p_c) at the cornea-tears interface . Surprisingly, for both models, we observe an increase in oxygen consumption near an oxygen tension of *105 mmHg* until a maximum is reached, then decreasing for higher levels of oxygen pressure. The averaged *in vivo* human corneal oxygen consumption rate of $1.47x10^{-4}$ cm^3 *of* O_2/cm^3 *tissue s*, with Monod kinetics model, considering all the lenses studied, is smaller than the average oxygen consumption rate value obtained using the Larrea *et al*. model. The impact that these calculations have on the oxygen partial pressure available at different depths in the corneal tissue is presented and discussed, taking into consideration the previous models used in this study.

Keywords: soft contact lenses; Monod kinetics model; oxygen consumption; oxygen tension; cornea.

1. Introduction

The cornea is an avascular tissue, which requires oxygen for its normal metabolic function. Oxygenation of the anterior cornea is achieved mainly from atmospheric air and from the anterior chamber (aquous humor), under open eye conditions. During the closed eye situation the oxygen is provided both, from the exposure to the palpebral conjuntiva[1,2] as well as from the aquous humor .

Wear of a low oxygen permeability contact lens will limit, the normal flow to the anterior cornea (hypoxia), causing corneal swelling, corneal acidosis, epithelial punctate staining, limbal hyperemia, loss of corneal transparency, and endothelial polymegethism.[3-5] The corneal oxygen-consumption rate (Q_c) has been suggested to be a parameter useful in the determination of normal levels of corneal metabolic activity (cellular energy (ATP) production) and the associated necessary oxygen levels at the pre-corneal, tear film interface.[6-11]

Then the determination of oxygen consumption rate is a critical parameter and direct index of corneal oxygen metabolism, to assess the normal metabolic reactions which maintain the corneal physiology needs[11].

From a physical point of view, the relationship between oxygen consumption Q_c and oxygen partial pressure p_c should be continuous, yielding a value of zero consumption when p_c is zero, and increasing along with p_c until a saturation level is reached. In this respect, Bonanno *et al.*[12,13] were able to determine the oxygen consumption rate in humans, by applying established oxygen diffusion models to estimations of tear oxygen tension p_c underneath hydrogel lenses. They used time-domain phosphorescence measurement techniques to provide tear film oxygen tension values during in vivo contact lens wear on human eyes[12,13] . This information is very useful to further study the processes of oxygen difussion and consumption in the cornea. Their experimental procedure permits an evaluation of oxygen tension at the cornea-tears-lens interface for both open-eye (OE) and close eye (CE) conditions in the steady state, and also for the transient response at the observation point where the sensor is situated.

The matemathical models used by some authors to obtain the oxygen consumption rate from measured tear-film oxygen tensions, however, has not been carefully treated as it has been assumed to be constant throughout the cornea because the diffusion equation has been considered at steady state, not as time dependent. Such consideration leads to negative values of oxygen tension in the cornea, yielding results with no-physical meaning[1,2,5,12]. Nevertheless the

metabolic model associated to biological tissues and organisms expresses, by mean of a nonlinear function, the relation between the oxygen consumption rate and oxygen tension[14-20]. The metabolic model consider that corneal oxygen consumption is function of oxygen partial pressure into the cornea as consequence of the aerobic metabolism.[18,20,39] It is clear that aerobic metabolism does not occur at zero oxygen tension and therefore Q_c is zero at 0 pO_2. At high oxygen pressures, the reaction is limited by the equilibrium concentration of activated complexes formed by reactions between oxygen and the enzymes which act as catalysts; the reaction is then saturated and Q_c is independent of the oxygen partial pressure. In these cases, aerobic metabolism is quantified by Monod kinetics model[21-23].

From an experimental point of view, direct measurements of oxygen diffusivity and oxygen consumption in the human cornea either have never been taken into account, or are not available. For this reason, some authors, such as Larrea *et al.,*[21] Alvord *et al.*[22] and Chhabra *et al.,*[23,24] proposed mathematical models of time-dependent oxygen diffusion, based on the nonlinear Monod kinetics model, in order to have an estimation of corneal oxygen consumption and diffusivity. The Monod kinetics model includes as parameters the maximum corneal oxygen consumption rate $Q_{c,max}$, the Monod kinetics constant K_m, the corneal oxygen solubility k_c, and the corneal oxygen diffusion coefficient D_c. We have made different assumptions for all parameters to calculate the oxygen diffusivity and consumption rate of each layer in the cornea as a function of oxygen tension in the corneal tear film interface.

Recently, Del Castillo *et al.*[25] have showed that the corneal oxygen consumption rate Q_c decreases as the oxygen pressure p_c decreases in the post-lens tear interface. Bonanno *et al.* observed that both corneal oxygen flux and oxygen consumption Q_c increase when post-lens tear oxygen tension increases with several contact lenses of different oxygen transmissibility are worn[13] reaching higher levels than those expected based on previous *in vitro* corneal measurements[12].In this work we proceeded with the analysis of the oxygen consumption using the metabolic models of Chhabra *et al*.[23] and Larrea *et al*.[21], as well as the predicted unsteady oxygen tension data from *in vivo* estimations of partial oxygen pressure in the post-lens tear interface provided by Bonanno *et al*.,[12,13] in order to obtain the optimum fitting parameters for their models.

We have fitted both models to ten data series, corresponding to different contact lenses (both SiHy and Hy lenses) from which Bonanno *et al*.[12,13] previously determined oxygen tension at the cornea-tears-lens interface by using time-domain phosphorescence measurement techniques. In our calculations, we consider the cornea as homogenous and therefore the oxygen permeability through cornea tissue has a constant value, independent of the lens being worn. The maximum oxygen consumption rate $Q_{c,max}$ should be also independent of the soft contact lens worn. From the values obtained for $Q_{c,max}$ in each of the models, the oxygen pressure profile into the cornea has been calculated for both open and closed eye conditions. Our study provides a generalized Monod kinetics model to describe the human corneal oxygen-consumption rate during soft contact lens wear. From the generalized model we can predict for the corneal oxygen consumption requirements the evidence of two different processes which clearly modify the dependence of $Q_{c,max}$ with the oxygen tension in the cornea. In the section of results and discussion will be shown that coupling oxygen tension with other reactive species in corneal metabolism modifies the Monod kinetic model, as was proposed by Chhabra et al.[24] The Monod kinetic model has been generalized here to include two coupling factors to represent other elements involved in corneal respiration: both pH and the concentration of glucose. We believe that this is, the first time wherein the change from aerobic to anaerobic glycolysis is explicitly shown in a metabolic model. Finally, the impact of the model parameters $Q_{c,max}$ on the partial pressure of oxygen available at different depths into the corneal tissue, is presented and discussed.

2. Methods

Variation of oxygen partial pressure p_c in the post-lens tear film interface in the steady state as a function of time, between closed-eye and open-eye conditions, was measured by Bonanno *et al.*[12,13] by using a phosphorescence dye technique. Experimental transitory data, in combination with Eq.(1), allowed some authors[12,21,23] to obtain the value of $Q_c(p)$ in different situations. For example, according to Bonanno *et al.,*[12] the Q_c is calculated from the assumption that oxygen output flux at the lens must be equal to the oxygen input flux into the cornea in the steady state. As a result, knowing corneal thickness, an estimation of Q_c can be obtained. In such situation, Q_c is constant in the cornea[12]. Other authors, such as Chhabra *et al.*[23] and Larrea *et*

al.,[21] used models where the oxygen consumption rate is considered non-constant, and the expressions for the oxygen consumption rate are functions of the oxygen pressure.

In this paper, following a similar procedure to that used by Chhabra *et al.,*[23] we have obtained the corneal oxygen consumption rate from the Bonanno *et al.,*[12,13] measurements of oxygen tension at the post-lens tear film as a function of time for four Hydrogel and six Silicone Hydrogel lenses (*Dk/t= 8.4-255 Barrer/cm*) on in-vivo human corneas. Parameters of thickness, permeabilities and transmissibilities are given in Table 1.

TABLE 1

The technical procedure followed to solve the partial differential equation (PDE) using FiPy, a finite volume PDE solver written in Python has been previously reported in reference[25]. Table 1 shows the different values for the parameters used in the numerical solution of the equations.

