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Authors

Kim, Young Hyun
Lin, Meng C
Radke, Clayton J

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Central-to-peripheral corneal edema during wear of embedded-component contact lenses

Young Hyun Kim [a,b,c], Meng C. Lin [a,c], Clayton J. Radke [a,b,*]

[a] Vision Science Group, University of California, Berkeley, CA, 94720, United States
[b] Chemical and Biomolecular Engineering Department, University of California, Berkeley, CA, 94720, United States
[c] Clinical Research Center, School of Optometry, University of California, Berkeley, CA, 94720, United States

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ABSTRACT

Purpose: With active investigation underway for embedded-circuit contact lenses, safe oxygen supply of these novel lenses remains a question. Central-to-peripheral corneal edema for healthy eyes during wear of soft contact (SCL) and scleral lenses (SL) with embedding components is assessed.

Methods: Various 2-dimensional (2D) designs of SL and SCL with embedded components are constructed on Comsol Multiphysics 5.5. Local corneal swelling associated with the designed lenses is determined by a recently developed 2D metabolic-swelling model. Settled central post-lens tear-film thicknesses (PoLTFs) are set at 400 μm and 3 μm for SL and SCL designs, respectively. Each lens design has an axisymmetric central and an axisymmetric peripheral embedment. Oxygen permeability (*Dk*) of the lens and the embedments ranges from 0 to 200 Barrer. Dimensions and location of the embedments are varied to assess optimal-design configurations to minimize central-to-peripheral corneal edema.

Results: By adjusting oxygen *Dk* of the central embedment, the peripheral embedment, or the lens matrix polymer, corneal swelling is reduced by up to 2.5 %, 1.5 %, or 1.4 % of the baseline corneal thickness, respectively, while keeping all other parameters constant. A decrease in PoLTF thickness from 400 μm to 3 μm decreases corneal edema by up to 1.8 % of the baseline corneal thickness. Shifting the peripheral embedment farther out towards the periphery and towards the anterior lens surface reduces peak edema by up to 1.3 % and 0.6 % of the baseline corneal thickness, respectively.

Conclusions: To minimize central-to-peripheral corneal edema, embedments should be placed anteriorly and far into the periphery to allow maximal limbal metabolic support and oxygen transport in the polar direction (i.e., the θ-direction in spherical coordinates). High-oxygen transmissibility for all components and thinner PoLTF thickness are recommended to minimize corneal edema. Depending on design specifications, less than 1 % swelling over the entire cornea is achievable even with oxygen-impermeable embedments.

1. Introduction

With the advance of micro-technology, the feasibility of fabricating embedded-circuit contact lenses is under active study to improve visual acuity, display augmented reality, or monitor health [1–14]. However, introduction of various embedments within a contact lens introduces potential risk to ocular health as semiconductor-based embedments typically have low permeability to oxygen [7]. Because the cornea is oxygenated predominately by the environment, localized oxygen impediment from the embedments may lead to significant localized corneal hypoxia. Corneal hypoxia, in turn, induces swelling of the stroma due to increased anaerobic metabolism and to changes in metabolic concentrations at the endothelium that regulate water flux into/out of the cornea [15].

Contact lenses made with oxygen-impermeable materials, such as polymethyl methacrylate (PMMA), cause significant corneal edema that adversely affects cornea health [16]. Corneal striae appear when swelling approaches 6–8 % [17]. Cornea clouding is subjectively visible when the cornea swells by more than 5 % due to increased light scattering within the stroma [18]. Moreover, chronic corneal hypoxia induced by 20 years of continuous PMMA contact-lens wear leads to endothelial polymegathism and potentially results in a decline of the

* Corresponding author at: Department of Chemical and Biomolecular Engineering, University of California, 101E Gilman Hall, Berkeley, CA 94720, United States.
E-mail address: radke@berkeley.edu (C.J. Radke).

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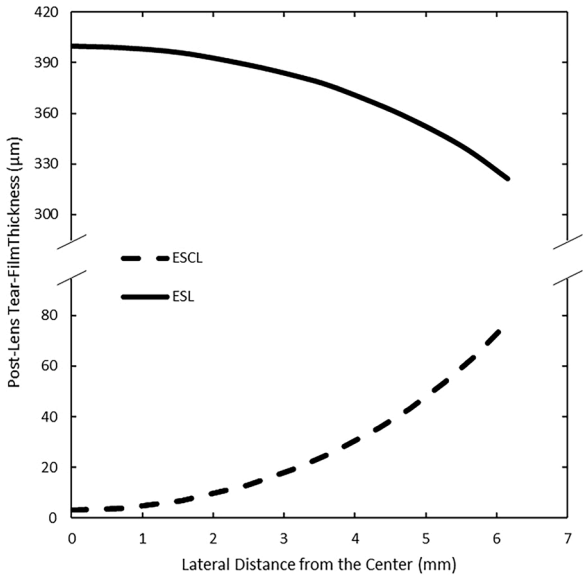

Fig. 1. Radial post-lens tear-film thickness profiles for the soft-contact-lens (ESCL) and scleral -lens (ESL) designs with embedments. Horizontal axis is the lateral distance from the central cornea to the peripheral cornea with the reference point (horizontal axis = 0) being the central cornea at the anterior epithelial surface. Vertical axis is the post-lens tear-film thickness.

cornea's ability to deswell [19]. These clinical risks motivated the development of oxygen-permeable lens materials such as silicone hydrogels and acrylates to minimize corneal hypoxia during contact-lens wear [20–25].

Two prominent methods are available to assess corneal hypoxia. The first is to measure central corneal edema clinically with, for example, ocular coherence tomography (OCT) or ultrasound pachymetry [26,27]. Unfortunately, due to the uncertainty of non-central corneal measurements [28], most clinical measurement of edema is performed centrally. This restriction limits measurement of local differences in corneal edema during the wear of contact lenses with circuit embedments. The second assessment method is to model mathematically the oxygen flux through the lens to interrogate oxygen tension across the cornea with various types of lens wear [25,29,30]. However, knowledge of oxygen tension alone does not allow determination of corneal swelling.

To provide direct comparison between mathematical and clinical analyses, Leung et al. [15] utilized metabolic kinetics [31] and the hydration pump-leak mechanism of Maurice [32] to determine central corneal swelling associated with different hypoxic conditions caused by various types of soft-contact-lens (SCL) wear. Recently Kim et al. [33] expanded this work to 2 dimensions (2D) to determine central-to-peripheral corneal swelling for SCL and scleral-lens (SL) wear. The metabolic-mathematical model revealed that limbal metabolic support significantly reduces mid-peripheral and peripheral corneal swelling. Further, the metabolic model disclosed that corneal efflux of lactate into the limbus and influx of limbus bicarbonate ions into the cornea are the primary contributors to reducing corneal edema at the mid-peripheral and peripheral regions of the cornea [33]. Surprisingly, supply of oxygen from the limbus had a marginal effect on reducing corneal edema everywhere [33].

The previously developed metabolic model of Kim et al. [33] is expanded here to assess the hypoxic safety of embedded-component contact lenses for various designs and parameters by quantifying central-to-peripheral corneal edema associated with lens wear. Embedded-component contact lenses can utilize various lens-encasement platforms. Here, iterations of one SCL and one SL design are evaluated that are common for commercial contact lenses of today.

Table 1
Lens Design Parameters.

Lens – Encasement Anterior Curvature	8.4 μm
Lens – Encasement Posterior Curvature	8.0 μm
Start of the Encasement Landing Zone	6.2 mm
Central – Embedment Anterior Curvature	8.25 mm
Central – Embedment Posterior Curvature	8.15 mm
Central – Embedment Lateral Length from the Central Cornea[a]	3.5 mm
Peripheral – Embedment Anterior Curvature	8.25 mm
Peripheral – Embedment Posterior Curvature	8.15 mm
Peripheral – Embedment Lateral Starting Point from the Central Cornea[a]	4.5 mm
Peripheral – Embedment Lateral Ending Point from the Central Cornea[a]	5.5 mm

[a] Central cornea is located at horizontal axis = 0 in Fig. 4.

2. Methods

2.1. Lens design

Details of the corneo-scleral anatomy are provided in Kim et al. [33]. SL and SCL with embedments are referred to as ESL and ESCL, respectively. Also, contact-lens matrix that encapsulates the embedments is defined as a lens encasement or simply an "encasement". Geometric design, metabolic species transport, and swelling calculations are computed using the COMSOL Multiphysics 5.5 platform (Comsol Inc, Burlington, MA, USA). Because commercially available SCLs are too thin to allow embedments [1], ESCL-encasement thickness (radial) is set at 400 μm. For direct comparison, the ESL-encasement thickness (radial) is also 400 μm. Therefore, the only hypoxia-relevant difference between the ESCL and ESL designs is the post-lens tear-film (PoLTF) thickness profile illustrated in Fig. 1. Lens landing zones, which have no effect on corneal edema [33], touch 8 mm laterally away from the central cornea. Because the curvature radii of the cornea (anterior curvature of 7.8 mm [33]) and the lenses are constant (see Table 1), prescription of the central PoLTF thickness results in a nonuniform central-to-peripheral PoLTF thickness profile. Accordingly, the non-central PoLTF thickness is larger with the ESCL design in Fig. 1 than what is typically seen clinically with commercially available SCLs. Overestimation of the PoLTF thickness profile results in overestimation of corneal edema. However, the region with the thickest PoLTF (i.e., at the corneal periphery) experiences significant limbal metabolic support and, consequently, exhibits minimal corneal swelling [33]. Therefore, the PoLTF thickness profile in Fig. 1 provides accurate swelling predictions for ESCL wear. With ESL wear, the PoLTF thickness is smaller at the periphery than at the center and provides a PoLTF thickness profile representative of commercially available SLs [21,34].

