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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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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. (J Biomed Mater Res B Appl Biomater, 2009a;90:202-209, Optom Vis Sci 2009b; 86:454-466) and Larrea and Büchler (Invest Ophthalmol Vis Sci 2009;50:1076-1080). We use oxygen tension from *in vivo* estimations provided by Bonanno [Bonanno et al., Invest Ophthalmol Vis Sci 2002;43:371-376, and Bonanno *et al* 2009]. 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. That is, when lowering the pressure of oxygen, the parameter $Q_{c,max}$ initially increases depending on the intensity of the change in pressure. Which, it could be related with the variation of the pH. Furthermore, it is also noted that to greater reductions in pressure, this parameter decreases, possibly due to changes in the concentration of glucose related to the anaerobic respiration. The averaged *in vivo* human corneal oxygen consumption rate of 1.47×10^{-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 and Büchler 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 previous models used in this study. © 2016 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 00B: 000–000, 2016.

Key Words: soft contact lenses, Monod kinetics model, oxygen consumption, oxygen tension, cornea

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INTRODUCTION

The cornea is an avascular tissue, which requires oxygen for its normal metabolic function. Oxygen reaches the cornea primarily from atmospheric air and secondarily from the anterior chamber (aquous humor), under open-eye conditions. During the closed-eye situation, oxygen is provided both from exposure to the tarsal 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

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endothelial polymegethism.[3–5] The corneal oxygen-consumption rate (Q_c) has been proposed as a useful parameter 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]

Determination of oxygen consumption rate is therefore a critical parameter and direct index of corneal oxygen metabolism 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] determined 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.

Matemathical models used by some authors to calculate theoretical oxygen consumption rates from measured tear-film oxygen tensions, however, has not been carefully treated. Oxygen consumption 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 considers that the corneal oxygen consumption is function of oxygen partial pressure into the cornea as consequence of aerobic metabolism[18,20,21] It is clear that aerobic metabolism does not ocur at zero oxygen tension and therefore Q_c is zero at 0 p_{O2}. This reaction is limited by the equilibrium concentration of activated complexes formed by reactions between oxygen and the enzymes which act as catalyst at high oxygen pressures; 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[22–25].

Direct measurements of oxygen diffusivity and oxygen consumption in the human cornea either have never been taken into account, or are not available from an experimental point of view. Larrea and Büchler[22], Alvord et al.[23], and Chhabra et al.[24,25] all proposed mathematical models of time-dependent oxygen diffusion based on the nonlinear Monod kinetics model in order to estimate both f 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 here make different assumptions for all parameters to calculate the oxygen diffusivity and consumption rate in the cornea as a function of oxygen tension in the corneal tear film interface.

Del Castillo et al.[26] *recently* 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 when several contact lenses of different oxygen transmissibility are worn[13] reaching higher levels than those expected based on previous *in vitro* corneal measurements[12].

We here proceeded with the analysis of the oxygen consumption using the metabolic models of Chhabra et al.[24] and Larrea and Büchler[22], 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 fitted both models to 10 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 the first place, we have selected these two models with the same features they related to the increase of the rate of oxygen consumption with the increase in tension, without any weighting. Then, we discarded the model proposed by Alvord et al.[23], which includes an inflection point around the pressure of 40 mmHg, which could modify in any way the conclusions obtained in the first cases. In these terms, the analysis of data provided by Bonanno et al.[12,13] using the model of Alvord et al.[23] is for a next task.

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 these models, the oxygen pressure profile into the cornea has been calculated for both OE and CE conditions. Our study provides a generalized Monod kinetics model to describe the human corneal oxygen-consumption rate during soft contact lens wear. From generalized model, we predict the evidence of two different processes for the corneal oxygen consumption requirements which clearly modify the dependence of $Q_{c,max}$ with the oxygen tension in the cornea. We show that coupling oxygen tension with other reactive species in corneal metabolism modifies the Monod kinetic model, as it was proposed by Chhabra et al.[25] 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

TABLE I. Lens Parameters[a,b]

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

[a] 1 Barrer = 10^{-11} (cm^2/s)(mL STp O_2/(ml.mmHg)), or 1 Fatt Dk units.
[b] 1 Barrer/cm = 10^{-9} (cm/s)(mL STp O_2/(ml.mmHg)), or 1 Fatt Dk/t units.

partial pressure of oxygen available at different depths into the corneal tissue is presented and discussed.

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 CE and OE 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[12,22,24] 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.[24]and Larrea and Büchler[22] 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 article, following a similar procedure to that used by Chhabra et al.[24], 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 4 Hyl and 6 Si-Hyl lenses ($Dk/t = 8.4$–255 Barrer/cm) on in-vivo human corneas. Parameters of thickness, permeabilities and transmissibilities are all shown in Table I.