3. Theoretical Development

Considering a one-dimensional model for the cornea (or for any homogeneous slab of oxygen-consuming tissue), oxygen tension as a function of time and position is given by the equation[25]

$$\frac{\partial^2 p_c}{\partial x^2} - \left(\frac{Q}{Dk}\right)_c = \frac{1}{D_c}\frac{\partial p_c}{\partial t} \qquad (1)$$

where $p_c(x,t)$ is the oxygen partial pressure or tension in the cornea (*mmHg*), D_c is the diffusion coefficient of oxygen in the corneal tissue (*cm²/sec*), k is the oxygen solubility coefficient in the corneal tissue, i.e., Henry's law constant (*cm³ of O_2 /cm³ of tissue/mm of Hg*), x is the distance perpendicular to the surface (*cm*), Q_c is the corneal oxygen consumption rate (*ml of O_2/cm³ of tissue layer /sec*), and t is time (*s*). Subscript *c* refers to quantities measured at the cornea. In steady-state conditions, Eq.(1) becomes

$$\frac{\partial^2 p_c}{\partial x^2} = \left(\frac{Q}{Dk}\right)_c \qquad 0 \le x \le x_c\,, \qquad (2)$$

with Dirichlet boundary conditions

$$p(x_c = 0) = p_0 = 24.1 \ mmHg$$
$$p(x_c) = p_{xc} \quad .$$

where x_c is the corneal thickness, i.e., the distance from aqueous humor to the corneal tear interface position, p_0 is the oxygen tension at the aqueous humor (x_c=0), and p_{xc} the oxygen tension in the corneal tear film interface.

For post-lens tear film and lens, the equations are, respectively,

$$\frac{\partial^2 p_{tear}}{\partial x^2} = 0 \qquad x_c \le x \le x_c + x_{tear} \tag{3}$$

$$\frac{\partial^2 p_{lens}}{\partial x^2} = 0 \qquad x_c + x_{tear} \le x \le x_c + x_{tear} + x_{lens} \tag{4}$$

where x_{tear} and x_{lens} are the thicknesses of the tear film and lens, respectively. p_{tear}, p_{lens} and p_c are the oxygen partial pressures in the tears, lens and cornea, respectively. We averaged over the three layers of the cornea (epithelium, stroma and endothelium) to estimate relative oxygen consumption. Thus, oxygen consumption was derived as a weighted value, taking into account the averaged epithelial, stromal and endothelial layer thicknesses, and the oxygen consumption for each layer.

The solutions of Eq.(2) in the cornea are functions of $Q_c(p_c)$ as a result of the aerobic metabolism, more specifically the Krebs cycle, where one mole of glucose reacts with six moles of oxygen to form six moles of carbon dioxide and water, producing energy in the form of *36 moles* of ATP.[23,26,27] In the succeeding sections we will describe the models of Q_c used.

3.1. Description of the Models

Several models have been proposed to describe the variation of the corneal oxygen consumption with pressure $Q_c(p_c)$, starting with the case of Q_c constant given by the quadratic model[1,2] (Fatt 1974, Freeman 1972), sigmoidal and linear oxygen consumption functions[22] (Alvord et al 2007), followed by the Chhabra *et al.*[23] and Larrea *et al.*[21] models, where the oxygen consumption rate is derived from reaction kinetics as a function of the oxygen tension such as been described in biological systems. In next subsections, Monod kinetics and Larrea models will be discussed in detail.

3.1.1. Monod kinetics model

The most used model which characterizes and quantifies the aerobic metabolism is the Monod kinetics model,[23] also known as Michaelis Menton model[28]. This is based on the study of kinetic oxygen absorption in the cornea, taking into account the transient post-lens tear film oxygen tension, and it relates the oxygen consumption with the oxygen tension by means of the expression

$$Q_c(p_c) = \frac{Q_{c,\max} \cdot p_c(x)}{(K_m + p_c(x))}, \quad (5)$$

where K_m is the Monod dissociation equilibrium constant and $Q_{c,max}$ represents the maximum oxygen consumption. Eq.(5) describes the $Q_c(p_c)$ versus p_c curve, from minimum corneal consumption $Q_c(p_c)=0$ to the maximum corneal consumption of oxygen $Q_{c,max}$, reached when the oxygen partial pressure is $p_{xc}=155\ mmHg$ in the corneal tear interface under open-eye condition. This value represents the oxygen tension when corneal aerobic metabolism reaches the maximum oxygen consumption (i.e., oxygen tension needed to achieve equilibrium in the cornea), and the aerobic metabolism reactions of glucose with oxygen (Krebs cycle) is saturated, bringing the system to an oxygen consumption independent of the partial pressure. As observed,[25] this model reproduces individual experiments for each lens (Balafilcon and Polymacon lenses), but it could not yield a good solution for both lenses simultaneously, even for two lenses of the same material but with different thicknesses, because the oxygen consumption rate is not the same in all cases.

Alvord *et al.*[22] have proposed another quadratic form to parameterize the oxygen consumption data of Bonanno *et al.*[12] They considered a sigmoidal curve that varies from zero consumption at zero oxygen pressure to the maximum consumption, which corresponds to $Q_{c,max}=2.2x10^{-4}\ cm^3\ O_2\ cm^{-3}\ tissue\ s^{-1}$ for an oxygen tension of $p_{xc}=99\ mmHg$. This maximum value was obtained considering a constant oxygen consumption rate.

Chhabra *et al.*[23] have established the oxygen consumption kinetics from transient post-lens tear film oxygen tensions; they used the nonlinear Monod kinetics model to describe the local oxygen consumption rate, giving a value of $K_m=2.2\ mmHg$ for the Monod kinetics constant. Additionally, they obtained different values for the maximum corneal oxygen consumption rate $Q_{c,max}$, depending on the contact lenses worn,[25] and calculated the spatial-averaged *in vivo* human

maximum corneal oxygen consumption rate as $1.05x10^{-4}\ mL{\cdot}cm^{-3}{\cdot}s^{-1}$. This value corresponds to the average of the values obtained ($Q_{c,max(ave)}$), and is *2.34* times higher than the one given by Brennan[11] ($Q_{c,max}=4.48x10^{-5}\ mL{\cdot}cm^{-3}{\cdot}s^{-1}$), and 1.8 times higher than the value reported by Larrea *et al.*[21], ($Q_{c,max}=5.75x10^{-5}\ mL{\cdot}cm^{-3}{\cdot}s^{-1}$). We are concerned that Chhabra *et al.*[23] results rely on two values for the corneal oxygen permeability, *140* and *90 barrer*, when a Balafilcon or a Polymacon lens is worn, respectively. We therefore believe that the results of Chhabra *et al,*[23] should be reviewed.

The expression of the nonlinear Monod corneal oxygen consumption in Eq.(5) was inserted in Eq.(1), and the solution was obtained following the procedure (described in the Appendix) of Del Castillo et al.,[25] where the parameters considered in the models are given in Table 2. An iterative procedure was used due to the nonlinear nature of the transport equations, by "sweeping" the solutions over few iterations All the calculations were performed on an Intel Core i7-3770K PC with OS Debian Linux. FiPy version 3.1 was used in all computations (see FiPy manual for details http://www.ctcms.nist.gov/fipy)[29]. "fmin_tnc" function in the Scipy package (http://www.scipy.org/) was used to multidimensional parameter optimization subject to bounds. In this way we were able to determine optimized values of the Q_{max} and K_m parameters for a predefined set of the remaining model parameters.

TABLE 2

3.1.2. Monod kinetics model of Larrea *et al.*

Larrea et al.[21] proposed a model, which describes the tendency of the oxygen consumption to slowly increase as p_c increases, neglecting the assumption of an independency of pressure in the interval of high pressures. They moreover assume that oxygen consumption depends only on the oxygen partial pressure, giving the following expression to describe the oxygen consumption rate:

$$Q(p_c)=\frac{Q^{*}\cdot p_c(x)\cdot(a+p^{*})}{p^{*}\cdot(a+p_c(x))}, \qquad (6)$$

where $Q^{*}=Q_{stroma}=0.11\ Q_{epithelium}=0.02\ Q_{endothelium}$. Eq.(6) represents the oxygen consumption rate at the saturated oxygen tension p^{*} (for open-eye conditions $p^{*}=155\ mmHg$), and the constant

a=20 mmHg determines the shape of the curve *Q* versus $p_c(x)$. On the other hand, to solve Eq.(1), Larrea *et al.*[21] assumed that the cornea was divided into three layers, i.e., epithelium, stroma and endothelium. Each layer´s diffusivity is interrelated and constrained by the ratios $D=D_{stroma}=1.59\ D_{epithelium}=5.66\ D_{endothelium}$, where oxygen diffusivity and stroma oxygen consumption $Q_{stroma}=5.75x10^{-5}\ cm^3\ of\ O_2\ cm^{-3}\ s^{-1}$ are according to Fatt *et al.*[1,10,19] . Larrea et al[21] also assumed that the consumption/diffusivity ratio between layers is the same as that measured in rabbits.

