

# Comparative ocular and systemic pharmacokinetics of lifitegrast delivered by an eye drop and chamber- and surface-loaded contact lenses in rabbits

**Woojin Kim**

Daegu Catholic University

**Woohyung Jung**

Daegu Catholic University

**Eunbin Kim**

Daegu Catholic University

**Seongwon Kim**

Daegu Catholic University

**Ahram Lee**

Daewon Pharm (South Korea)

**Ha Ryong Kim**

Korea University

**Du Hyung Choi**

Daegu Catholic University

**Tae Hwan Kim**

thkim@cu.ac.kr

Daegu Catholic University

---

## Research Article

**Keywords:** Ocular pharmacokinetics, Drug delivery system, Therapeutic contact lens, Lifitegrast

**Posted Date:** October 8th, 2026

**DOI:** <https://doi.org/10.21203/rs.3.rs-11095677/v1>

**License:**   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

**Additional Declarations:** No competing interests reported.



# Abstract

Drug-loaded contact lenses have emerged as a promising alternative for ocular drug delivery, but direct evidence that lens delivery increases ocular exposure of lifitegrast remains limited. This study compared ocular and systemic exposure to lifitegrast delivered using an eye-drop solution and two prototype contact lens loading configurations in rabbits. An eye drop (0.4 mg/eye), a chamber-loaded lens (0.4 mg/eye), and a surface-loaded lens (1.25 mg/eye) were administered to New Zealand white rabbits, and lifitegrast in plasma, cornea, conjunctiva, sclera, and aqueous humor was quantified by LC-MS/MS. In vitro and in vivo drug release from the lenses was also determined. A release-linked population pharmacokinetic model incorporating distinct input pathways for the two lens configurations was used to characterize corneal exposure. The components of the drug solution were classified as non-irritant in an ocular irritation assay. Both lens formulations increased systemic and ocular exposure relative to the eye drop, with dose-normalized corneal  $AUC_{last}$  (0–12 h for the lenses; 0–8 h for the eye drop) increasing 3-fold with the chamber-loaded lens and 111-fold with the surface-loaded lens. The model estimated apparent precorneal elimination rate constants of 4.64 and 2.19 h<sup>-1</sup> for the eye drop and lens regimens, respectively. In conclusion, this study demonstrates the potential of contact lens delivery to increase ocular tissue exposure to lifitegrast, offering a strategy to overcome the pharmacokinetic limitations of conventional eye drops.

## 1. Introduction

Pharmacological treatment of ocular disease depends on achieving and sustaining adequate drug concentrations in target ocular tissues [1]. The global burden of ocular diseases is substantial and continues to grow with population aging [2], driving demand for therapies that deliver drug efficiently to its site of action. Dry eye disease (DED), for example, is one of the most frequently encountered ocular diseases [3]. DED is a chronic, multifactorial disorder of the ocular surface in which an unstable and hyperosmolar tear film, together with local inflammation and epithelial damage, leads to persistent ocular discomfort [4], with reported prevalence ranging from 5% to 50% across studies [5].

Delivering drug to the eye from the systemic circulation is inefficient, since the blood–aqueous and blood–retinal barriers limit drug entry into ocular tissue [1]. Topical instillation therefore remains the most commonly used non-invasive route for anterior segment and ocular surface disease [1]. Direct application to the eye, however, does not ensure delivery to the target tissue. The cornea itself is one obstacle. Drug on the ocular surface must permeate this membrane, and this is difficult for most compounds since the cornea comprises a lipophilic epithelium and a hydrophilic stroma in series [6]. Hydrophilic drugs are restricted at the epithelium, whereas lipophilic drugs cross the epithelium but partition poorly into the stroma. The ocular surface itself poses a further obstacle. The conjunctival sac has a standard volume of 7–10 µL, expanding to a maximum of approximately 30 µL without overflow, whereas a typical eye drop delivers several times that volume. A substantial fraction of the instilled dose overflows immediately, and instillation induces reflex lacrimation that further dilutes the remaining drug [7, 8]. Blinking displaces the residual volume toward the puncta, and tear turnover clears it through the

nasolacrimal duct within minutes [7, 9]. Precorneal clearance is therefore rapid, drug-cornea contact time is short, and less drug is available at the precorneal site [7].