The technical procedure followed to solve the partial differential equation (PDE) used FiPy, a finite volume PDE solver written in Python has been previously reported[26]. Table I shows the different values for the parameters used in the numerical solution of the equations.

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[26]

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

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 (cm^2/sec), k is the oxygen solubility coefficient in the corneal tissue, that is, Henry's law constant (cm^3 of O_2/cm^3 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/cm^3 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

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

with Dirichlet boundary conditions

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

where x_c is the corneal thickness, that is, 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_{tean}, 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.[24,27,28] In the succeeding sections, we will describe the models of Q_c used.

Description of the models

Several models have been proposed to describe the variation in corneal oxygen consumption with pressure $Q_c(p_c)$, starting with the case of constant Q_c given by the quadratic model[1,2], sigmoidal and linear oxygen consumption functions[23], followed by the Chhabra et al.[24] and Larrea and Büchler[22] models, where the oxygen consumption rate is derived from reaction kinetics as a function of the oxygen tension such as has been described in biological systems. In next subsections, Monod kinetics and Larrea models will be discussed in detail.

Monod kinetics model. The most used model which characterizes and quantifies the aerobic metabolism is the Monod kinetics model,[24] also known as Michaelis Menton model[29]. 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 relates the oxygen consumption with oxygen tension by means of the expression

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

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 $Q_{c,max}$, achieved when oxygen partial pressure is $p_{xc} = 155$ mmHg at the corneal tear interface under open-eye condition. This value represents the oxygen tension when corneal aerobic metabolism reaches its maximum oxygen consumption (that is, 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 into an oxygen consumption independent of partial pressure. As observed,[26] 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.[23] 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 $Q_{c,max} = 2.2 \times 10^{-4}$ 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.[24] established 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,[26] and calculated the spatial-averaged *in vivo* human maximum corneal oxygen consumption rate as 1.05×10^{-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] ($Q_{c,max} = 4.48 \times 10^{-5}$ $mL{\cdot}cm^{-3}{\cdot}s^{-1}$), and 1.8 times higher than the value reported by Larrea and Büchler[22], ($Q_{c,max} = 5.75 \times 10^{-5}$ $mL{\cdot}cm^{-3}{\cdot}s^{-1}$). We are concerned that Chhabra et al.[23] results rely on only two values for 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.[26] where the parameters considered in the models are given in Table II. 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)[30]. The "fmin_tnc" function in the Scipy package (http://www.scipy.org/) was used to multidimensional parameter optimization subject to bounds. We thereby were able to determine optimized values of the Q_{max} and K_m parameters for a predefined set of the remaining model parameters.

Monod kinetics model of Larrea and Büchler. Larrea and Büchler[22] 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:

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

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 $p_c(x)$. Larrea and Büchler[22] assumed that the cornea was divided into three layers, that is, epithelium, stroma, and endothelium, to solve Eq. (1). 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

TABLE II. 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	T_{en}	1.5	μm
Water Permeability	Dk_{water}	99	Fatt units

[a]Dk units (barrer) = 10^{-11} (cm^2/sec)[ml O_2· ml^{-1}·$mmHg^{-1}$)] or Fatt units.)
[b]Dk/t_{av} units (barrers/cm) = 10^{-09} (cm ml O_2)/(ml sec mmHg)
[c]$D_c = 3.0 \times 10^{-5}$ cm^2/s.
[d]$k_c = 3.1 \times 10^{-5}$ cm^3 of O_2(sTP)/cm^3 of tissue/mmHg
[e]Corneal oxygen diffusion coefficient, $D_w = 3 \times 10^{-5}$ cm^2/s
[f]Corneal oxygen solubility, $k_w = 3.3 \times 10^{-5}$ cm^3 of O_2(sTP)/cm^3 of tissue/mmHg

$Q_{stroma} = 5.75 \times 10^{-5}$ cm^3 of O_2 cm^{-3} s^{-1} are according to Fatt[1,10] and Fatt and Bieber[19]. Larrea and Büchler[22] 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, that is, the expression of the model of Larrea and Büchler[22] is similar to the Chhabra et al.[24] 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.[24]model; and $Q^* = Q_{stroma} = 5.75 \times 10^{-5}$ cm^3 of O_2 cm^{-3} s^{-1} instead of the values observed by Chhabra et al.[24] for the Polymacon and Balafilcon lenses (0.9×10^{-4} and 1.2×10^{-4} cm^3 of O_2 cm^{-3} s^{-1}, respectively).

TABLE III. 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 10 hydrogel 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, that is, 2.2 and 20 mmHg, respectively.