Fig. 2 depicts the corneo-scleral anatomy, two lens designs, and the coordinate axes. One axisymmetric central and one axisymmetric peripheral embedment are inserted in the encasement. Dimensions of the lenses are provided in Table 1. Because the designed systems are axisymmetric, swelling profiles are graphed from the center of the cornea to one end of the periphery. The parameters listed in Table 1 and Fig. 1 are utilized for all analyses unless noted otherwise. Oxygen *Dk*s of the encasement, peripheral embedment, and central embedment are varied as is the placement of the embedments. Because radial thicknesses for these three different components are uniform in the corneal region, component oxygen transmissibility (*Dk/L*) is constant for the specified *Dk* value. To gauge the importance of embedment placement on corneal edema, embedment location is adjusted along the curvature radii (θ-polar coordinate in Fig. 2) and sagittal (y coordinate in Fig. 2) directions.

Mathematical details of the metabolic-edema model are available in previously published manuscripts [22,33]. A brief non-mathematical summary is provided here. Metabolites of interest are those directly

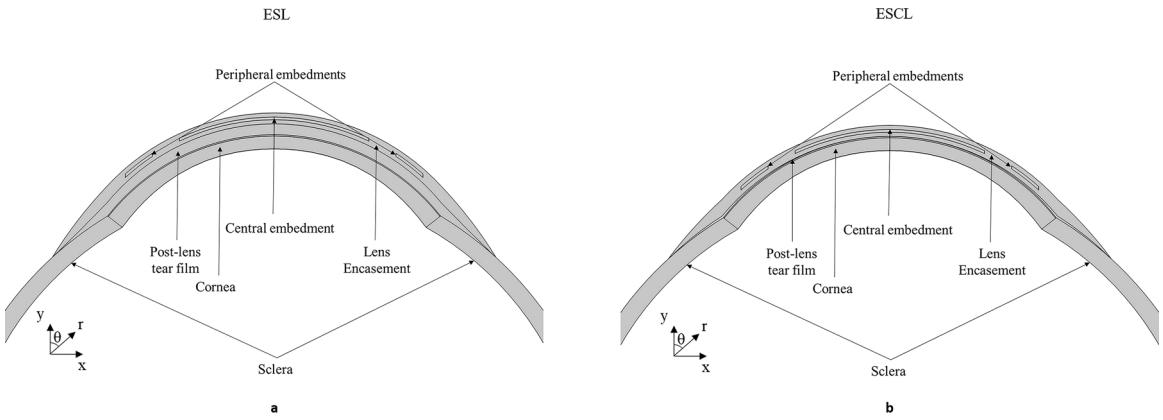

Fig. 2. Axisymmetric corneo-scleral and contact-lens designs with two embedments: (a) ESL and (b) ESCL. Each major component is labeled. Vertical axis (y axis) is the sagittal direction and horizontal axis (x axis) is the lateral distance. Radial and polar coordinates of the spherical coordinate system are given as r and θ, respectively. A polar coordinate of 0° is equivalent to the sagittal axis (y axis).

involved in aerobic and anaerobic metabolic reactions: oxygen, carbon dioxide, bicarbonate, lactate, glucose, and hydrogen ion. Sodium and chloride ions maintain local electroneutrality. Introduction of a contact lens on the ocular surface restricts oxygen delivery from the atmosphere to the cornea and leads to increased anaerobic metabolism to maintain corneal cell function. Increased anaerobic glucose consumption produces excess lactate and hydrogen ions according to the chemical reaction

$$C_6H_{12}O_6 \rightarrow 2C_3H_5O_3^- + 2H^+ \quad (1)$$

Hypoxic corneal acidosis from Eq. (1) is mitigated by the buffering equilibrium reaction

$$HCO_3^- + H^+ \leftrightarrow CO_2 + H_2O \quad (2)$$

The net increase in lactate and decrease in bicarbonate ions at the endothelium alters the local osmotic pressure and, consequently, changes the water influx/efflux balance of the pump-leak process at the corneal endothelium [22,35,36]. A decreased osmotic outflow results in higher water retention in the cornea and initiates corneal edema.

Alongside oxygen supply from the atmosphere, the cornea is directly supplied with metabolites from the anterior chamber and from the limbus. In addition, the peripheral cornea is approximately 35 % thicker than is the central cornea and has a higher metabolic demand [29]. Due to the various sources of metabolites and the different metabolic demands within the cornea, transport of metabolites occurs in both polar (center to/from periphery) and radial (corneal epithelium to/from corneal endothelium) directions in spherical coordinates (see Fig. 2). Corneal Nernst-Planck equations, epithelium/endothelium Kedem-Katchalsky membrane equations, boundary conditions, stroma-hydration isotherm, and accompanying parameters are available elsewhere [15,22,31,33].

The two-dimensional (2D) steady-state conservation equations used for the various metabolic species are written in rectangular coordinates and solved numerically in Comsol Multiphysics 5.5 using nonlinear finite element analysis.[33] Boundary conditions for the embedments include local species phase equilibria and continuity of species flux. Triangular mesh size and convergence tolerance (relative tolerance = 0.001) were set to ensure accurately converged solutions in reasonable computational times (~10−15 min).

2.2. Comparison to clinical data

Previously, the metabolic-edema model provided good comparison with clinically measured central and central-to-peripheral corneal edema during contact-lens wear [15,22,33]. Introduction of contact-lens

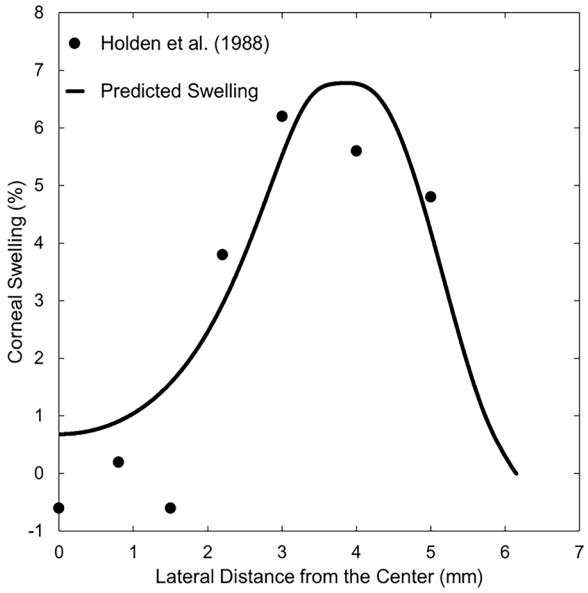

Fig. 3. Comparison between the clinical data of Holden et al. [37] and the metabolic model with literature parameters. [37] Horizontal axis is the lateral distance from the central cornea to the peripheral cornea with the reference point (horizontal axis = 0) being the central cornea at the anterior epithelial surface. Vertical axis is the percentage of corneal swelling. No data error estimates are available from Holden et al. [37].

embedments can result in localized regions with both extremely hypoxic and well oxygenated corneal regions. Therefore, the metabolic model is further compared here to the clinical data of Holden et al. [37]. These authors studied central-to-peripheral corneal edema during wear of a low-water-content hydroxyethyl methacrylate (HEMA) lens having a central-aperture region of high oxygen delivery to the cornea with the peripheral-lens region having low oxygen delivery from the environment. The lens was a 38 %-water-content HEMA hydrogel that typically has an oxygen *Dk* of 8.9 Barrer [38]. However, the customized lens studied was ~300 μm thick at the non-aperture region and, therefore, had an oxygen transmissibility of ~ 3 hBarrer/cm (i.e., hecto-Barrer/cm). Metabolic theory (line) and comparison data (closed circles) are portrayed in Fig. 3. Swelling at both the lens-center aperture and at the low-oxygen-*Dk* periphery are clearly identified. The decrease in swelling near the lens edge is due to limbal support of metabolites