Several formulation strategies have been developed to improve topical ocular delivery [10, 11]. Viscosity-enhancing vehicles, mucoadhesive polymers and in situ gelling systems resist precorneal washout by reducing the mobility of the formulation or by interacting with the mucin layer of the tear film [10, 12], and formulations of these types have increased aqueous humor exposure severalfold relative to conventional eye drops in preclinical studies [13–16]. Nanoparticulate carriers have been used for poorly soluble drugs, improving their solubility and, in several formulations, their ocular bioavailability [6, 17]. Permeation enhancers act on the barrier itself, in part by transiently loosening epithelial junctions, although their use is constrained by concentration- and exposure-dependent corneal epithelial toxicity [8]. These approaches share a common limitation. Since the applied volume exceeds the capacity of the tear film, part of the dose is lost immediately. The remainder is incorporated into the tear film and removed by the precorneal clearance processes. Slowing these processes extends the duration of exposure, but the whole dose undergoes clearance simultaneously rather than being supplied over time.

A drug-loaded contact lens, in contrast, can supply drug over an extended period. The lens remains on the ocular surface and delivers drug continuously over the period of lens wear [10]. Application of a contact lens also changes the structure of the tear film. Tear film after lens wear is divided into two layers: a pre-lens layer, exposed to the environment, and a post-lens layer, approximately 10  $\mu\text{m}$  thick, enclosed between the lens and the cornea [18]. Only 1–2% of the post-lens tear volume is exchanged per blink [19], so that drug released into this layer is retained close to the cornea for tens of minutes [20]. Evaluation of contact lens drug delivery has generally involved in vitro release testing, pharmacodynamic endpoints, tear fluid concentrations, or direct quantification of drug in ocular tissues [21,22]. A recent study of lifitegrast-eluting lenses in rabbits, for example, reported prolonged tear fluid exposure and a longer mean residence time than eye drops [23]. However, tear fluid concentrations reflect available drug only at the ocular surface rather than the amount that enters the tissue. Prolonged residence on the ocular surface has been proposed as a plausible mechanism [7, 9, 21], but direct evidence that contact lens delivery increases ocular exposure to lifitegrast is lacking. Whether, through what mechanism, and to what extent contact lens delivery increases ocular exposure to lifitegrast therefore remains unresolved.

DED is a chronic condition requiring instillation of an eye drop over long periods, and successful treatment depends on consistently maintaining drug at the ocular surface. It is difficult to achieve this consistent exposure, however, since each instillation delivers a variable fraction of the applied dose [8]. In contrast, the amount of drug loaded into a contact lens is fixed at the time of manufacture, potentially reducing dose-to-dose variability. Lifitegrast, an integrin antagonist approved as a 5% ophthalmic solution for DED, is a suitable compound for the present question. It blocks the interaction between lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1) that recruits and activates T cells at the cornea and conjunctiva [24], the tissues in which lifitegrast concentrations are highest following topical administration in rabbits [25, 26].

The aim of the present study was to determine whether distinct input pathways delivered by two lens loading configurations increase ocular tissue exposure to lifitegrast. Drug release from the lens and drug concentrations in cornea, conjunctiva, sclera and aqueous humor were determined, and how two lens loading configurations alter the corneal pharmacokinetics of lifitegrast was further characterized by a population pharmacokinetic model linking drug release to corneal concentrations.