	Model *Chhabra et al.*		Model *Larrea and Büchler*	
Lens	$Q_{c,max,}$	P_{est} (mmHg)	$Q_{c,max,}$	P_{est} (mmHg)
Polymacon	0.9×10^{-4}	28.1	5.5×10^{-5}	27.9
Balafilcon	1.6×10^{-4}	101.1	8×10^{-5}	101.5
Biomedics	5×10^{-5}	53.1	3×10^{-5}	53.0
Acuvue2	5×10^{-5}	75.0	3.5×10^{-5}	73.0
Advance	1.35×10^{-4}	98.4	7×10^{-5}	97.8
Purevision	2.0×10^{-4}	103.7	1.0×10^{-4}	103.0
Optix	1.9×10^{-4}	110.3	9×10^{-5}	110.0
Oasys	3.3×10^{-4}	106.5	4.4×10^{-4}	106.0
N&D	1.7×10^{-4}	117.7	2×10^{-4}	118.5
N&D UT	1.2×10^{-4}	132.9	1.7×10^{-4}	132.0

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 II. 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 $D_c = 30 \times 10^{-6} cm^2/s$; $k_c = 3.1 \times 10^{-5} cm^3$ of O_2/cm^3 tissue/mmHg, in water solution at 25°C, respectively.[31] On the other hand, by using the transient diffusion model used by Larrea and Büchler[22] our calculations also yield the $Q_{c,max}$ values gathered in Table III.

We plot the fitting curves of these two models for the 10 contact lenses in Figures 1–3: (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 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 1–3 (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 35°C, using the diffusion models of Chhabra et al.[24] and Larrea and Büchler[22], respectively. The values found for the oxygen tension at the stationary state are shown in Table III. In the same figures, the right plot corresponds to the steady-state oxygen tension profile through corneal thickness, (OE mean open-eye condition, and CE means closed-eye conditions) where the boundary condition for the tension at the contact-lens-palpebral conjunctiva interface considered is 61.5 mmHg.