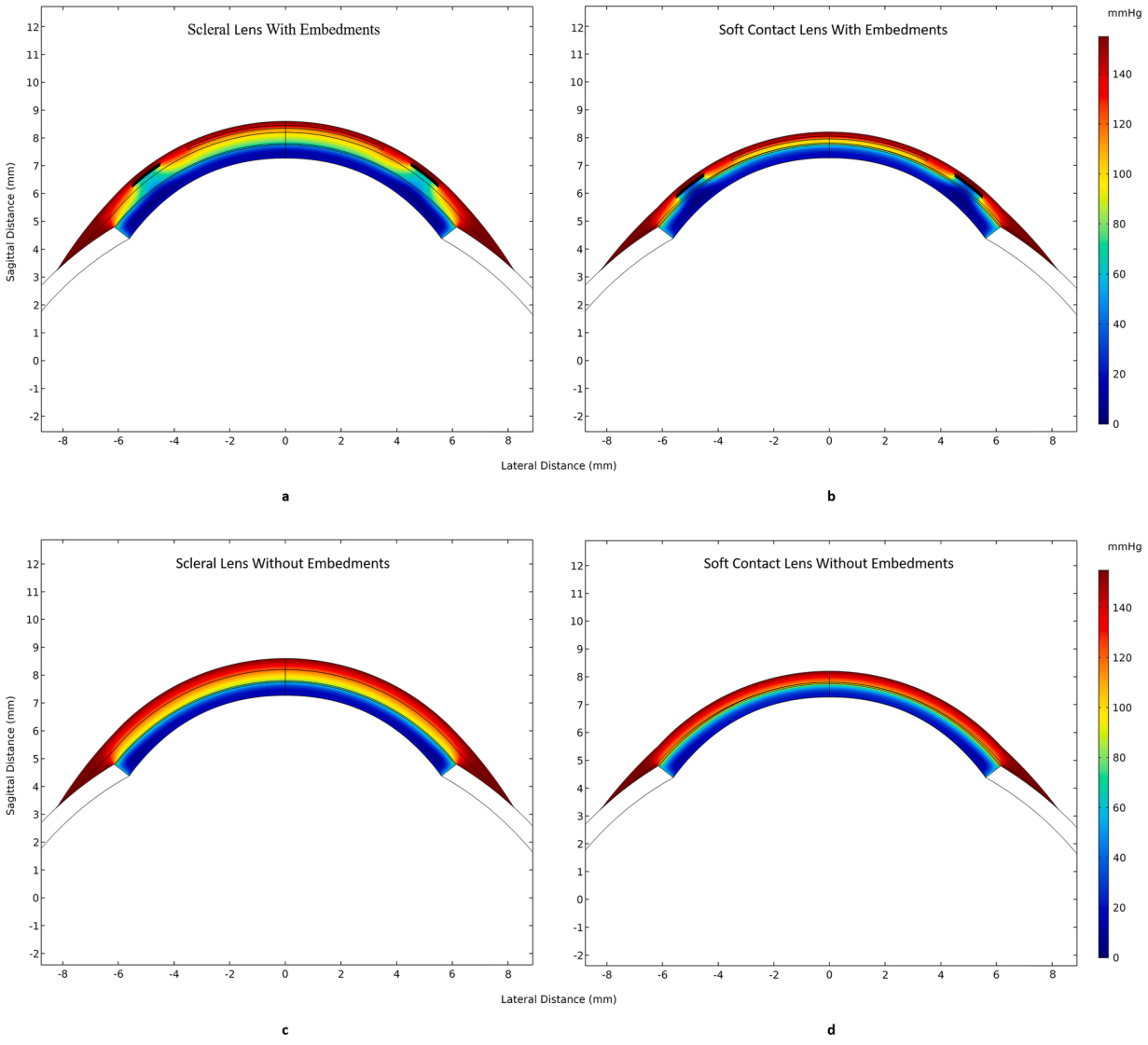

Fig. 4. Oxygen-tension contours throughout the lens and the cornea for (a) scleral lens with embedments (ESL) and (b) soft contact lens with embedments (ESCL). Oxygen permeability (*Dk*) of the peripheral embedment, central embedment, and lens encasement is 0, 30, and 100 Barrer, respectively. Oxygen-tension contours for (c) scleral lens (SL) and (d) soft contact lens (SCL) without embedments. The only difference between ESL and ESCL designs is the thickness profile of the PoLTF. Oxygen tension within the sclera is that of oxygenated blood (61.5 mmHg) and is not shown. Red, navy, and black colors indicate high, low, and zero oxygen tension, respectively. The unit of oxygen tension is in mmHg. Horizontal axis is the lateral distance with 0 being the central cornea and the vertical axis is the sagittal distance.

[33]. Model predictions correlate well with the measured data using no adjustable parameters. Fig. 3 constitutes a second clinical validation of the 2D metabolic model [33]. Additional clinical validation of the metabolic model comes from studies of overnight central corneal edema with SL wear [39,40]. The metabolic model successfully predicts the observed central corneal swelling of approximately 8 % with overnight wear [39,40].

3. Results

Fig. 4 illustrates oxygen-tension contours during wear of the SL and the SCL with and without embedments. Peripheral-embedment, central-embedment, and encasement oxygen *Dk*s are 0, 30, and 100 Barrer, respectively. Qualitatively, polar (i.e., θ-direction) oxygen transport provides meaningful oxygen support up to ~0.5 mm laterally away from each side of the central embedment. With a central-embedment oxygen *Dk* of zero Barrer (not shown), which has maximum possible polar oxygen flux, the effect of polar-direction oxygen transport diminishes ~1 mm laterally into each side of the central embedment. For contact lenses with embedments, the cornea underneath the peripheral embedment, which has a *Dk* of zero Barrer, experiences the greatest deprivation of oxygen, whereas the regions without embedments have the highest oxygen tensions. Polar transport of oxygen is seen from high oxygen-tension regions to low oxygen-tension regions in the lens, the PoLTF, and the cornea. Therefore, corneal regions directly below the peripheral embedment remain oxygenated to some level. Interestingly, although oxygen tension is higher with the ESCL than with the ESL at most corneal surface regions, oxygen tension at the ocular surface

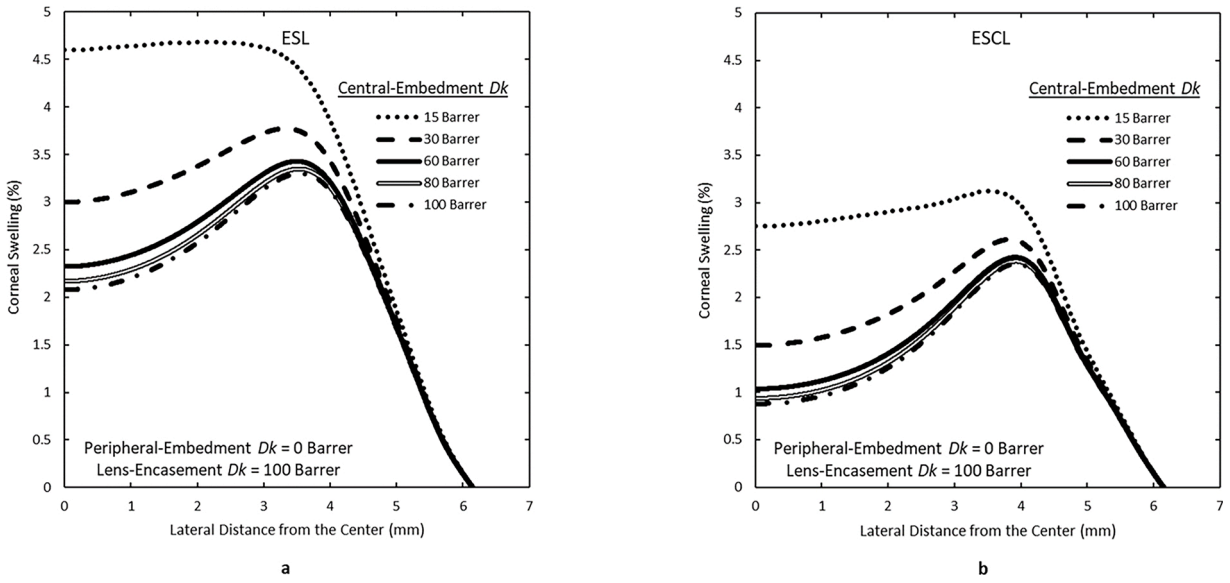

Fig. 5. Central-to-peripheral corneal edema with (a) ESL and (b) ESCL wear for varying central-embedment oxygen permeabilities (*Dk*). Peripheral-embedment and lens-encasement oxygen *Dk*s are fixed at 0 and 100 Barrer, respectively. Central-embedment oxygen permeabilities are 15, 30, 60, 80, and 100 Barrer for both lens designs. Horizontal axis is the lateral distance from the central cornea to the peripheral cornea with the reference point (horizontal axis = 0) being the central cornea at the anterior epithelial surface. Vertical axis is the percentage of corneal swelling.

immediately below the peripheral embedment for the ESL design is higher than that at the same location of the ESCL. This is due to the thicker PoLTF of the ESL design allowing more room for oxygen transport in the polar direction.

Dashed lines in Fig. 5a and b represent swelling profiles corresponding to Fig. 4a and b, respectively. Despite the higher oxygen tension beneath the peripheral embedment at the ocular surface for the ESL design than that for the ESCL design, corneal swelling in the corresponding region is larger with the ESL design. The reason behind this seemingly contradictory result is the greater polar fluxes of oxygen and other metabolites within the anterior cornea for ESCL wear compared to ESL wear at the region below the peripheral embedment. Polar-direction oxygen flux in this region is greater with ESCL wear due to the higher oxygen tension at the regions uncovered by the peripheral embedment than with ESL wear (see Fig. 4a and b). This results in a greater oxygen-tension gradient between the regions uncovered by the peripheral embedment and the region covered by the peripheral embedment. Similarly, there is less anaerobic metabolism (i.e., less production of lactate and less consumption of bicarbonate) in those regions uncovered by the peripheral embedment during ESCL wear. This results in a greater