The Eq.(6) can be expressed as

$$Q(p_c)=\frac{Q^{*}\cdot p_c(x)\cdot 1{,}129}{(a+p_c(x))}=\frac{Q^{*}_{c,\max}\cdot p_c(x)}{(a+p_c(x))}, \qquad (7)$$

because the *a/p** relation is a constant equal to 0.129, i.e., the expression of the model of Larrea *et al.*[21] is similar to the Chhabra *et al.*[23] Monod kinetics model. The only differences are in the parameter values of: $a = K_m = 20\ mmHg$ instead of *2.2 mmHg* in Chhabra *et al*[23] model; and $Q^{*}=Q_{stroma}=5.75x10^{-5}\ cm^3\ of\ O_2\ cm^{-3}\ s^{-1}$ instead of the values observed by Chhabra *et al*[23]. for the Polymacon and Balafilcon lenses ($0.9x10^{-4}$ and $1.2x10^{-4}\ cm^3\ of\ O_2\ cm^{-3}\ s^{-1}$, respectively).

4. Results and discussion

Considering the Monod kinetics model given by eq.(5) and fitting Eq.(1) to the experimental data given by Bonanno *et al.,*[12,13] our calculations yield the maximum oxygen consumption rate $Q_{c,max}$ values for the analyzed corneal lens system in Table 2. In these calculations we have assumed a constant value for the parameter $K_m=2.2\ mmHg$ and the oxygen permeability coefficient of the cornea $(Dk)_c=93$ *barrers or Fatt units,* considering that the oxygen diffusion coefficient and solubility are $D_c= 30x10^{-6} cm^2/s$; $k_c=3.1x10^{-5} cm^3\ of\ O_2/cm^3\ tissue/\ mmHg$, in water solution at 25ºC, respectively[30]. On the other hand, by using the transient diffusion model used by Larrea *et al.*,[21] our calculations also yield the $Q_{c,max}$ values gathered in Table 3.

TABLE 3

We plot the fitting curves of two models for ten lenses in Figures 1,2 and 3: four Hydrogel and six Silicone-Hydrogel lenses (Dk/t = 14 to 255 barrer/cm). The same lenses were used by Bonanno *et al.*[13] to determine the tear oxygen tension under contact lenses in human subjects. This is a

similar procedure to the one described for Balafilcon and Polymacon lenses, using the time-domain phosphorescence measurement techniques.[12]

In Figures 1, 2 and 3 (left), we plot the post-lens tear film oxygen tension as a function of time for Polymacon, Balafilcon, Biomedics, Acuvue2, Advance, Purevision, Oasys, Night and Day, Optix, and N&D UT lenses at 35ºC, using the diffusion models of Chhabra *et al*.[23] and Larrea *et al*.[21], respectively. The values found for the oxygen tension at the stationary state are shown in Table 3. In the same figures the right plot corresponds to the steady-state oxygen tension profile through corneal thickness, where OE mean open eye condition and CE is closed eye conditions, and where the boundary condition for the tension at the contact-lens-palpebral conjunctiva interface considered is 61.5 mmHg. The lens is considered a separate phase without oxygen consumption, sandwiched by two thin tear films (pre- and post-lens tear films), where the resistance to the oxygen flux can be considered negligible in comparison with that of the lens.[31,32] Figures 1, 2 and 3 show that the values of the parameters presented in Table 3 provide a good explanation to the distribution of oxygen partial pressure in the cornea, and perfectly reproduce the experimental data of Bonanno *et al*.[12,13] in both open- and closed-eye conditions.

Considering a constant corneal oxygen permeability approximately equal to that of the water oxygen (*93 Barrer*) for all analyzed corneal lens systems, in addition to the Figures 1, 2 and 3 and the data presented in Table 3, oxygen consumption rate values are seen to be different from those provided by both Chhabra *et al*.,[23] and Larrea *et al*.,[21] models where K_m *=2.2 mmHg* was considered constant for all the fits of Chhabra *et al*.[23], and α=20 mmHg in case of Larrea *et al*.[21]

FIGURE 1,

FIGURE 2,

FIGURE 3,

Overall, the values of maximum oxygen consumption rate $Q_{c,max}$ varies depending on the type of lens worn. In a recent study, we observed similar behavior for Polymacon and Balafilcon lenses.[25] Following the same procedure, we found that this parameter also varies depending on the lens worn, because it is a function of the oxygen tension at the cornea-lens interface, where the average $Q_{c,max}$ value using the metabolic model used by Chhabra *et al.* is *1.50x10^{-4} cm^3 of*

O_2/cm³ tissue s, while in the case of Larrea et *al*. the value obtained is *2.09x10⁻⁴ cm³ of O_2/cm³ tissue s*.

FIGURE 4

In Figure 4 we plot the variation in average oxygen consumption rate with corneal which should be observed according the expressions of Larrea *et al.* [21] model described by the Eq.(6 or 7) and Chhabra *et al*.[23] Monod kinetic model by means of Eq. (5). Notice that the averaged oxygen consumption rate is that obtained according the fitting of each model to the experimental data of Bonanno *et al.*[12,13] Its values are given for all the lenses considered in this study in Table 3.

As can be concluded, the metabolic model with the parameters given in Table 3 successfully reproduces experimental results for transient oxygen tension after closed-eye contact lens wear, and for the steady-state oxygen tension in several lenses with different oxygen transmissibilities. The parameters used for Monod dissociation equilibrium constant and corneal oxygen permeability are constant, regardless of the type of lenses worn.

The human maximum corneal oxygen consumption rate $Q_{c,max}$ was expected to be the same for all studied lenses. However, this consumption varied from one lens to another. For example, for the N&D lenses, the consumption was *1.79x10⁻⁴ cm³ of O_2/cm³ tissue s*, which was higher than that for the UT lens where this consumption was *1.29x10⁻⁴ cm³ of O_2/cm³ tissue s*. On the other hand, the oxygen tension in the corneal tear film interface was about *124 mmHg* in the case of N&D, while the oxygen tension for the UT lens was *130 mmHg*.

The fact that lenses which produce low oxygen tension in the post-lens tear film interface produce low oxygen consumption rate in the cornea, compared with others, is quite relevant. For example, in the case of Balafilcon lens, the oxygen consumption at *99 mmHg* was about *1.7x10⁻⁴ cm³ of O_2/cm³ tissue s*, quite similar to the value obtained by Bonanno *et al.* (c.a. *1.6x10⁻⁴ cm³ of O_2/cm³tissue s*), where a constant oxygen consumption rate was assumed. When the oxygen tension in the interface is higher, the oxygen consumption that we can obtain with the model of Chhabra *et al*.[23] is very close to the values obtained considering steady state tear p_c under a contact lens of known *Dk/t* [13,]. In the cases where the oxygen tension is lower, such as in Polymacon lenses (about *27 mmHg*), the oxygen consumption rate is very close to the data

obtained , assuming a constant oxygen flux into the cornea, j_c, which leads to an estimate of consumption rate of about 7.54*x10^{-5} cm^3 of O_2/cm^3 tissue s*. These results are similar to that obtained for Biomedics and Acuvue2 lenses where the value estimated by mean of Modified Monod kinetics Model is about 7.0*x10^{-5} cm^3 of O_2/cm^3 tissue s*. By considering all studied lenses, there was obtained an averaged *in vivo* human corneal oxygen consumption rate of *1.5x10^{-4} cm^3 of O_2/cm^3 tissue s* for the Monod kinetics model. However, this value is lower than the average rate of 2.07x10^{-4} *cm^3 of O_2/cm^3 tissue s*, obtained considering the eq.(7) of Larrea *et al.*, and both of them are higher than the value *4.85x10^{-5} cm^3 of O_2/cm^3 tissue s*, obtained *in vivo* for humans by Harvitt *et al*.[4,5] and Weissman[33], considering constant the oxygen consumption rate into the cornea. In the other hand, the value of *1.5x10^{-4} cm^3 of O_2/cm^3 tissue s* is higher than the oxygen consumption rate value (6.49 *x10^{-5} cm^3 of O_2/cm^3 tissue s*) obtained previously[21]. These differences can be related to limitations in the cited models, and therefore a revision of those models should be generalized to acquire a better description of the behavior of the cornea in humans.