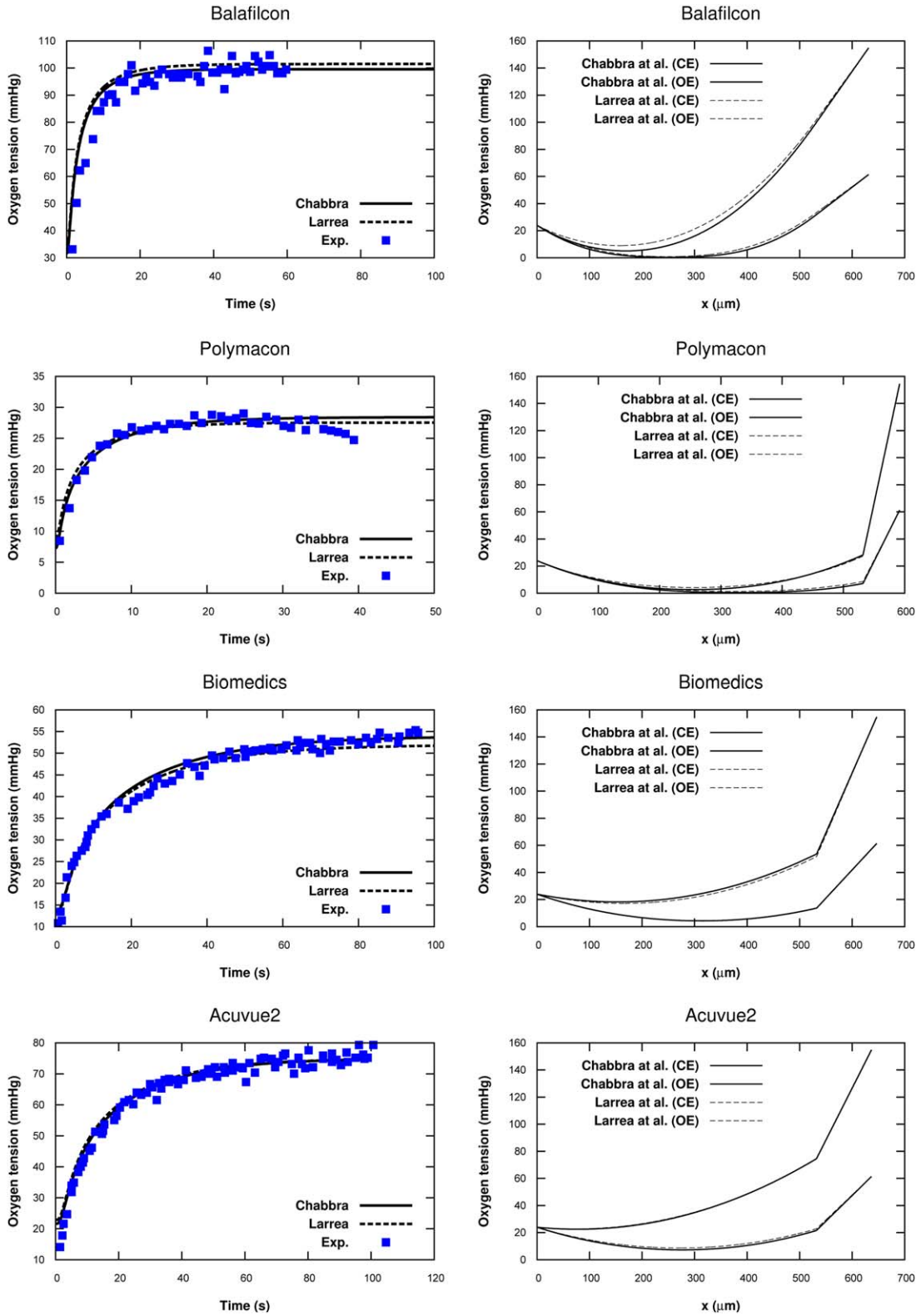

FIGURE 1. (Left) Results representative for the tear-film oxygen tension after 5 min of CE lens wear for Balafilcon, Polymacon, Biomedics and Acuvue2, lenses, respectively. Data provided from Bonanno et al.[12,13]. (Right) The steady state oxygen tension profile through cornea thickness, for the same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