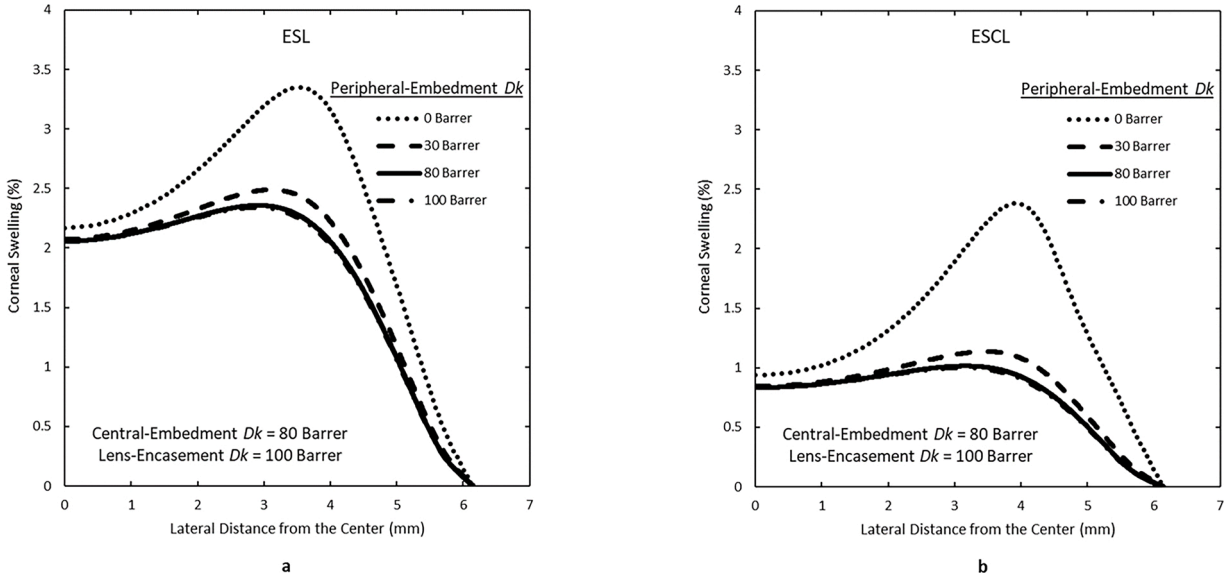

Fig. 6. Central-to-peripheral corneal edema with (a) ESL and (b) ESCL wear for varying peripheral-embedment oxygen permeabilities (*Dk*). Central-embedment and lens-encasement oxygen permeabities are fixed at 80 and 100 Barrer, respectively. Peripheral-embedment oxygen permeabilities are 0, 30, 80, and 100 Barrer for both lens designs. Dotted lines in Fig. 6a and b correspond to the double-solid lines in Fig. 5a and b, respectively. Horizontal axis is the lateral distance from the central cornea to the peripheral cornea with the reference point (horizontal axis = 0) being the central cornea at the anterior epithelial surface. Vertical axis is the percentage of corneal swelling.

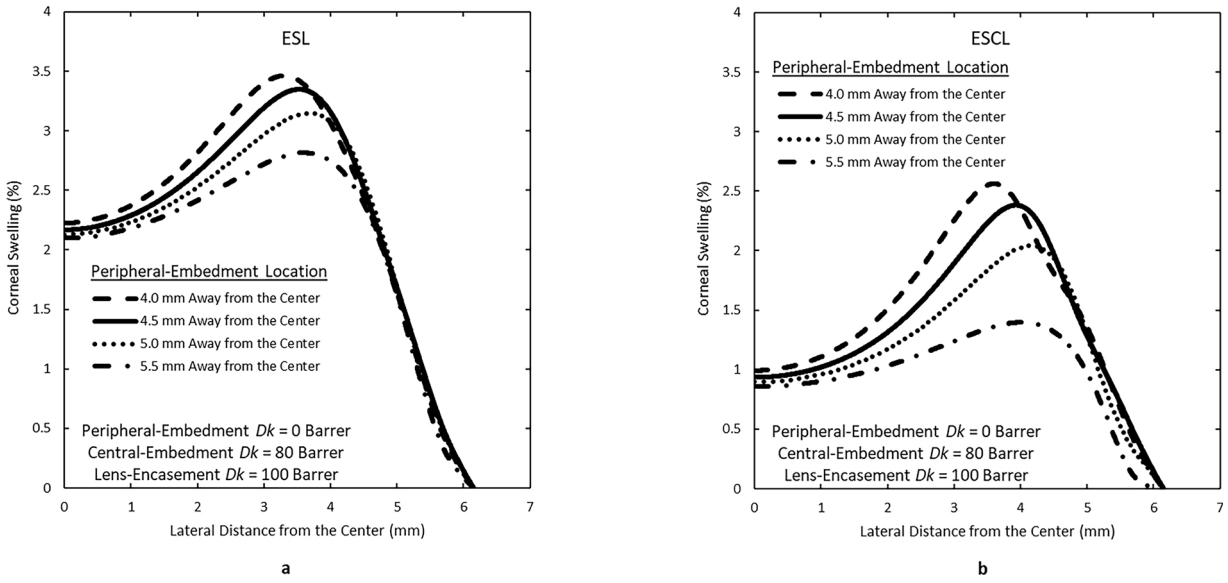

Fig. 7. Central-to-peripheral corneal edema with (a) ESL and (b) ESCL wear for varying peripheral-embedment locations along curvature radii. Peripheral-embedment, central-embedment, and lens-encasement oxygen permeabilities (*Dk*s) are 0, 80, and 100 Barrer, respectively. Starting edge locations of the peripheral embedment are 4.0, 4.5, 5.0, and 5.5 mm laterally away from the center. Peripheral-embedment lateral length is 1.0 mm. Fig. 7a and b solid lines are equivalent to Fig. 5a and b double-solid lines, respectively. Horizontal axis is the lateral distance from the central cornea to the peripheral cornea with the reference point (horizontal axis = 0) being the central cornea at the anterior epithelial surface. Vertical axis is the percentage of corneal swelling.

θ-directed flux of bicarbonate and lactate ions below the region covered by the peripheral embedment. Therefore, at the endothelium, where the pump-leak mechanism resides [15,22,33,41], the ESCL design has lower lactate and higher oxygen and bicarbonate concentrations resulting in less swelling than that in the ESL design.

Central-to-peripheral corneal swelling is always lower with thinner PoLTFs, as shown by comparison of Fig. 5a and b. However, for a PoLTF thickness to cause more than 1 % of the baseline corneal thickness change, the PoLTF thickness needs to change by more than 200 μm (during open-eye lens wear). The reason why peak swelling occurs ~3.5 – 4.0 mm laterally away from the center, despite the starting point of the peripheral embedment being 4.5 mm away from the center, is because environmental oxygen transport occurs radially. Also, metabolic demand of the cornea is non-uniform with limbal-metabolic support diminishing towards the central cornea. The small difference in the location of peak swelling between ESCL and ESL designs is the additional polar oxygen transport in the PoLTF of the ESL design and the thickness differences in the PoLTF profiles between the two lens designs.

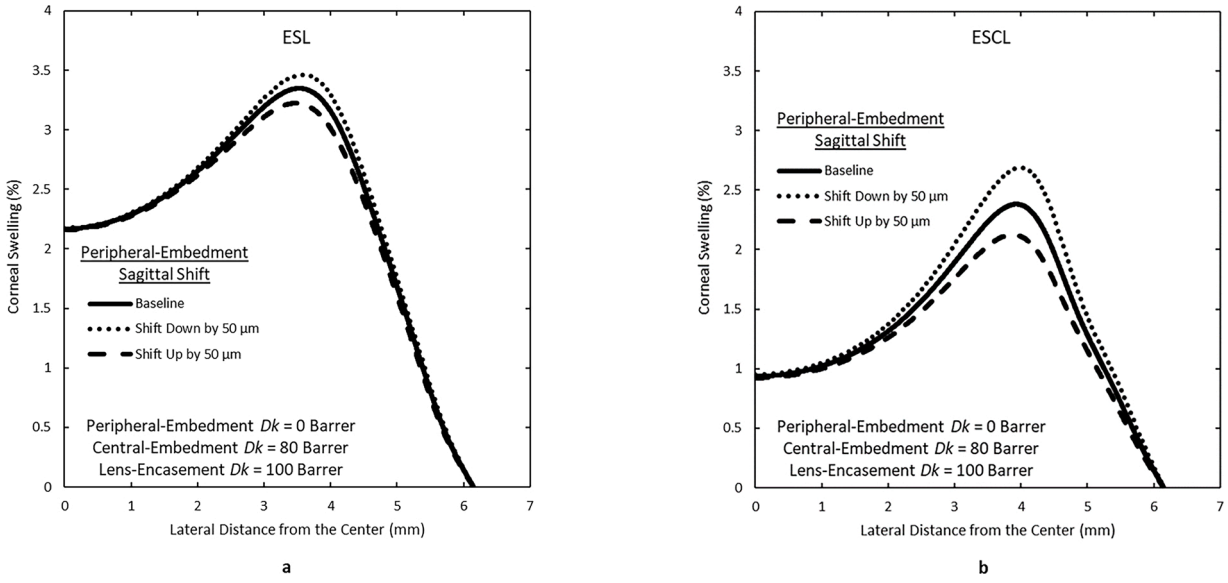

Fig. 8. Central-to-peripheral corneal edema with (a) ESL and (b) ESCL wear for varying peripheral-embedment sagittal locations. Peripheral-embedment, central-embedment, and lens-encasement oxygen permeabilities (*Dk*s) are 0, 80, and 100 Barrer, respectively. Baseline curves in Fig. 8a and b are equivalent to the double-solid lines in Fig. 5a and b, respectively. The peripheral embedment is shifted up and down 50 μm from the baseline to assess the effect of sagittal location on corneal edema. Horizontal axis is the lateral distance from the central cornea to the peripheral cornea with the reference point (horizontal axis = 0) being the central cornea at the anterior epithelial surface. Vertical axis is the percentage of corneal swelling.