## 2. Materials and methods

### 2.1. Chemicals and reagents

Lifitegrast was purchased from MSN Life Sciences (Chandampet, Telangana, India), and lifitegrast-d6 (isotopic purity 96.2%), used as the internal standard, from Acanthus Research (Mississauga, Ontario, Canada). Sodium phosphate dibasic anhydrous (extra pure grade,  $\geq 99\%$ ) and sodium hydroxide (NaOH; extra pure grade,  $\geq 93\%$ ) were purchased from Duksan Pure Chemicals (Ansan, Republic of Korea). Sodium thiosulfate pentahydrate (ReagentPlus,  $\geq 99.5\%$ ) and formic acid were purchased from Sigma-Aldrich (St. Louis, Missouri, USA). Hypromellose (HPMC; Metolose 90SH-100000SR, substitution type 2208, nominal viscosity 100,000 mPa·s) was purchased from Shin-Etsu Chemical (Tokyo, Japan). Acetonitrile and water (HPLC grade) were purchased from J.T. Baker (Phillipsburg, New Jersey, USA).

### 2.2. Preparation of drug solutions and drug-loaded lenses

A prototype contact lens comprised two poly(2-hydroxyethyl methacrylate) components, a lens body and a sealing membrane (Fig. 1A). The lens body contained an annular drug chamber approximately 150  $\mu\text{m}$  in height, surrounding a central optical zone of 3 mm radius. Eight radial release structures, each 1 mm wide and 1.2 mm long, were arranged around its periphery. Both components were produced by cast molding and thermal curing, and bonded at 90°C after plasma treatment. The assembled lens was 13.34 mm in outer diameter and 12.84 mm in inner diameter, with a radius of curvature of 7.52 mm.

Drug solutions were prepared at final lifitegrast concentrations of 8, 40, and 125 mg/mL for eye drop, chamber-loaded lens and surface-loaded lens administration, respectively. Lifitegrast was added to 20 mM disodium hydrogen phosphate solution and mixed, and the pH was raised to 7.4 by dropwise addition of 1 M NaOH to dissolve the drug. Once dissolution was complete, sodium thiosulfate pentahydrate was added as an antioxidant to a final concentration of 3 mg/mL. Since the surface-loaded lens was designed to deliver the drug in direct contact with the cornea rather than through a chamber, HPMC was added to a final concentration of 5 mg/mL to retain the solution on the lens surface. The final pH was adjusted to 7.4 with 1 M NaOH.

For the chamber-loaded lens, the tip of a 25  $\mu\text{L}$  syringe (Hamilton Company, Reno, Nevada, USA) was placed at one of the release structures and the solution was injected until no further volume could be accommodated, corresponding to approximately 10  $\mu\text{L}$  per lens (Fig. 1B). The loaded volume was checked from the change in lens weight prior to and following filling. For the surface-loaded lens, 10  $\mu\text{L}$  of the solution was applied onto the central optical zone with a micropipette. Drug-loaded lenses were

placed concave side up in sealed containers and applied to the eye within 30 min of filling. Among several container types tested, the sealed container used in this study was the only type showing no detectable change in mass over 24 h; other types exhibited mass loss over time, indicative of leakage, and were not used.

## 2.3. Ocular irritation test

Ocular irritation was assessed using MCTT HCE™, a reconstructed human cornea-like epithelium model (Biosolution, Seoul, Republic of Korea), according to Organization for Economic Co-operation and Development (OECD) Test Guideline 492. Test articles were lifitegrast alone in 20 mM disodium hydrogen phosphate at pH 7.4 at concentrations of 25, 50, 75 and 100 mg/mL, complete drug solution used for chamber loading (40 mg/mL lifitegrast with 3 mg/mL sodium thiosulfate pentahydrate), and HPMC at 10 mg/mL. Dulbecco's phosphate-buffered saline (DPBS) and 5% (w/v) benzalkonium chloride (BKC) were used as negative and positive controls, respectively. Briefly, corneal models were equilibrated overnight, exposed in duplicate to 40 µL of test article for 10 min, rinsed with DPBS and post-incubated for 16 h. Cell viability was determined by the water-soluble tetrazolium salt-1 (WST-1) assay, and relative viability was calculated as the absorbance at 450 nm relative to that of the negative control. Under OECD Test Guideline 492, a liquid maintaining viability above 35% is classified as non-irritant. The test was conducted under non-GLP conditions.