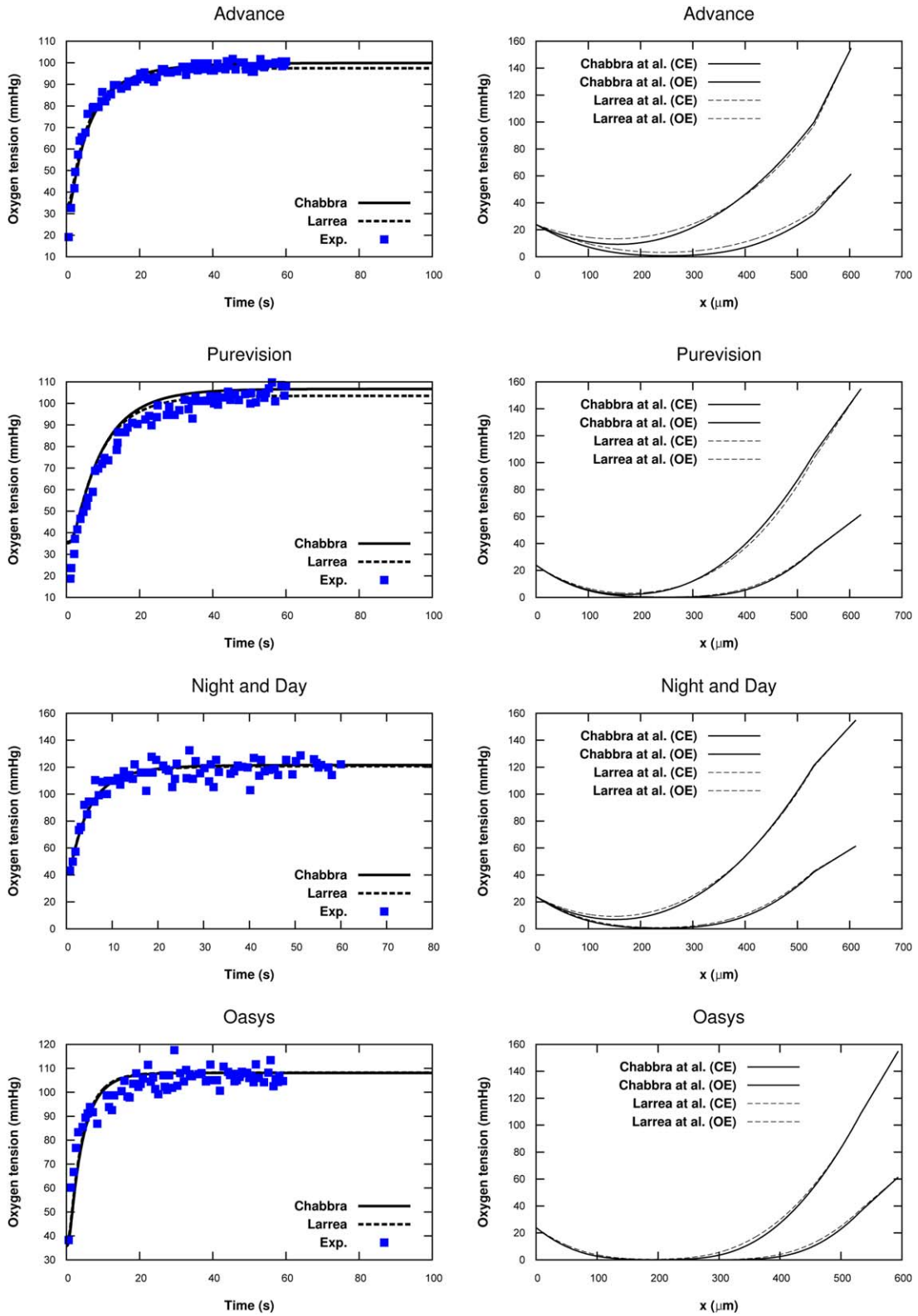

FIGURE 2. (Left). Results representative for the tear-film oxygen tension after 5 min of CE lens wear for Advance, PureVision, Night & Day and Oasys lenses. Data provided from Bonanno et al.[12,13]. (Right) The steady state oxygen tension profile through cornea thickness, for the same lenses, respectively.

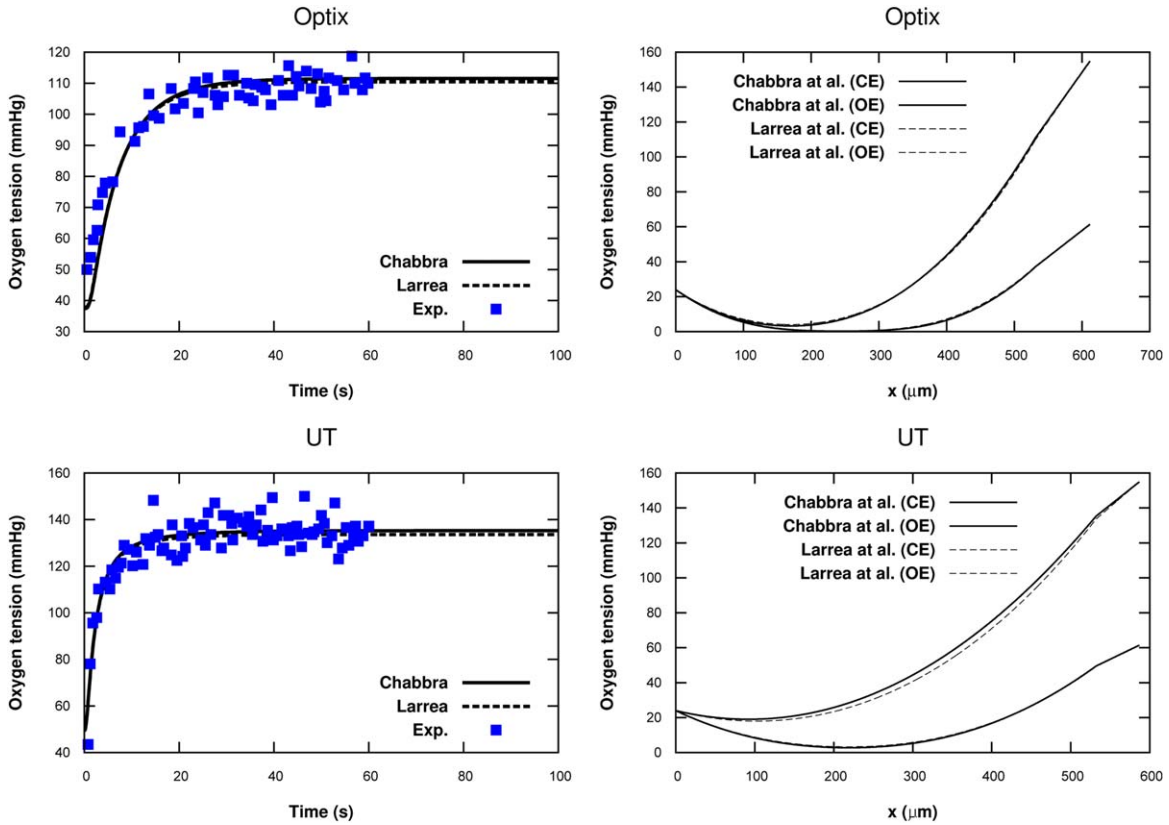

FIGURE 3. (Left). Results representative for the tear-film oxygen tension after 5 min of CE lens wear for Optix and N&D UT lenses. Data provided from Bonanno et al.[12,13]. (Right) The steady state oxygen tension profile through cornea thickness, for the same lenses, respectively.