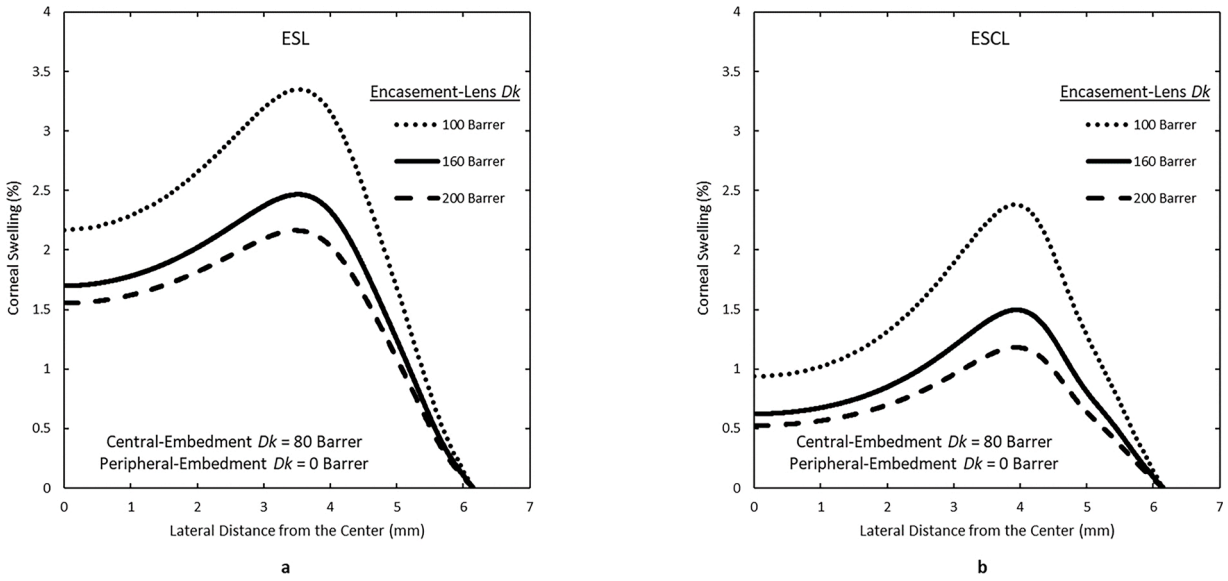

Fig. 9. Central-to-peripheral corneal edema with (a) ESL and (b) ESCL wear for varying lens-encasement oxygen permeabilities (*Dk*). Peripheral-embedment and central-embedment oxygen *Dk*s are 0 and 80 Barrer, respectively. Lens-encasement oxygen permeabilities are 100, 160, and 200 Barrer for both lens designs. Dotted lines in Fig. 9a and b are equivalent to the solid-open lines in Fig. 5a and b, respectively. Horizontal axis is the lateral distance from the central cornea to the peripheral cornea with the reference point (horizontal axis = 0) being the central cornea at the anterior epithelial surface. Vertical axis is the percentage of corneal swelling.

A large number of lens-design configurations is possible. Examples are given for changing the oxygen *Dk*s of the embedments and the encasement, the sizes of the embedments, and the placement of the embedments. Swellings between about 4 %, corresponding to no-lens-wear sleep [20], and 5 %, where Maurice noticed corneal hazing [18], are adopted as qualitative guidelines for safe lens wear.

Fig. 5a and b also illustrates central-to-peripheral edema for various central embedment oxygen *Dk*s with the ESL and ESCL designs, respectively. Encasement and peripheral-embedment oxygen *Dk*s are maintained at 100 and 0 Barrer, respectively. A central-embedment oxygen *Dk* of 100 Barrer (dot-dashed lines) is equivalent to having no central embedment as the oxygen *Dk* of the central embedment is the same as that of the lens encasement. With a central-embedment oxygen *Dk* of 30 Barrer or greater, there is a noticeable peak swelling at ~3.8 mm and ~4.0 mm laterally away from the center for ESL and ESCL designs, respectively. For a central-embedment oxygen *Dk* of 15 Barrer, the cornea is significantly deprived of oxygen everywhere but in the peripheral region. Therefore, for this oxygen-*Dk* value, swellings of ~4.5 % and ~2.8 % are predicted throughout the central-to-mid-peripheral region for ESL and ESCL designs, respectively. Swelling in the central-to-mid-peripheral region increases whenever the encasement and/or the central-embedment oxygen *Dk* decreases. Even with a high-oxygen-*Dk* encasement (e.g., *Dk* of 160 Barrer), central-to-mid-peripheral swelling can reach physiologically unsafe levels (i.e., greater than 4–5 % [17,18,20]) with a central-embedment oxygen *Dk* of less than 13 Barrer for the ESL design and less than 8 Barrer for the ESCL design. For all central-embedment oxygen *Dk*s, swelling declines in the peripheral regions for both lens designs due to metabolic support from the limbus [33].

Fig. 6a and b highlights the effect of changing the peripheral-embedment oxygen *Dk* on central-to-peripheral swelling for the ESL and ESCL designs, respectively. Dotted lines in Fig. 6a and b correspond to the double-solid lines in Fig. 5a and b, respectively. A peripheral-embedment oxygen *Dk* of 100 Barrer (dot-dashed lines) corresponds to no peripheral embedment as the encasement-oxygen *Dk* is 100 Barrer. For both lens designs, changing the peripheral-embedment oxygen *Dk* has a negligible effect on central corneal edema. Meanwhile, increasing the oxygen *Dk* of the peripheral embedment lowers the peak swelling of the cornea. A peripheral embedment can raise local swelling of the cornea by up to ~1.3 % of the baseline corneal thickness for both ESCL and ESL designs.

Location of the peripheral embedment is varied to understand the importance of embedment placement on corneal edema. Fig. 7a and b accentuates predicted swelling profiles associated with various peripheral-embedment placements along their curvature radii. The starting edge of the peripheral embedment is set to 4.0, 4.5, 5.0, and 5.5 mm laterally away from the center, and the lateral length of the peripheral embedment is kept at 1.0 mm. Sagittal shifts corresponding to the various lateral shifts can be determined by the posterior and anterior curvature radii provided in Table 1. Shifts described here follow the curvature radii and are equivalent to polar angle changes (in spherical coordinates). Solid lines in Fig. 7a and b are identical to the double-solid lines in Fig. 5a and b, respectively. For both lens types, moving the peripheral embedment closer to the central cornea also shifts the location of peak swelling towards the center. Moreover, with a peripheral embedment placed closer to the central cornea, peak swelling increases. Comparison of the swelling of the starting peripheral edge at 4.0 mm and at 5.5 mm in Fig. 7 reveals that peak swellings differ by ~0.8 % and ~1.3 % relative to the unswollen cornea for ESL and ESCL lens types, respectively. Although not shown here, reduction of the lateral length of the peripheral embedment from 1.0 mm to 0.5 mm reduces peak swelling by ~0.8 % and ~1.1 % of the baseline corneal thickness for ESL and ESCL wear, respectively.

Fig. 8a and b accentuates the effect of translating the peripheral embedment in the sagittal direction for ESL and ESCL wear, respectively. Solid lines in Fig. 8a and b are equivalent to the double-solid lines in Fig. 5a and b, respectively. Sagittal shifts of the central embedment for ESL and ESCL wear have a negligible effect on central-to-peripheral corneal swelling. Lack of swelling influence by the sagittal shift for the central embedment is also true for extremely low and high central-embedment oxygen *Dk*s. Depending on the sagittal location of the peripheral embedment, peak swelling changes by ~0.3 % and ~0.6 % of the baseline corneal thickness for ESL and ESCL designs, respectively.

Fig. 9a and b illustrates swelling profiles for various encasement

oxygen *Dks* during ESL and ESCL wear, respectively. Dotted lines in Fig. 9a and b are equivalent to the double-solid lines in Fig. 5a and b, respectively. Increases in the encasement oxygen *Dk* reduce central-to-peripheral corneal edema for both ESL and ESCL designs. Similar analyses to Figs. 4–8 but for encasement oxygen *Dk* of 160 Barrer are provided in Appendix A.

4. Discussion

Lens embedments should be constructed with high oxygen-*Dk* materials to minimize central-to-peripheral edema. Unfortunately, applicable elastomer and semiconductor embedment devices typically exhibit lower oxygen *Dk*s [7] than those of silicone-containing materials in use today for commercially available contact lenses [42]. Therefore, incorporation of embedments into a contact lens changes oxygen-transport behavior compared to that of contact lenses without embedments. In addition to the PoLTF thickness and oxygen *Dk/L* of the lens-encasement, corneal edema induced by embedded-component contact-lens wear is sensitive to the location of embedments, to the embedment lengths, and to the embedment-oxygen *Dk/L*s. In the analysis of embedment-oxygen *Dk/L*s, the oxygen *Dk*s are varied rather than the thickness of the embedments. However, the thickness of the embedments can also be altered to change the embedment-oxygen *Dk/L*s.

Limbal metabolic support, notably that from lactate, bicarbonate, and oxygen species, adds to the list of variables influencing corneal edema. The SENSIMED Triggerfish IOP-sensor lens provides a relevant example [12]. This lens has a high *Dk* silicone central region surrounded by a peripheral annular sensor circuit of low but unspecified *Dk*. However, because the sensor is peripheral, limbal metabolic supply protects the cornea from hypoxia. This model prediction is in agreement with the limited 5-subject central-swelling measurements of Pajic et al. [43].