We plot the relationship between the oxygen consumption rate into the cornea and the oxygen tension at the interface cornea-post lens tear film, for all the lenses studied in Figure 5. We see, as expected from the commentes above, a similar behavior in both models used by Chhabra *et al*.[23], and Larrea *et al*.[21]. Surprisingly, however; we observe an increase in oxygen consumption near 30 mmHg and another more important maximum about *105 mmHg* of oxygen tension. After reaching the maximum, we then observe a decrease, for higher levels of oxygen pressure.

FIGURE 5

It is clear that the oxygen consumption rate is a function of the oxygen tension (see equations of models). However, we can see from Figure 5 that around the oxygen tension of 105-110 mmHg, an apparent discontinuity similar to one phase transition is observed. The evidence that is strengthened by observing the same behavior in both models.

A close inspection of figure 5 shows that the behavior is a lambda-like, similar to that which appears when matter exists a phase transition. The corneal oxygen consumption rate increases with the acidosis and decreases with the anaerobic transition[5]. To include this effect in

the models of oxygen distribution with a contact lenses wear, they should be modified by adding at least an additional term with the aim to reproduce such behavior.

To explain the data behavior shown in Figure 5, we first consider the pressure p_s= 106.5 mmHg at which we have a maximum, and those data for pressures above p_s (interval compress between 106 and 135 mmHg). Then defining the differences $\Delta Q = Q_{c,max} - Q_s < 0$ and $\Delta p = p_c - p_s < 0$, and plotting $\Delta Q/Q_s$ versus Δp, such is shown in Figure 6, we can see that experimental data has a behavior such as indicated by mean of presented solid line. This fit has been obtained following the expression:

$$-\frac{\Delta Q}{Q_S} = \frac{\Phi}{Q_S}\left[\frac{\Delta p}{K_m + \Delta p}\right] \qquad (8),$$

where the parameters used to plot the Figure 6 are K_m = 5.0 and $\frac{\Phi}{Qs} = 0.8$, respectively.

Equation (8) can be rewritten considering the expressions $\Delta p = a(7.6 - \mathrm{pH})$ and $K_{pH} = \frac{K_m}{a}$.

According with Leung et al[32], for K_{pH}=0.1 the estimation of the parameter a = 50 mmHg is satisfied. Therefore, we get

$$Q_{c,\max} = Q_S\left[1 - 0.8\frac{7.6 - pH}{K_{pH} + 7.6 - pH}\right] \qquad (9)$$

The minus sign in eq. (9) reflects the fact that the reference value is to the left of the pressure interval considered, where the oxygen consumption decreases.

FIGURE 6

On the other hand, considering the interval of pressures below the maximum p_s= 106.5 mmHg, (values p_s between 50 and 106 mmHg), defining the differences $\Delta Q = Q_s - Q_{c,max} > 0$ and $\Delta p = p_s - p_c > 0$, and plotting $\Delta Q/ Q_s$ versus Δp, such is shown in figure 7, the solid line represents the fitting data, by mean of the equation,

$$\frac{\Delta Q}{Q_S} = \frac{\Delta p}{K_0 + \Delta p} \qquad (10),$$

where the value of the parameter K_0 is 5.0 mmHg.

The last equation can be rewritten, considering that $\Delta p = bC_G$ and $K_G = \frac{Ko}{b}$, where C_G is the lactic acid concentration[32], and *b* is estimated as b=12.2nM from the value of K_G=0.4 mM, such as expressed in eq.(11)

$$\frac{\Delta Q}{Q_S} = \frac{C_G}{K_G + C_G} \qquad (11),$$

that can be also expressed as

$$Q_{c,\max} = Q_S\left[1 + \frac{C_G}{K_G + C_G}\right] \qquad (12)$$

FIGURE 7

so that, the rate of change in oxygen consumption obtained from Chhabra and Larrea models at low and moderate pressures, does not correspond to the tendency of the values estimated by Bonanno *et al.*[12] at low ($p_c \approx 8.1$ *mmHg*) and moderate oxygen partial pressures ($p_c \approx 30.6$ *mmHg*). Additionally, at *25 mmHg*, Weissman[33] has estimated the *in vivo* human corneal oxygen consumption as Q_c= 4.85x10^{-5} *cm^3 of O_2 cm^{-3} s^{-1}*, which is similar to the values obtained by Bonanno *et al.,*[12] considering constant oxygen consumption for an oxygen tension of *30 mmHg* in the corneal tear interface . This suggests the occurrence of a kinetic transition that should be assumed as discontinuous. This kinetic transition can be understood not only as the result of the metabolic reactions that occur in the Krebs cycle, but also of the other observed corneal reactions [24,32]. Therefore, in the range from low to moderate pressures, phenomena other than those previously mentioned may take place, such as corneal swelling, corneal acidosis, loss of corneal transparency, keratitis, neovascularization and limbal hyperemia, among others,[3,34,35] which may be described as a nonlinear function of the pressure.[11,32,36] As we have suggested, the simplest way to describe this transition is to modify the Monod kinetics model expression by adding a factor term containing variables other than pressure (see equations 9 and 12).

This assumption is based on different clinical studies. For example Holden and Mertz's[37] showed that corneal swelling versus oxygen flux presents a nearly linear change when a contact lens is worn. On the other hand, Bonano et al.[6,7] and Giasson et al.[38,39] observed that soft-contact-lens wear can induce acidosis. Harvitt and Bonanno[5] state that acidosis increases the corneal

oxygen consumption rate by up to 1.8 times the rate at normal pH, considering that acidosis leads to activation of pH-regulatory mechanisms. Therefore, the increase in energy demand for these processes causes increased corneal oxygen consumption to produce additional ATP molecules via oxidative phosphorylation.The maximum presented in the figure 3, therefore, could be explained in biochemical terms. Finally, the low pressure region of figure 3, could also be explained following Frahm et al.[40], in which it is notorious that the oxygen consumption falls due to concentration of glucose decreases because of respiration. Only the excess glucose in respiration is independent of glucose concentration. In short, the Monod kinetics model for oxygen consumption reaction with glucose describes a maximum, as a transition from aerobic to anaerobic metabolism.

As a further observation, considering the minimum observed in the oxygen tension profiles the condition $(\frac{\partial p_c}{\partial x}) = 0$ is satisfied due to the balanced oxygen flux from the anterior and posterior corneal surfaces is balanced. Therefore the oxygen flux in this position is equal to zero (*j=0*), and taking into account the Fick's law in Eq.(2), $(\frac{\partial^2 p_c}{\partial x^2}) > 0$ will be positive. As a result, the absence of flows and driven forces produce a local equilibrium state in a point (x_{min}) in the cornea. Around this point there is no oxygen flow, but there is both oxygen partial pressure and consumption. At this point, there might be hypoxia under several conditions as during contact lens wear and this position shifts with the change in the partial pressure of oxygen at the epithelial surface.

The metric used to know if contact lens wear induced corneal swelling has changed in the last years[3-20,41,42]. Polse and Mandel[43] initially found human corneal swelling below a cornea-tear interface oxygen tension of 11 to 19 mmHg, but this "critical oxygen tension" was later raised to 70-125 mmHg by other authors[26,44,45], based their estimations on the analysis of the of the biological oxygen apparent transmissibility (BOAT)[44,45], and the critical oxygen tension (COT)[26].

Furthermore, the situations and conditions under which the cornea has oxygen deprivation and corneal edema begins can be related, such as has been described by Hideji et al.[46] in rabbit corneas, with contact lens oxygen transmissibility. They obtained an excellent correlation between the percentage corneal swelling with contact lens transmissibility and conclude that the largest useful Dk/L total for a rigid contact lens may be 56 hBarrer/cm. Chhabra

et al.[24] proposed an oxygen deficiency factor (ODF) as an new index of corneal oxygen consumption which permit measurements of the extent and severity of corneal hypoxia. The determination of this parameter allows a comparison between different contact lenses.