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.[32,33]

Figures 1–3 show that the values of the parameters presented in Table III 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 OE- and CE 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 Figures 1–3 and the data presented in Table III, oxygen consumption rate values are seen to differ from those provided by both Chhabra et al.[24] and Larrea and Büchler[22] models where $K_m = 2.2$ mmHg was considered constant for all the fits of Chhabra et al.[24], and $a = 20$ mmHg in case of Larrea and Büchler[22]

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.[26] 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 of Chhabra et al. is 1.50×10^{-4} cm^3 of O_2/cm^3 tissue s, while in the case of Larrea and Büchler the value obtained is 2.09×10^{-4} cm^3 of O_2/cm^3 tissue s.

In Figure 4, we plot the variation in average oxygen consumption rate with corneal which should be observed according the expressions of Larrea and Büchler[22] model described by the Eqs. (6) or (7) and Chhabra et al.[24] Monod kinetic model by means of Eq. (5). Notice that the averaged oxygen consumption rate is obtained according the fitting of each model to the experimental data of Bonanno et al.[12,13]

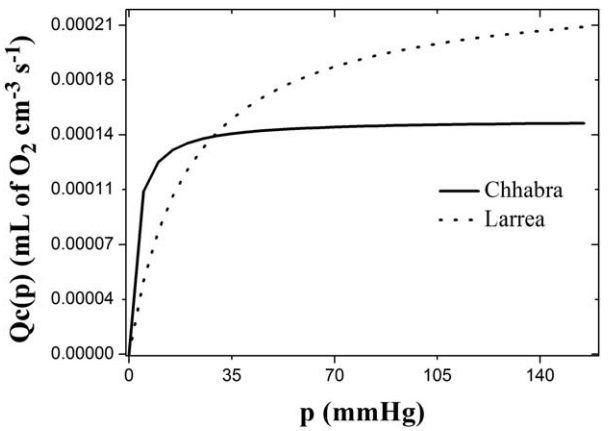

FIGURE 4. Average oxygen consumption rate versus oxygen pressure in the cornea (a) Chhabra et al.[24], (b) Larrea et al.[22]. model.

Its values are given for all the lenses considered in this study in Table III.

The metabolic model (with the parameters given in Table III) 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. We found, however, that consumption varies from one lens to another. For example, for the N&D lenses, the consumption was 1.79×10^{-4} cm^3 of O_2/cm^3 tissue s, which was higher than that for the UT lens where this consumption was 1.29×10^{-4} cm^3 of O_2/cm^3 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 finding that contact lenses which produce low oxygen tension in the post-lens tear film interface produce low oxygen consumption rates in the cornea is quite relevant. For example, in the case of Balafilcon lens, the oxygen consumption at 99 mmHg was about 1.7×10^{-4} cm^3 of O_2/cm^3 tissue s, quite similar to the value obtained by Bonanno et al. (c.a. 1.6×10^{-4} cm^3 of O_2/cm^3tissue 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.[24] 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), 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 7.54×10^{-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 Monod kinetics Model is about 7.0×10^{-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 1.5×10^{-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 2.07×10^{-4} cm^3 of O_2/cm^3 tissue s, obtained considering the Eq. (7) of Larrea and Büchler and both of them are higher than the value 4.85×10^{-5} cm^3 of O_2/cm^3 tissue s, obtained *in vivo* for humans by Harvitt and Bonanno[4,5] and Weissman[34], considering a constant oxygen consumption rate. On the other hand, the value of 1.5×10^{-4} cm^3 of O_2/cm^3 tissue s is higher than the oxygen consumption rate value (6.49×10^{-5} cm^3 of O_2/cm^3 tissue s) obtained previously[22]. 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 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 comments above, a similar behavior in both the Chhabra et al.[24] and Larrea and Büchler[22] models. 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.

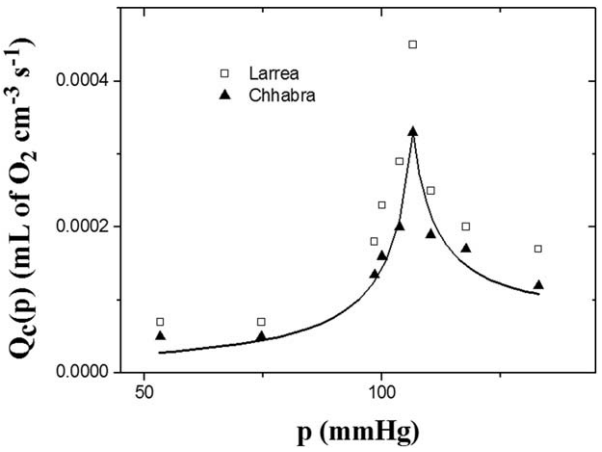

FIGURE 5. Variation of oxygen consumption rate versus oxygen tension at the interface cornea-tears film, obtained for all the lenses studied following the expressions of Chhabra et al.[23] and Larrea et al.[21] used for the models. The solid continuous line shows the fitting to the prediction data using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