Comparison of swelling profiles of ESL and ESCL designs in Figs. 5–9 and A2–A5 reveal that decreasing PoLTF thickness reduces corneal edema. Increasing a settled, central PoLTF thickness from 3 μm to 400 μm increases localized swelling by up to an additional 1.8 % of the baseline corneal thickness. The effect of PoLTF thickness on swelling increases with lower central-embedment, peripheral-embedment, and encasement oxygen *Dk*s until the series-resistance combined encasement and embedment oxygen *Dk/L* is less than ~5 hBarrer/cm. At such a low oxygen transmissibilities, oxygen-diffusion resistance of the lens (i.e., $\frac{L_{lens}}{Dk_{lens}} = \frac{L_{encasement}}{Dk_{encasement}} + \frac{L_{embedment}}{Dk_{embedment}}$) dominates PoLTF oxygen-diffusion resistance. This finding is consistent with central-corneal-edema analyses with wear of contact lenses without embedments [15,22]. A thicker PoLTF means more polar oxygen diffusion but less radial oxygen diffusion. Even with a 400-μm PoLTF thickness and a zero *Dk* central embedment, however, polar-directional diffusion supply is marginal ~1.0 mm laterally away from each side of the embedments for encasement oxygen *Dk*s of 100 and 160 Barrer. These observations emphasize the importance of oxygen diffusion through embedment material rather than relying on polar-directed oxygen transport posterior to the embedment.

The significant peak swelling in a high oxygen-*Dk* central embedment with a zero-oxygen-*Dk* peripheral embedment (Figs. 5 and A2) also emphasizes that polar oxygen diffusion is not adequate to reduce corneal hypoxia everywhere. Nevertheless, as shown in Figs. 8 and A5, relocating the peripheral embedment in the sagittal-anterior direction to allow more θ-directed oxygen transport can meaningfully reduce localized corneal edema. This is because the peripheral-embedment lateral length is 1 mm and polar transport of oxygen increases oxygen tension posterior to the peripheral embedment. The effect of polar-directed diffusive-oxygen supply rapidly diminishes ~1 mm laterally from each side of the embedments. Thus, shifting the central embedment in the anterior sagittal direction has minimal effect on corneal edema for both lens types because of the long length (i.e., 7 mm) of the central embedment (not shown). The importance of embedment-lateral length also explains why reducing the length of the peripheral embedment diminishes peak corneal edema significantly (not shown). Therefore, the central-embedment lateral length should not exceed ~ 2 mm when the chosen material is impermeable to oxygen.

Interestingly, sagittal-placement shifts with thicker PoLTFs in Fig. 8a result in less reduction of edema than those for thinner PoLTFs in Fig. 8b. There is a diminishing return on corneal edema of θ-directed oxygen supply via thicker PoLTFs and/or via more anterior-located embedments. Another way to increase the polar oxygen flux is to create greater oxygen concentration differences between the high and low oxygen tension regions by increasing the encasement oxygen *Dk*.

In Figs. 7 and A4, relocation of the peripheral embedment toward the central cornea increases peak corneal edema. This finding is not due to the non-uniform PoLTF as the ESCL design in Fig. 7b has a thicker PoLTF at the periphery. Rather, the reason for the dependence of corneal swelling on the peripheral-embedment polar location is because limbal-metabolic support diminishes towards the central cornea [33]. Figs. 7 and A4 also show that θ-direction shifting of the peripheral embedment from 4.5 mm to 5.0 mm decreases peak swelling more than does shifting of the embedment from 4.0 mm to 4.5 mm. Moving the peripheral embedment as far into the periphery as possible, while still remaining within the corneal zone, reduces peak swelling substantially.

Encasement oxygen *Dk* for Figs. 5–8 is 100 Barrer as commercial silicone-based lenses are available with this oxygen permeability. Encasement oxygen *Dk* of 160 Barrer, which is also commercially available, is discussed in Appendix A. For lower encasement-oxygen *Dk*, the effects of PoLTF thickness, embedment placements, embedment lengths, and embedment oxygen *Dk/L* all increase swelling more than what is presented in Figs. 5–8 because the cornea is in a more hypoxic state [15,20,22,33]. Unlike commercially worn contact lenses today, which have oxygen *Dk/L* greater than 20 hBarrer/cm, lenses with embedments can have a combined series-resistance encasement and embedment oxygen *Dk/L* of around ~10 hBarrer/cm. Therefore, the effect of PoLTF on swelling is greater with embedded-component contact lenses than that for conventional SL wear, where a change of 200 μm in settled-PoLTF thickness produces clinically insignificant swelling [22].

The metabolic-model analysis does not incorporate oxygen supplied from fresh tear at the lens edge. However, SCL and SL exhibit smaller lens movements than those of PMMA lenses that deliver inadequate oxygen to the cornea through tear mixing [44–47]. Therefore, the amount of oxygen supplied from fresh tear is minor compared to that supplied by diffusion through the lens. With ESL assessment, settled PoLTF thicknesses greater than 400 μm were not investigated because Kim et al. [22] calculated that thicknesses greater than 400 μm permit buoyancy-driven fluid convection that dominates oxygen mixing compared to molecular diffusion. Therefore, model prediction is accurate up to thicknesses of about 400 μm [22] beyond which a diminishing effect of PoLTF thickness on central corneal edema is expected and in agreement with Fisher et al. [48]. Because heat generated by battery-powered embedments may affect buoyancy-driven fluid convection, investigation of PoLTF-temperature profiles is warranted with ESL wear.

The presented metabolic model assesses corneal swelling in the steady state. Time to reach steady state is affected by whether the eyes

are open or closed, by the oxygen transmissibility of the tear film and the embedded lens components, by how fast the lens settles on the ocular surface, and by how quickly the stroma swells/deswells upon changes in metabolic species concentrations, among others. Of these effects, swelling/deswelling appears to be rate determining. Li and Tighe [49] mathematically showed that it takes approximately 3–4 h for the cornea to reach steady state after being subjected to a 1-h hyperosmotic shock of 15 mOsM. More recently, Tan et al. [21] showed clinically that the time it takes to reach maximum swelling with SL wear occurs after about 1.5 h of lens wear during open eye. Then, the swelling decreased by 0.2 % of the baseline corneal thickness in a subsequent 3.5 h most likely because of the slow lens settling. Niimi et al. [50] also showed that deswelling after no-lens-wear overnight swelling occurred mostly within 2 h of awake time. The change in concentration of metabolites due to open-eye lens-wear hypoxia is smaller than the hyperosmotic shock considered by Li and Tighe [49]. Therefore, the time to reach steady state with open-eye ESL and ESCL is likely to be closer to the 1.5–2 h observed by Tan et al. [21].

Possible transport resistances of metabolites from scleral-blood vessels into the limbus is not accounted for in the present metabolic model [33]. Therefore, the current model provides an optimistic estimate of limbal-metabolic support. However, comparison of the model to the central-to-peripheral clinical data of Wang et al. [26] provided in Kim et al. [33] and to those of Holden et al. [37] in Fig. 3 is good using no adjustable parameters. Moreover, the model accurately predicts various contact-lens wear induced central corneal edema for open and overnight closed eyes [15,20,22,39,40]. Therefore, transport resistances of metabolites between the limbus and the cornea are likely to be small.

As previously mentioned, the provided design of ESCL results in mid-peripheral and peripheral PoLTF thicknesses that are thicker than what is typically seen with commercially available SCL wear. However, a change in the PoLTF thickness by 80 μm results in corneal-thickness change of less than 0.35 % of the baseline corneal thickness. Further, the region with the thickest PoLTF, which is the peripheral cornea, has minimal corneal edema due to limbal-metabolic support. Therefore, the 2D metabolic model provides accurate assessment of corneal edema with ESCL wear despite the possibility that the designed ESCL may slightly overestimate mid-peripheral and peripheral corneal edema compared to that of an actual ESCL. When ESCL and ESL PoLTF thickness profiles are available, those data can readily be incorporated into the present metabolic-edema model to assess corneal edema caused by specific designs of ESCLs and ESLs.

Although this manuscript focuses on circuit-embedded contact lenses, guidance on minimizing corneal edema is also applicable to contact lenses that have other multiple components, such as drug-eluting lenses [51]. For ESCLs, embedments may inhibit ion transport across the lens, potentially adhering the lens to the ocular surface [52,53]. Assessment of ion transport through ESCLs requires further investigation.

Countless lens configurations and corresponding central-to-peripheral corneal-edema profiles can arise. This is especially true since most contact lenses have non-uniform thickness profiles [54,55]. For these multifaceted embedded-lens designs, the metabolic-model calculations provide guidance on how best to minimize corneal edema. Figs. 5, 6, and 9 show the importance of having a high oxygen *Dk* for embedments and, most importantly, for the lens encasement regardless of embedment location and PoLTF thickness. Recommended designs to minimize central-to-peripheral edema are those with the highest oxygen *Dk/L* for the lens encasement and embedments as well as the thinnest PoLTF. Embedments do not hinder oxygen delivery to the cornea when they are implanted far into the conjunctival region. When an embedment is placed within the corneal periphery near the limbus, limbal-metabolic support in the peripheral region negates most of the swelling. Therefore, mid-peripheral peak swelling with a zero-oxygen-*Dk* peripheral embedment located near the limbus (i.e., Fig. 7 dot-dashed lines) is greater than that with no peripheral embedment (i.e., equivalent to Fig. 6 dot-dashed lines) by only ~0.4 % of the baseline corneal thickness. Consequently, embedments should be placed as far into the periphery as possible. Finally, embedment lengths should be minimized; they should be placed as anteriorly as possible to maximize polar-directed oxygen transport. Accordingly, swellings of less than 1 % everywhere should be achievable even with low-oxygen-*Dk* embedments.