In order to correlate the oxygen tension in each minimum with the position respect to the aqueous humor, where the oxygen fluxes are balanced, we plotted Figure 8. In this figure, oxygen tension in the minimum varies with the distance measured from the aqueous humor, following a linear tendency in both models. At first approximation, the position where the oxygen flux is balanced is dependent of the corneal oxygen consumption rate induced by the oxygen tension profile caused by the transmissibility of the system tears-lens. When the lens transmissibility provides a deficiency oxygen flux (i.e. a deficiency of oxygen tension profiles into the cornea), then the cells are exposed to less oxygen, they are more stressed and then their metabolism shifts from aerobic to anaerobic. As we have indicated above, this is related with a kinetic transition that can be understood not only as the result of the metabolic reactions that occur in the Krebs cycle, but also of the reactions observed in the cornea.

FIGURE 8

Using the Monod Model, the minimum points (x_{min}, $p(x_{min})$) are in the stroma, which prevents corneal edema. All the models assume that the middle and posterior stroma will be under hypoxic conditions which are very unlikely under non-lens wearing open eye conditions, as demonstrated by the absence of edema response under such circumstances[47].

The determination of this position can give us information on the distribution of the partial pressure of oxygen across the cornea. The location of the minimum oxygen availability, where oxygen flux is balanced between aqueous humor (forward flux) and atmospheric (backward flux) sources, was calculated. In Figure 8, for each one of lenses, we illustrate a combined cornea-contact lens system, as a cross-section view of the cornea under different contact lenses, which produce a certain value of partial pressure of oxygen at the post-lens tear film layer.

According to the criteria outlined above, the cornea could be in hypoxia conditions when p_c is about 9-*10%* of oxygen atmospheric pressure[37,48]. In table 4 we show the results obtained from both models for the minimum points (x_{min}, $p(x_{min})$). When the minimum is situated below this

value, the model describes the oxygen tension at the interface cornea-lens that produces values of oxygen consumption which surely tend to produce anoxia in a small part of the stroma, and the basal epithelial cells are hypoxic[49,50].

TABLE 4

A comparison of models shows that the Larrea model predicts behavior better than the Chhabra model, as we can see for Optix, Night&Day, Advance, Polymacon and PureVision lenses, where the values of the minimum oxygen tension, p_{min}, into the cornea are below 10 mmHg. In summary, the Monod kinetic model suggests how the position where the cornea experiences maximal hypoxic stress (x_{min}) changes and broadens as a function of oxygen tension at the epithelial surface and promotes discussion of the potential implications for the actual corneal histological structure as evidenced with modern imaging techniques or calculation of the "oxygen deficiency factor" (ODF) to measure the extent and severity of hypoxia in the cornea. Determination of this parameter[24] allows a comparison between different contact lenses. This treatment will be the object of future work.

5. Conclusions

The application of the Monod kinetics model following the expression given by Chhabra *et al.*[23] and Larrea *et al.*[21] to the experimental data provided by Bonanno *et al.*[12,13], successfully reproduces experimental results for transient oxygen tension after closed-eyes contact lens wear, and steady state oxygen tension, over all the lens studied.

Both models gives corneal oxygen consumption rate values with no aphysical oxygen tension predictions into the cornea. This has been achieved in Monod kinetics model keeping the same value for the oxygen permeability of the cornea as being practically the same that water oxygen permeability (i.e. *93 barrers*).

We have observed, however, that in all the models the corneal oxygen-consumption rate Q_c decreases as the oxygen tension p_c decreases at cornea-post lens tears interface, but when the oxygen tension at the interface cornea-tears-lens increases, Q_c does not tend to a constant value but reaches a maximum value. It is surprising, for both models, to observe an increase in

oxygen consumption near *105 mmHg* oxygen tension, until is reached a maximum, then it is observed a decreasing in Q_c for higher levels of oxygen pressure. These differences can be related to limitations in all the models cited, and therefore a generalization of them should be performed to acquire a better description of the behavior of the cornea in humans.

It is surprising the observation of an increase of the oxygen consumption near to 100 *mmHg* of oxygen tension, where at the interface cornea-post lens tears-film there is an apparent discontinuity similar to one phase transition. Are there two processes which modify the dependence of $Q_{c,max}$ with the oxygen tension at the cornea p_c*?*. This value could be a critical oxygen tension (COT) below which the cornea would receive insufficient oxygen to maintain its thickness. From the analysis to the data it seems that the two processes do not occur simultaneously, but separately. That is, when pressure decreases then the oxygen consumption increase because of acidosis, and this is followed by an anaerobic transition. The change in the participation of the processes is abrupt, producing a singularity in the dependence of oxygen consumption relative to the pressure of oxygen in the cornea, as shown in Figure 3 of the paper.

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Figure captions

Figure 1. (Left) Results representative for the tear-film oxygen tension after 5 minutes of CE lens wear for Balafilcon, Polymacon, Biomedics and Acuvue2, lenses, respectively. Data provided from Bonanno *et al.*[12,13]. **(Right)** The steady state oxygen tension profile through cornea thickness, for the same lenses, respectively.

Figure 2. (Left). Results representative for the tear-film oxygen tension after 5 minutes of CE lens wear for Advance, PureVision, Nigth&Day and Oasys lenses. Data provided from Bonanno *et al.*[12,13]. **(Right)** The steady state oxygen tension profile through cornea thickness, for the same lenses, respectively.

Figure 3. (Left). Results representative for the tear-film oxygen tension after 5 minutes of CE lens wear for Optix and N&D UT lenses. Data provided from Bonanno *et al.*[12,13]. **(Right)** The steady state oxygen tension profile through cornea thickness, for the same lenses, respectively.

Figure 4. Average oxygen consumption rate versus oxygen pressure in the cornea a) Chhabra *et al*[23], b) Larrea *et al*[21]. model.

Figure 5. Variation of oxygen consumption rate versus oxygen tension at the interface cornea-tears film, obtained for all the lenses studied following the expressions of Chhabra *et al*[23]. and Larrea *et al*[21] used for the models. The solid continuous line shows the fitting to the prediction data using the generalized Monod kinetic model to experimental data using equations (8) and (11).

Figure 6. Plot of $\frac{-\Delta Q}{Q_s}$ versus Δp from equation (8), and considering pressures above p_s, with $Q_s = 3.30\ x\ 10^{-4}$ *cm³ of O₂/cm³ tissue s*, $P_S = 106.5\ mmHg$, $Km = 5.0$ and $\frac{\Phi}{Qs} = 0.8$.

Figure 7. Plot of $\frac{\Delta Q}{Q_s}$ versus Δp from equation 11, and considering pressures below p_s, with $Q_s = 3.30\ x\ 10^{-4}$ *cm³ of O₂/cm³ tissue s*, $P_S = 106.5\ mmHg$ and $K_0 = 5.0$ mmHg.

Figure 8. Values of the oxygen pressure at the minimum versus of the distance from the endothelium. The black squares correspond to Monod kinetic model with K_m*=2.2 mmHg* and white squares to Larrea *et al.* model. Each point in this plot corresponds to different oxygen partial pressures at the cornea-tear film interface observed from the fit to Bonanno date given in Figures 1, 2 and 3, respectively.

Tables:

Table1. Lens parameters

Lens	Manufacturer	Thickness (μm)	Dk (Barrer)	Dk/t (Barrer/cm)
Polymacon	Metroptics	60	8.4	14
Biomedics	Cooper Vision	115	19.7	17.1
Acuvue2	J&J	105	28	27
Advance	J&J	71	60	85
Balafilcon	Bausch&lomb	100	99	99
Purevision	Bausch&lomb	90	112	124
Optix	Alcon	80	110	138
Oasys	J&J	62	103	166
N&D	Alcon	80	140	175
N&D UT	Alcon	55	140	255

1Barrer=10^{-11} (cm^2/s)(*mL STp* O_2/(*ml.mmHg*)), or *1 Fatt Dk* units

1 Barrer/cm= 10^{-9} (*cm/s*)(*mL STp* O_2/(*ml.mmHg*)), or *1 Fatt Dk/t* units

Table 2. Parameters considered in the models to obtain the partial pressure of oxygen at different depths into the cornea.

Parameter	**Symbol**	**Value**	**Units**
Atmospheric Partial Pressure of Oxygen under Open Eye Conditions	p_{tc}	155	mmHg
Aqueous Partial Pressure of Oxygen	p_{tc}'	24	mmHg
Palpebral conjunctiva oxygen pressure	p_{pc}	61.5	mmHg
Corneal permeability	Dk_{cornea}	93	Fatt units
Central Corneal Thickness	**CCT**	531.5	μm
Epithelium	T_{ep}	50	μm
Stroma	T_{st}	480	μm

Endothelium	$\mathbf{T_{en}}$	1.5	μm
Water permeability*	$\mathbf{Dk_{water}}$	99	Fatt units

Dk units (barrer) = 10^{-11} (cm^2/sec)[ml O_2· ml^{-1}·$mmHg^{-1}$)] or Fatt units.)