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 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 lambda-like, similar to that which appears when matter exists as 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:

$$-\frac{\Delta Q}{Q_S} = \frac{\Phi}{Q_S}\left[\frac{\Delta p}{K_m + \Delta p}\right] \tag{8}$$

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

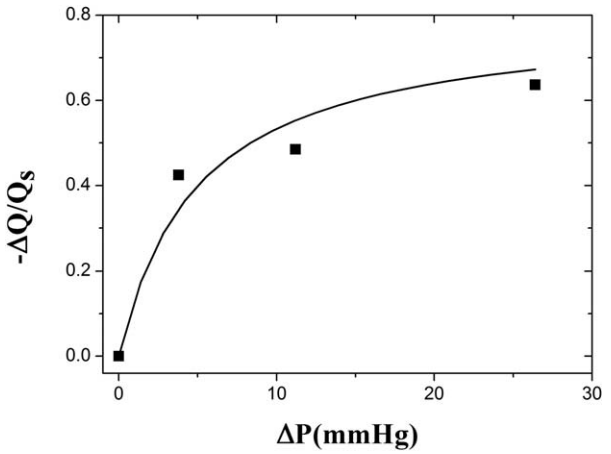

FIGURE 6. Plot of $\frac{-\Delta Q}{Q_s}$ versus Δp from Eq. (8), and considering pressures above p_s, with Q_s=3.30 × 10^{-4} cm^3 of O_2/cm^3 tissue s, P_S=106.5 mmHg, Km=5.0 and $\frac{\Phi}{Qs}$=0.8.

Equation (8) can be rewritten considering the expressions $\Delta p = a(7.6 - pH)$ and $K_{pH} = \frac{K_m}{a}$. According to Leung et al.[33], for $K_{pH} = 0.1$ the estimation of the parameter a = 50 mmHg is satisfied. Therefore, we get

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

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.

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,

$$\frac{\Delta Q}{Q_S} = \frac{\Delta p}{K_0 + \Delta p} \tag{10}$$

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 $K_G = \frac{K_0}{b}$, where C_G is the lactic acid concentration[33], and b is estimated as b = 12.2 nM from the value of K_G = 0.4 mM, such as expressed in Eq.(11)

$$\frac{\Delta Q}{Q_S} = \frac{C_G}{K_G + C_G} \tag{11}$$

that can be also expressed as

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

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[34] has estimated the *in vivo* human corneal oxygen consumption as $Q_c = 4.85 \times 10^{-5}$ 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[25,33]. 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,[3,35,36] which may be described as a nonlinear function of the pressure.[11,33,37] As we have suggested above, we believe that 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 Eqs. (9) and (12)].

This assumption is based on different clinical studies. For example Holden and Mertz's[32] showed that corneal swelling versus oxygen flux presents a nearly linear change when a contact lens is worn. On the other hand, Bonano and Polse[6,7] and Giasson and Bonanno[21,39] observed that Hy 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 Figure 5, therefore, could be explained in biochemical terms. Finally, the low pressure region of Figure 5 could also be explained by following Frahm et al.[40], in which it is notorious that the oxygen consumption falls as concentration of glucose

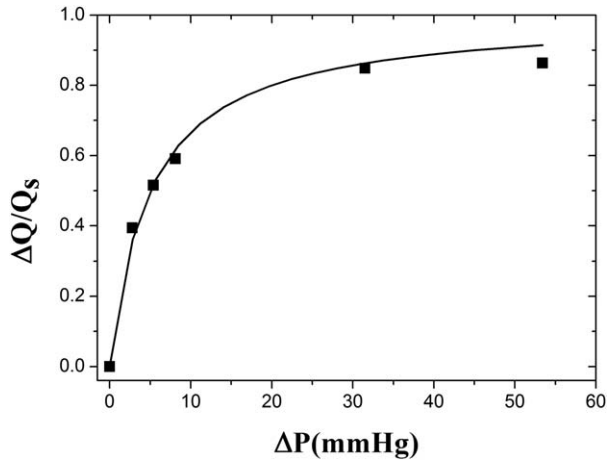

FIGURE 7. Plot of $\frac{\Delta Q}{Q_s}$ versus Δp from Eq. (11), and considering pressures below p_s, with Q_s=3.30 × 10^{-4} cm^3 of O_2/cm^3 tissue s, P_S= 106.5 mmHg and K_0=5.0 mmHg.