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Corneal Swelling Profiles with Encasement Oxygen *Dk* of 160 Barrer

Fig. A1 illustrates oxygen-tension contours during wear of the ESL, ESCL, SL, and SCL that compare with Fig. 4 except that encasement oxygen *Dk* is now 160 Barrer. Peripheral-embedment and central-embedment oxygen *Dk*s for ESL and ESCL are 0 and 30 Barrer, respectively. Dashed lines in Fig. A2a and b reflect swelling profiles corresponding to the oxygen-tension contours in Fig. A1a and b, respectively.

Fig. A2a and b illustrates the effect of changing central-embedment *Dk* on central-to-peripheral edema for an encasement oxygen *Dk* of 160 Barrer for ESL and ESCL wear, respectively. Results are similar to those of Fig. 5a and b, except that swelling is decreased with the higher encasement oxygen *Dk*.

The effect of changing-peripheral embedment *Dk* on central-to-peripheral corneal edema for encasement oxygen *Dk* of 160 Barrer for ESL and ESCL is shown in Fig. A3a and b, respectively. The trend seen in Fig. A3a and b is comparable to that in Fig. 6a and b, respectively. Dotted lines in Fig. A3a and b correspond to the solid lines in Fig. A2a and b, respectively.

Polar-directed shifts of the peripheral embedment are assessed with an encasement oxygen *Dk* of 160 Barrer as illustrated in Fig. A4a and b for ESL and ESCL, respectively. Again, the trends seen in Fig. A4a and b are comparable to those in Fig. 7a and b, respectively. Solid lines in Fig. A4a and b are identical to the solid lines in Fig. A2a and b, respectively. With an encasement oxygen *Dk* of 160 Barrer, reduction of the lateral length of the peripheral embedment from 1.0 mm to 0.5 mm reduces peak swelling by ~0.6 % and ~0.7 % of the baseline corneal thickness for ESL wear and for ESCL wear, respectively.

The effect of a sagittal shift of the peripheral embedment with an encasement oxygen *Dk* of 160 Barrer is illustrated in Fig. A5a and b for ESL and ESCL, respectively. As above, solid lines in Fig. A5a and b are equivalent to the solid lines in Fig. A2a and b, respectively. Similar to Fig. 8a and b, shifting the peripheral embedment anteriorly reduces peak edema.

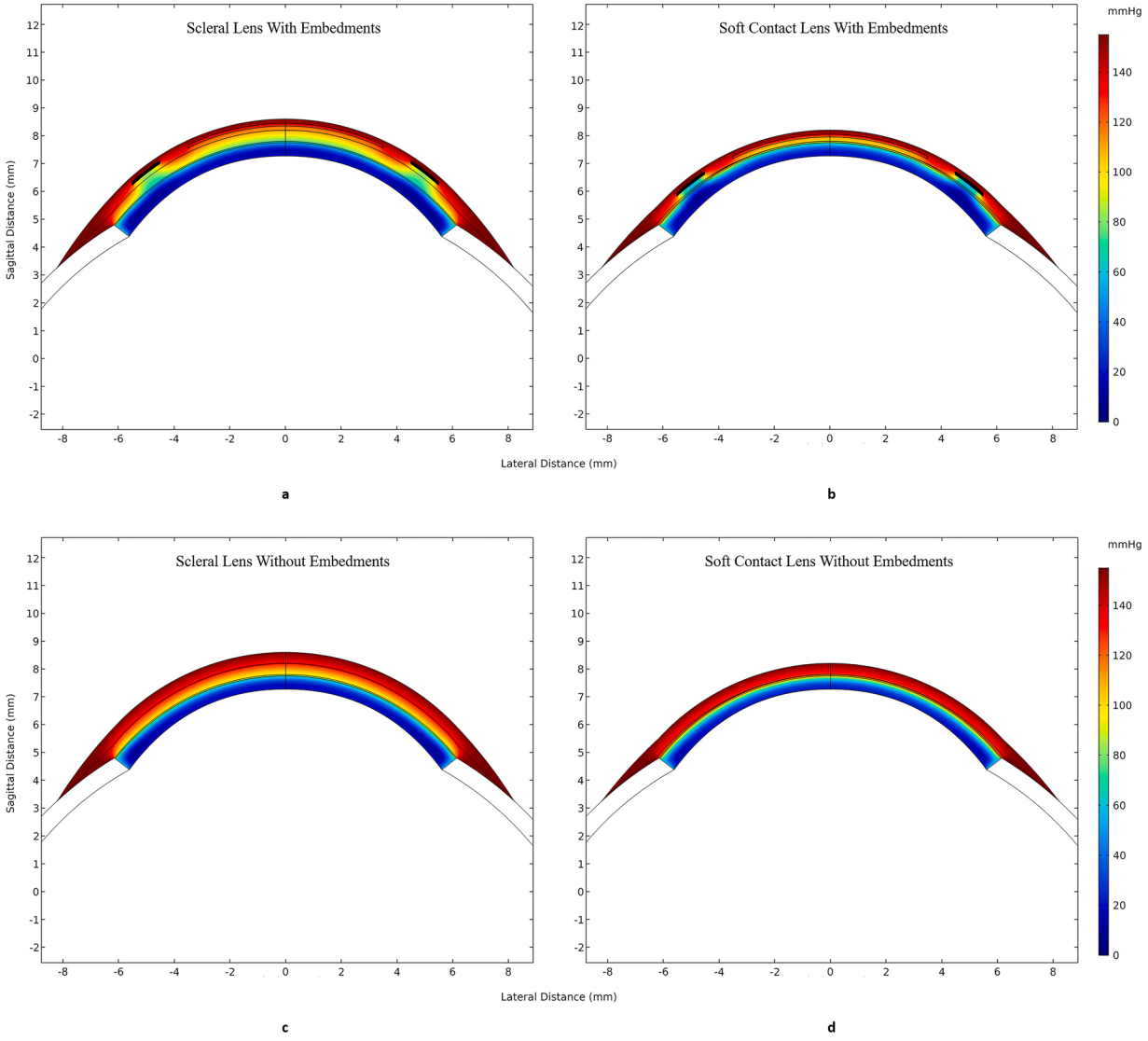

Fig. A1. Oxygen-tension contours throughout the lens and the cornea for (a) scleral lens with embedments (ESL) and (b) soft contact lens with embedments (ESCL). Oxygen permeabilities (*Dks*) of the peripheral embedment, central embedment, and lens encasement are 0, 30, and 160 Barrer, respectively. Oxygen-tension contours for (c) scleral lens (SL) and (d) soft contact lens (SCL) without embedments. The only difference between ESL and ESCL designs is the thickness profile of the PoLTF. Oxygen tension within the sclera is that of oxygenated blood (61.5 mmHg) and is not shown. Red, navy, and black colors indicate high, low, and zero oxygen tensions, respectively. The unit of oxygen tension is in mmHg. Horizontal axis is the lateral distance with 0 being the central cornea and the vertical axis is the sagittal distance.

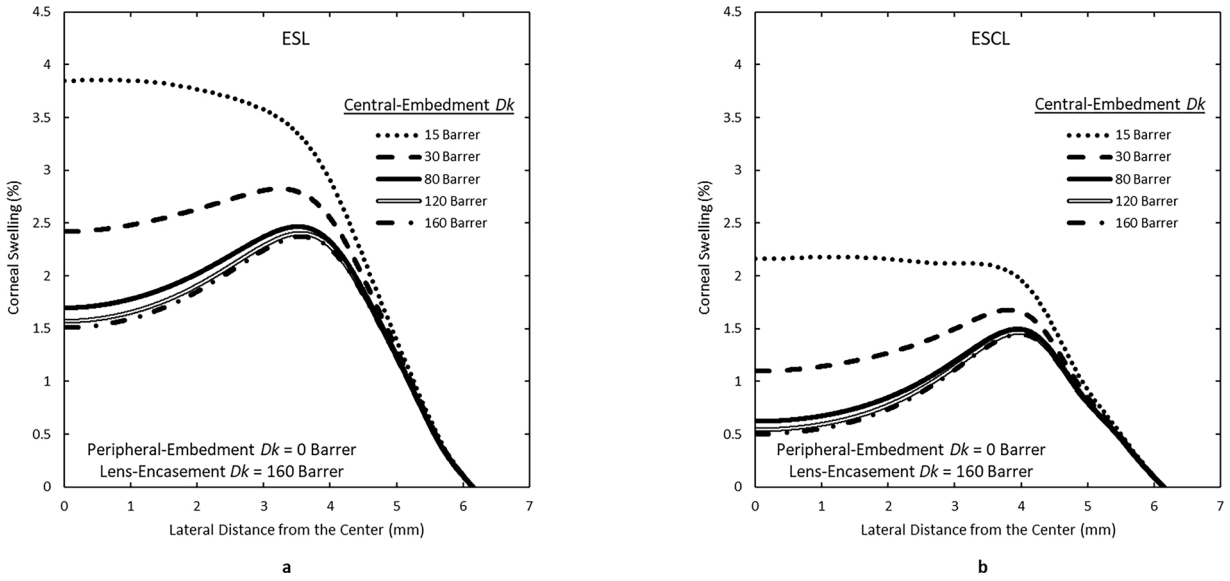

Fig. A2. Central-to-peripheral corneal edema with (a) ESL and (b) ESCL wear for varying central embedment oxygen permeabilities (*Dks*). Peripheral-embedment and lens-encasement oxygen *Dk*s are fixed at 0 and 160 Barrer, respectively. Central-embedment oxygen permeabilities are 15, 30, 80, 120, and 160 Barrer for both lens designs. Horizontal axis is the lateral distance from the central cornea to the peripheral cornea with the reference point (horizontal axis = 0) being the central cornea at the anterior epithelial surface. Vertical axis is the percentage of corneal swelling.