Dk/t_{av} units (barrers/cm) = 10^{-09} (cm ml O_2)/(ml sec mmHg)

D_c= 3.0x10^{-5} cm^2/s.

k_c=3.1x10^{-5} cm^3 of O_2(sTP)/cm^3 of tissue / mmHg

Corneal oxygen diffusion coefficient, D_w= 3x10^{-5} cm^2/s

Corneal oxygen solubility, k_w=3.3x10^{-5} cm^3 of O_2(sTP)/cm^3 of tissue / mmHg

Table 3. Comparison between the values of $Q_{c,max}$ in *cm^3 of O_2/cm^3 tissue s* obtained using the Monod kinetics model[23], and Larrea et al.[21] on the experimental data of Bonanno *et al.*[12,13], for ten hidrogel and Siloxane-hydrogel contact lenses to determine the tear oxygen tension in human subjects. The oxygen permeability through cornea tissue has a constant value $(Dk)_c$=93 *barrers;1 Barrer = 10^{-11}* (cm^2/s)(*ml O_2* (*STp*)/cm^3 /*mmHg*).). The values of the parameters K_m and *a* used has been the values given by Chhabra et al[23] and Larrea et al[21] models, i.e. *2.2 and 20 mmHg*, respectively.

Lens	Model *Chhabra et al.*		Model *Larrea et al.*	
	$Q_{c,max}$,	P_{est} *(mmHg)*	$Q_{c,max}$,	P_{est} *(mmHg)*
Polymacon	0.9x10^{-4}	28.1	5.5x10^{-5}	27.9
Balafilcon	1.6x10^{-4}	101.1	8x10^{-5}	101.5
Biomedics	5x10^{-5}	53.1	3x10^{-5}	53.0
Acuvue2	5x10^{-5}	75.0	3.5x10^{-5}	73.0
Advance	1.35x10^{-4}	98.4	7x10^{-5}	97.8
Purevision	2.0x10^{-4}	103.7	1.0x10^{-4}	103.0
Optix	1.9x10^{-4}	110.3	9x10^{-5}	110.0
Oasys	3.3x10^{-4}	106.5	4.4x10^{-4}	106.0
N&D	1.7x10^{-4}	117.7	2x10^{-4}	118.5
N&D UT	1.2x10^{-4}	132.9	1.7x10^{-4}	132.0

Table 4. Values found from the oxygen tension profiles under open eye condition for the position of minimum measured from endothelium and its corresponding values of oxygen tension.

Lens	Chhabra et al.		Larrea et al.	
	x_{min} (μm)	p_{min} (mmHg)	x_{min} (μm)	p_{min} (mmHg)
Polymacon	254.8	2.67	255.9	4.64
Balafilcon	169.2	5.10	166.7	9.33
Biomedics	153.9	18.27	151.9	18.92
Acuvue2	77.8	22.52	94.4	22.0
Advance	168	9.34	150.9	13.0
Purevision	175.9	2.22	176.8	6.5
Optix	169.8	3.26	163.6	9.0
Oasys	195.8	1.82	194.1	2.7
N&D	152.2	6.92	136.3	13.8
N&D UT	92.2	19.05	108.2	17.9

FIGURES:

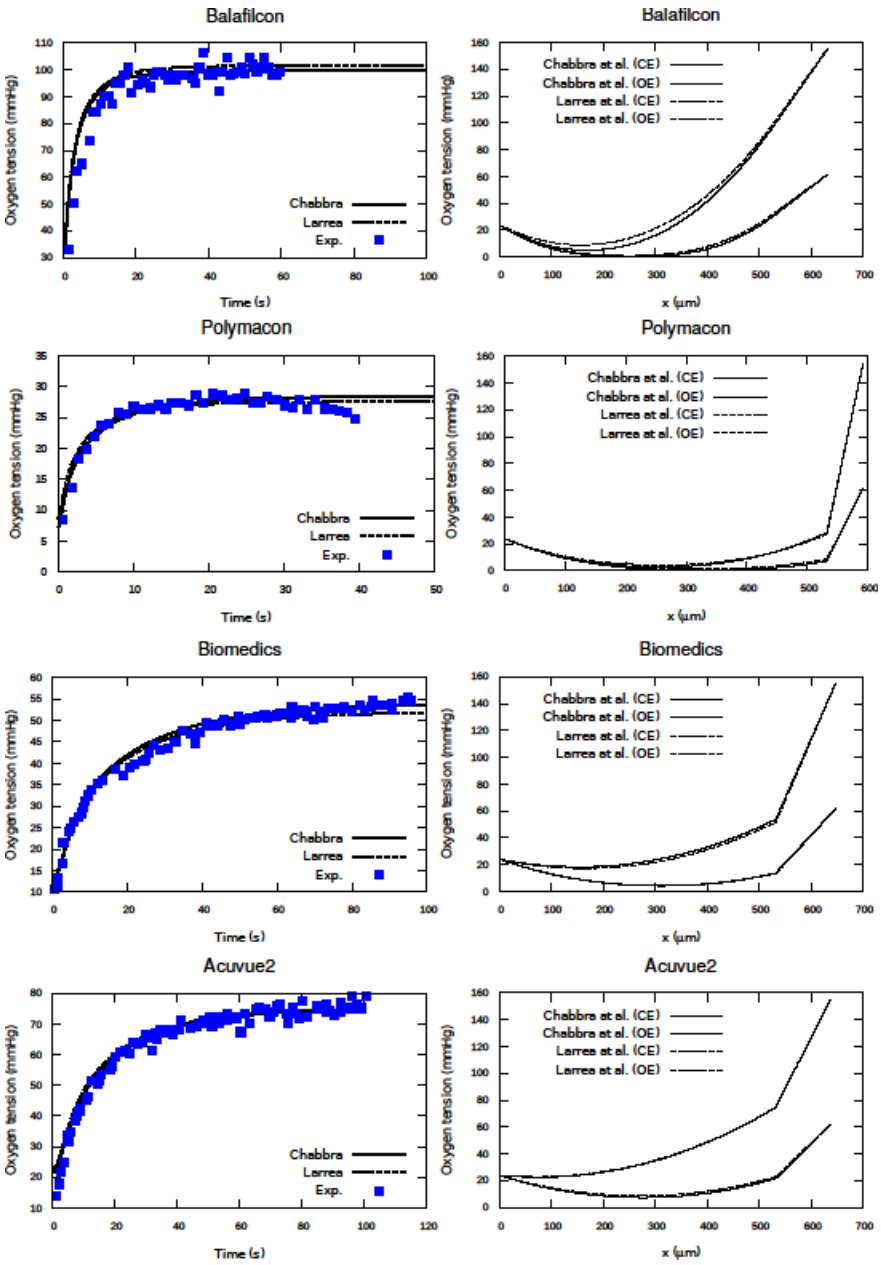

Balafilcon
Oxygen tension (mmHg)
Time (s)
Chabbra
Larrea
Exp.
Balafilcon
Oxygen tension (mmHg)
x (µm)
Chabbra et al. (CE)
Chabbra et al. (OE)
Larrea et al. (CE)
Larrea et al. (OE)
Polymacon
Oxygen tension (mmHg)
Time (s)
Chabbra
Larrea
Exp.
Polymacon
Oxygen tension (mmHg)
x (µm)
Chabbra et al. (CE)
Chabbra et al. (OE)
Larrea et al. (CE)
Larrea et al. (OE)
Biomedics
Oxygen tension (mmHg)
Time (s)
Chabbra
Larrea
Exp.
Biomedics
Oxygen tension (mmHg)
x (µm)
Chabbra et al. (CE)
Chabbra et al. (OE)
Larrea et al. (CE)
Larrea et al. (OE)
Acuvue2
Oxygen tension (mmHg)
Time (s)
Chabbra
Larrea
Exp.
Acuvue2
Oxygen tension (mmHg)
x (µm)
Chabbra et al. (CE)
Chabbra et al. (OE)
Larrea et al. (CE)
Larrea et al. (OE)