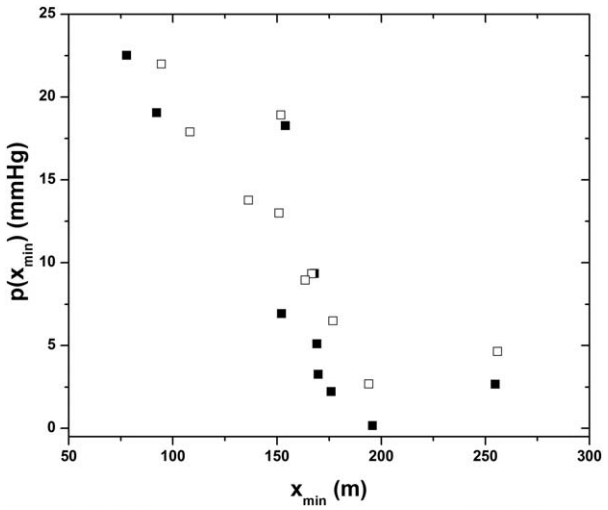

FIGURE 8. Values of the oxygen pressure at the minimum versus of the distance from the endothelium. The black squares correspond to Monod kinetic model with $K_m = 2.2$ mmHg and white squares to Larrea and Büchler model. Each point in this plot corresponds to different oxygen partial pressures at the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

decreases because of respiration. Only excess glucose is independent of glucose concentration in respiration. 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 balance in oxygen flux from the anterior and posterior corneal surfaces. 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 few years[3–20,38,41]. Polse and Mandell[42] initially found human corneal swelling below a cornea-tear interface oxygen tension of 11–19 mmHg, but this "critical oxygen tension" was later raised to 70–125 mmHg by other authors[27,43,44], based on their estimations on the analysis of the of the biological oxygen apparent transmissibility (BOAT)[43,44], and the critical oxygen tension (COT)[27].

Furthermore, the situations and conditions under which the cornea experiences oxygen deprivation, and corneal edema begins, can be related with contact lens oxygen transmissibility Hideji et al.[45] obtained an excellent correlation between the percentage corneal swelling with contact lens transmissibility in rabbit corneas, concluding that the largest useful Dk/L total for a rigid contact lens may be 56 hBarrer/cm. Chhabra et al.[25] proposed an oxygen deficiency factor (ODF) as a new index of corneal oxygen consumption to permit measurement of the extent and severity of corneal hypoxia. The determination of this parameter allows another metric for comparison between different contact lenses.

Figure 8 shows oxygen tension in each minimum with the position in respect to the aqueous humor, where the oxygen fluxes are balanced. 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 to a kinetic transition that can be understood not only as a result of the metabolic reactions that occur in the Krebs cycle, but also of the reactions observed in the cornea.

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[46].

The determination of this position provides information on oxygen partial pressure distribution 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 lens, we illustrate a combined cornea-contact lens system in cross-section, to 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[38,41]. Table IV shows the

TABLE IV. 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

	Chhabra et al.		Larrea and Büchler	
Lens	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

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[47,48].

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[25] allows a comparison between different contact lenses. This treatment will be the object of future work.

CONCLUSIONS

The application of the Monod kinetics model following the expression given by Chhabra et al.[24] and Larrea and Büchler[22] 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 calculate corneal oxygen consumption rate values with no aphysical oxygen tension predictions into the cornea. This has been achieved in Monod kinetics model while maintaining corneal oxygen permeability practically equal to water oxygen permeability (i.e., 93 barrers).

We have observed in both used models that the maximum corneal oxygen-consumption rate $Q_{c,max}$ is constant independently of the oxygen tension p_c at cornea-post lens tears interface. However, from our analysis of experimental data of Bonano at al.[12,13], we found that when the oxygen partial pressure decreases, there is an increase in $Q_{c,max}$ until a maximum is reached near *105 mmHg* oxygen tension, then a decrease in $Q_{c,max}$ for lower levels of oxygen pressure is observed. These variations 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, allowing a modification of $Q_{c,max}$. In fact, from the analysis of experimental data, we can see that there are two processes that do not occur simultaneously, but separately. That is, when pressure decreases the corneal oxygen consumption rate increases with the acidosis and this is followed by an anaerobic transition with a decrease of Q_c. The change in the participation of both processes seems to be abrupt, producing a singularity in the dependence of oxygen consumption relative to the pressure of oxygen in the cornea, as shown in Figure 5. For oxygen tension p_c at cornea-post lens tears interface between 105 and 130 mmHg, the used equation for $Q_{c,max}$ was the monod pH dependence,[33] namely

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

In this relation, the parameters were specified in Eq. (9).

However, for oxygen tension p_c between 30 and 105 mmHg the equation for $Q_{c,max}$ was the monod glucose dependence[4,24,25], namely

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

In this relation, the parameters were specified in Eq. (12).

Finally, from the pressure profile, the position of the minimum value of O_2 was obtained, and it was observed to be in the first part of the stroma for all studied lens.

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