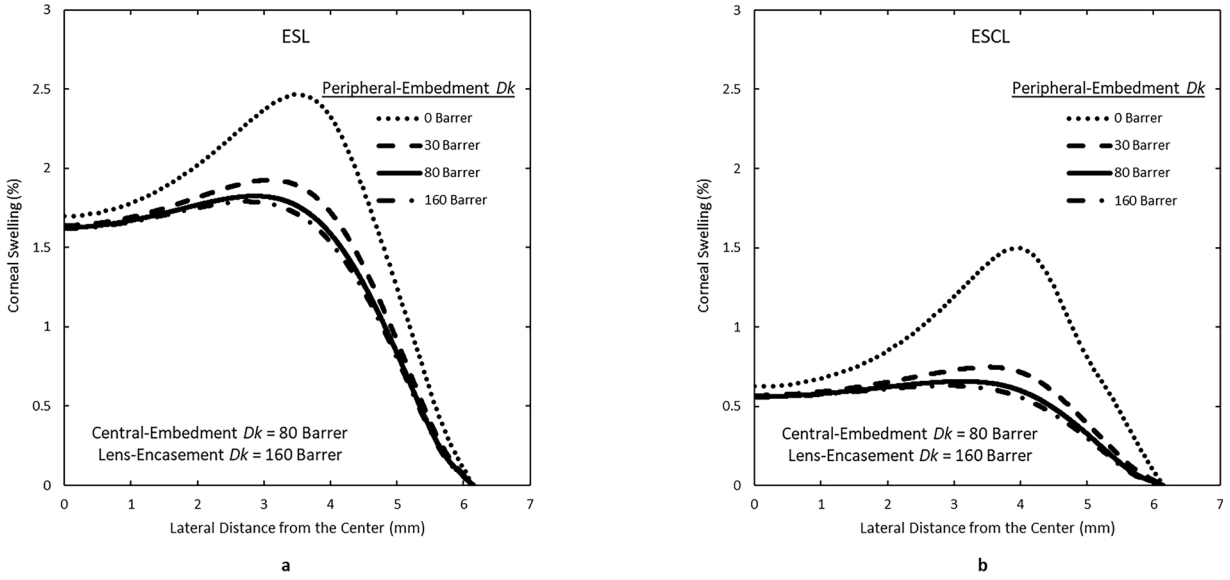

Fig. A3. Central-to-peripheral corneal edema with (a) ESL and (b) ESCL wear for varying peripheral-embedment oxygen permeabilities (*Dks*). Central-embedment and lens-encasement oxygen *Dk*s are fixed at 80 and 160 Barrer, respectively. Peripheral-embedment oxygen permeabilities are 0, 30, 80, and 160 Barrer for both lens designs. Dotted lines in Fig. A3a and b correspond to the solid lines in Fig. A2a and b, respectively. Horizontal axis is the lateral distance from the central cornea to the peripheral cornea with the reference point (horizontal axis = 0) being the central cornea at the anterior epithelial surface. Vertical axis is the percentage of corneal swelling.

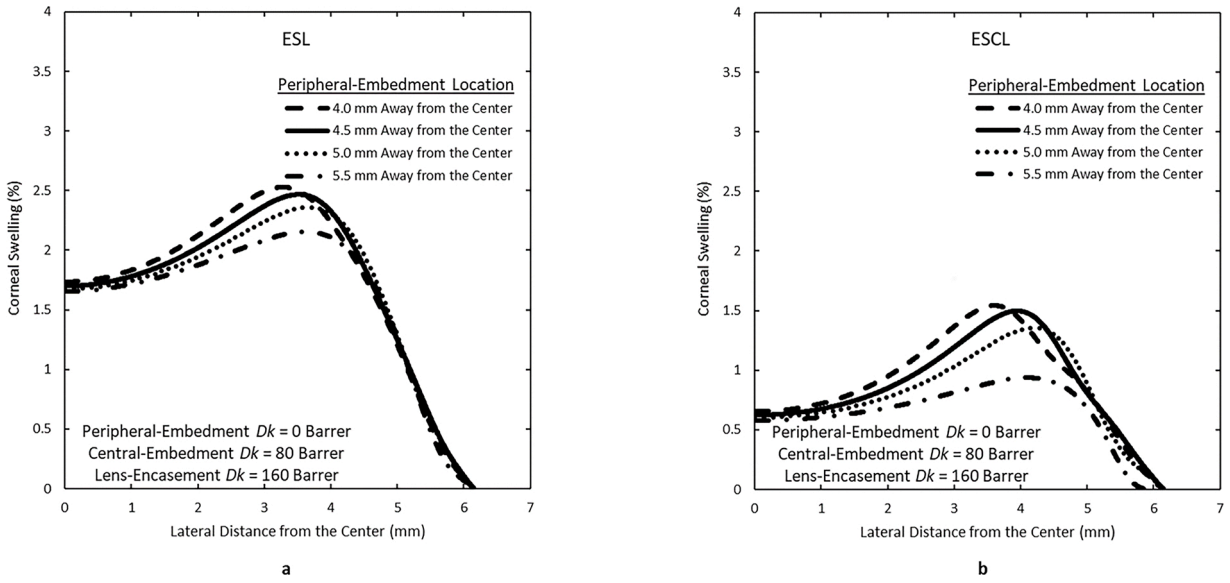

Fig. A4. Central-to-peripheral corneal edema with (a) ESL and (b) ESCL wear for varying peripheral-embedment locations along curvature radii. Peripheral-embedment, central-embedment, and lens-encasement oxygen permeabilities (*Dk*s) are 0, 80, and 160 Barrer, respectively. Starting edge locations of the peripheral embedment are 4.0, 4.5, 5.0, and 5.5 mm laterally away from the center. Peripheral-embedment lateral length is 1.0 mm. Fig. A4a and b solid lines are equivalent to Fig. A2a and b solid lines, respectively. Horizontal axis is the lateral distance from the central cornea to the peripheral cornea with the reference point (horizontal axis = 0) being the central cornea at the anterior epithelial surface. Vertical axis is the percentage of corneal swelling.

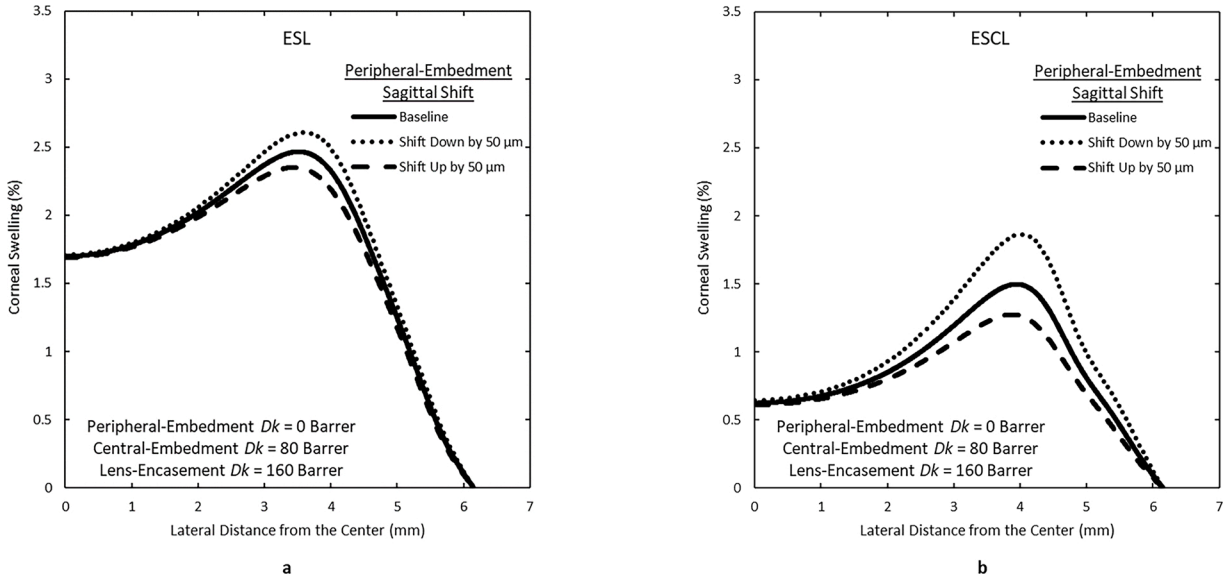

Fig. A5. Central-to-peripheral corneal edema with (a) ESL and (b) ESCL wear for varying peripheral-embedment sagittal locations. Peripheral-embedment, central-embedment, and lens-encasement oxygen permeabilities (*Dk*s) are 0, 80, and 160 Barrer, respectively. Baseline curves in Fig. A5a and b are equivalent to the solid lines in Fig. A2a and b, respectively. The peripheral embedment is shifted up and down 50 µm from the baseline to assess the effect of sagittal location on corneal edema. Horizontal axis is the lateral distance from the central cornea to the peripheral cornea with the reference point (horizontal axis = 0) being the central cornea at the anterior epithelial surface. Vertical axis is the percentage of corneal swelling.

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