Figure 1

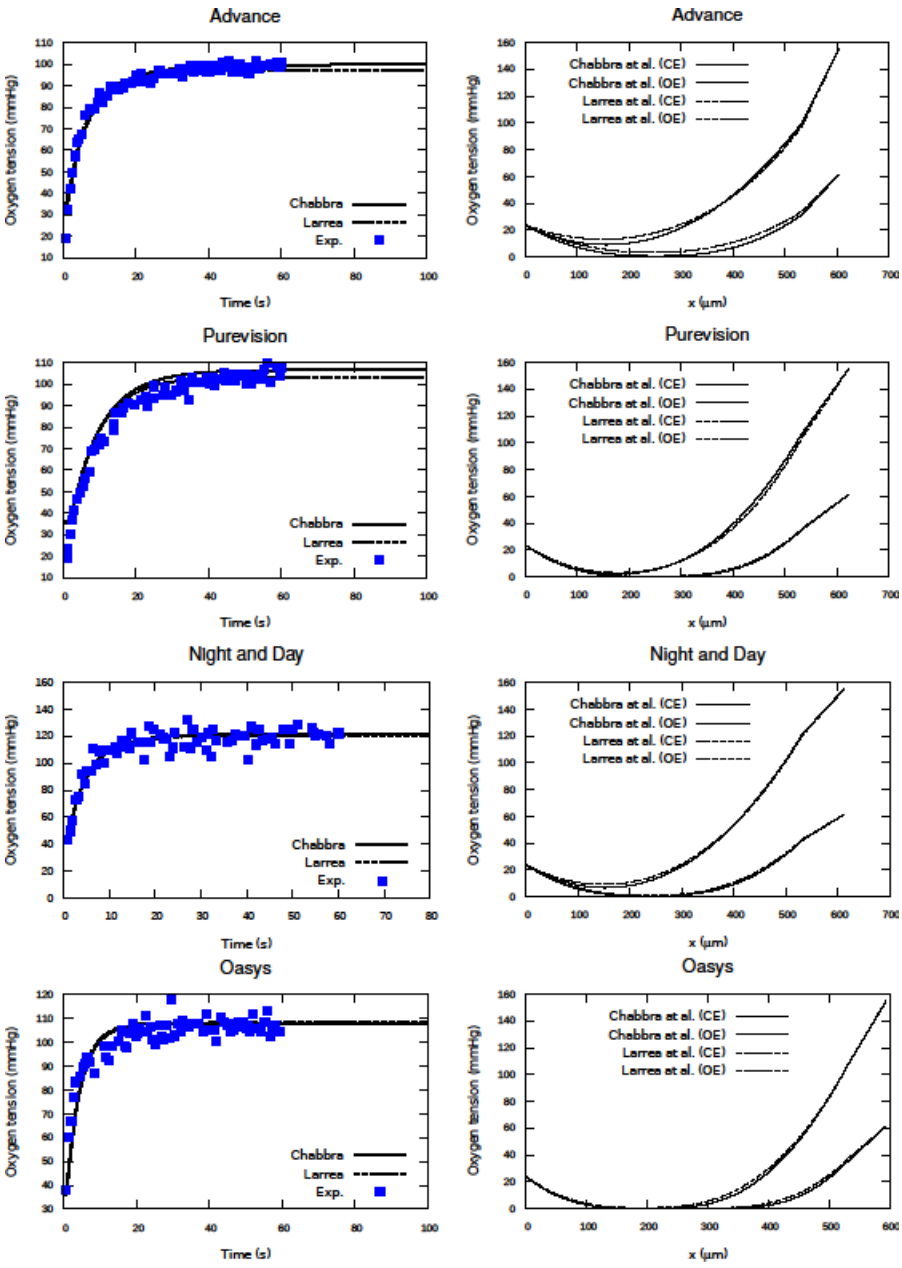

Advance
Oxygen tension (mmHg)
Time (s)
Chabbra
Larrea
Exp.
Advance
Oxygen tension (mmHg)
x (µm)
Chabbra et al. (CE)
Chabbra et al. (OE)
Larrea et al. (CE)
Larrea et al. (OE)
Purevision
Oxygen tension (mmHg)
Time (s)
Chabbra
Larrea
Exp.
Purevision
Oxygen tension (mmHg)
x (µm)
Chabbra et al. (CE)
Chabbra et al. (OE)
Larrea et al. (CE)
Larrea et al. (OE)
Night and Day
Oxygen tension (mmHg)
Time (s)
Chabbra
Larrea
Exp.
Night and Day
Oxygen tension (mmHg)
x (µm)
Chabbra et al. (CE)
Chabbra et al. (OE)
Larrea et al. (CE)
Larrea et al. (OE)
Oasys
Oxygen tension (mmHg)
Time (s)
Chabbra
Larrea
Exp.
Oasys
Oxygen tension (mmHg)
x (µm)
Chabbra et al. (CE)
Chabbra et al. (OE)
Larrea et al. (CE)
Larrea et al. (OE)

Figure 2.

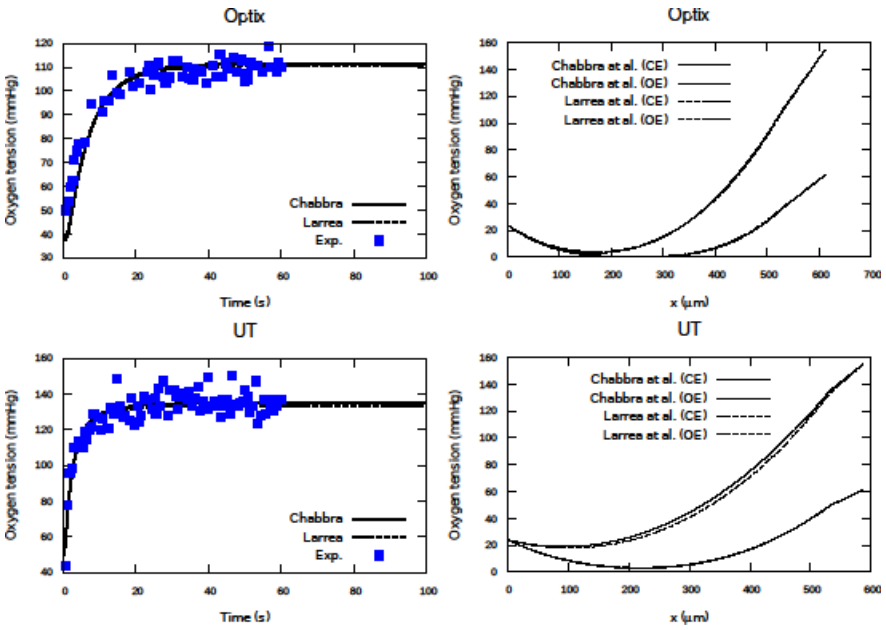


Figure 3.

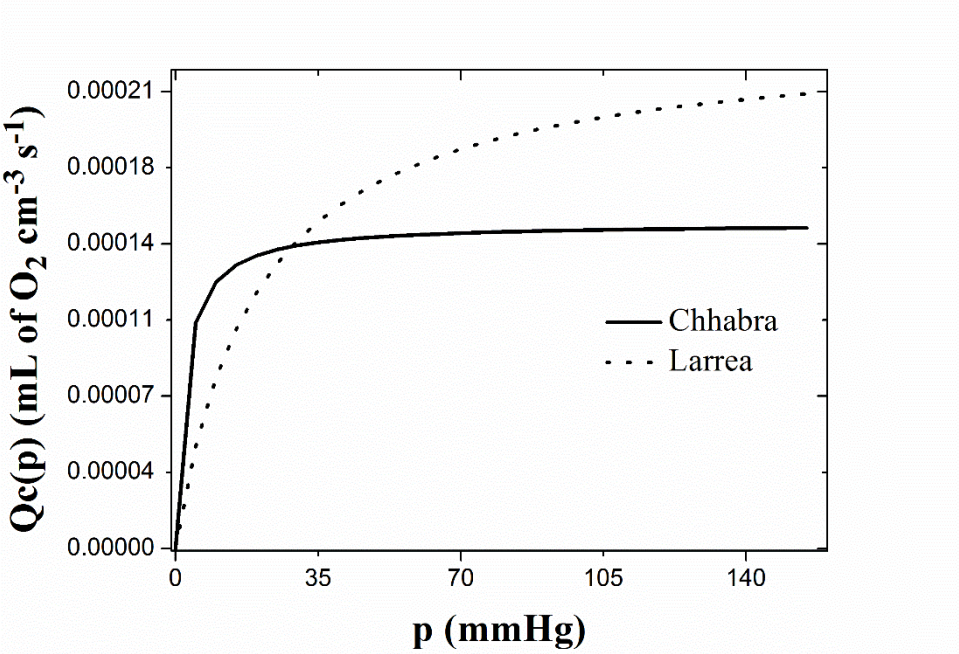


Figure 4.

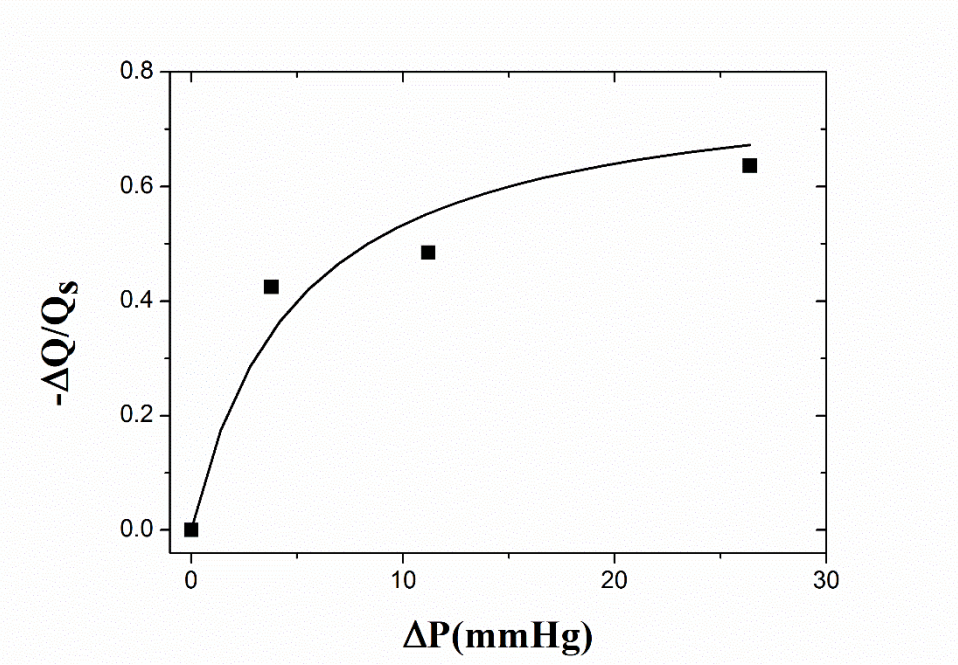


Figure 5.

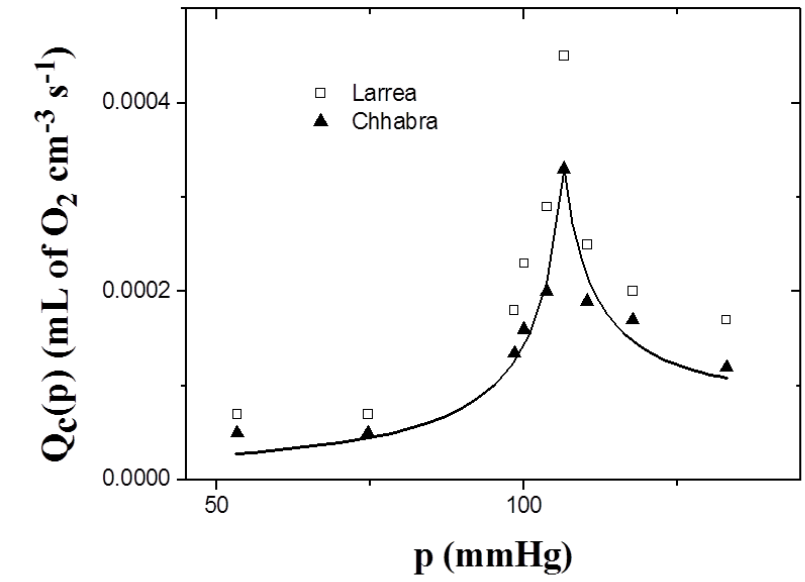
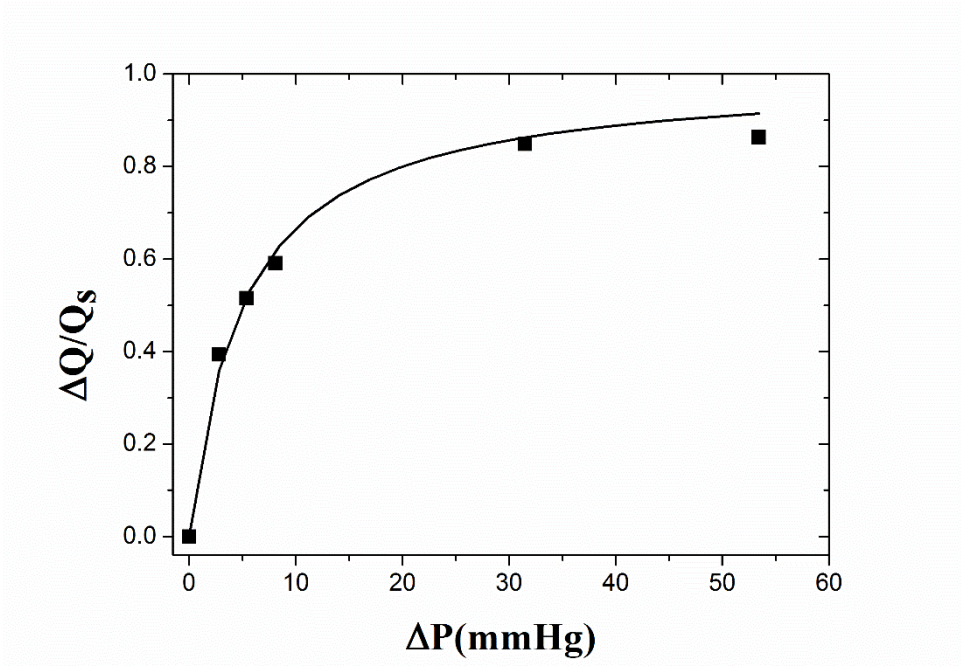


Figure 6.



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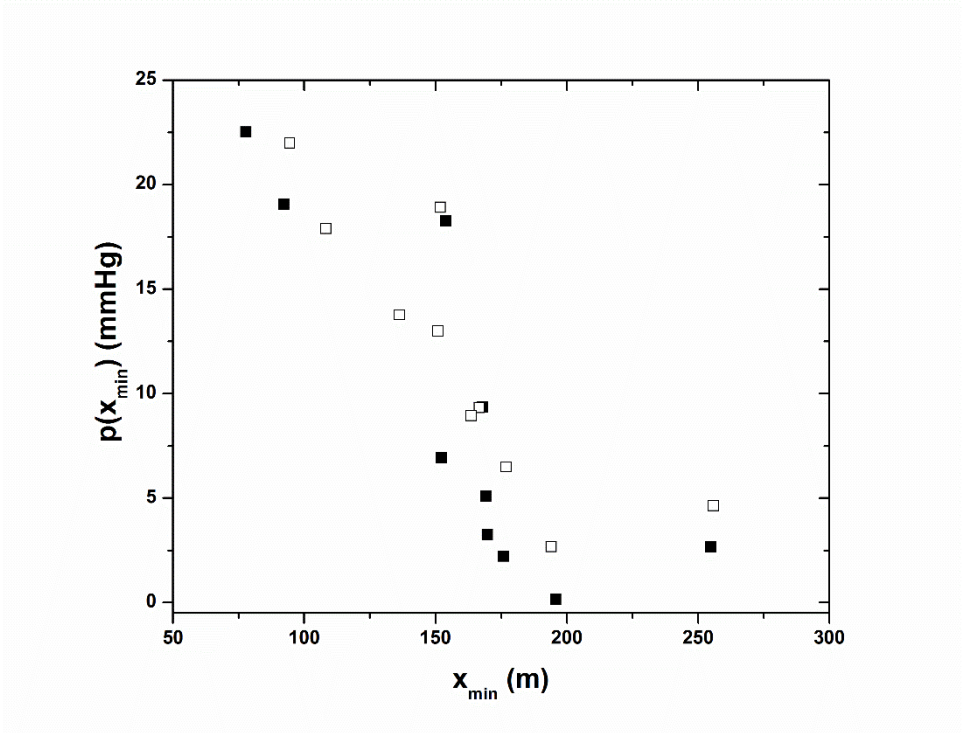

Figure 8.