## 2.4. Animal studies

The protocols of the animal studies were approved by the Institutional Animal Care and Use Committee at HLB bioStep (formerly KNOTUS; Incheon, Republic of Korea), where the studies were conducted (approval nos. 22-KE-0310, 24-HB-0698, 24-HB-0699 and 24-HB-0713), and all animals received care in compliance with the guidelines of the Committee.

Male New Zealand white rabbits weighing approximately 2.5 kg were acclimated for 7 days prior to study initiation. The animals were housed individually in stainless steel cages (W 500 × L 800 × H 500 mm) at a temperature of 23 ± 3°C, relative humidity of 55 ± 15%, ventilation of 10–20 air changes per hour, illumination of 150–300 lux, and a 12 h light–dark cycle. Standard laboratory diet (Cargill Agri Purina, Seongnam, Republic of Korea) and purified water supplied in polycarbonate drinking bottles were freely consumed.

Ocular pharmacokinetics of lifitegrast were characterized following administration of eye drop, chamber-loaded lens, and surface-loaded lens. For the eye drop, 50 µL of the 8 mg/mL drug solution was instilled onto the center of the cornea of both eyes with a pipette (0.4 mg/eye). For lens administration, animals were anesthetized and the lens containing approximately 10 µL of drug solution was applied to both eyes, followed by third eyelid flap and tarsorrhaphy to keep the eyelids closed. Doses of 0.4 and 1.25 mg/eye were administered for the chamber-loaded lens and surface-loaded lens, respectively. The surgical site was disinfected with 0.5% povidone-iodine solution prior to and following the procedure. Lenses were removed at 6 h in animals sampled at that time point or later; in animals subjected to earlier

tissue collection, lenses were removed immediately prior to euthanasia. Collected lenses were stored at -70°C until analysis.

Blood was collected from the jugular vein into heparinized tubes (5 IU/mL) and centrifuged at 3,000 rpm and 4°C for 10 min to obtain plasma. Blood sampling was conducted at 0.25, 0.5, 1, 2, 4, 6 and 8 h in the eye drop group and at 0.25, 0.5, 1, 2, 4, 6, 8, 10 and 12 h in both lens groups. Ocular tissues (cornea, conjunctiva, sclera, and aqueous humor) were collected at 0.5, 4 and 8 h in the eye drop group, at 0.5, 2, 6 and 12 h in the chamber-loaded lens group, and at 0.25, 0.5, 1, 2, 4, 8 and 12 h in the surface-loaded lens group. Solid tissues were gently wiped with gauze prior to weighing. Plasma and ocular tissues were stored at -70°C until analysis.

## 2.5. Drug release from the lenses

Drug release in vitro was determined by immersing a chamber-loaded lens containing drug solution in 10 mL of unstirred water at 25°C, with the release structures submerged. Aliquots of 100 µL were withdrawn at 0.25, 0.5, 1, 2, 3, 4 and 6 h without replacement of the medium. The lens was retrieved at 6 h. Residual drug in lenses collected from both in vitro and in vivo studies was also determined. The sealing membrane was separated from the lens body with forceps and each part was finely cut. The fragments were vortex-mixed in 5 mL of water for 30 s and extracted on a rolling shaker (HWLAB® RM1; Zhejiang Huawei Scientific Instrument, Linhai, China) at 50 rpm for 1 h.

Lifitegrast concentration in the medium and lens extract was quantified by HPLC-UV (Waters 2690 separations module coupled with a Waters 996 photodiode array; Waters, Milford, Massachusetts, USA). Chromatographic separation was performed on an Atlantis dC18 column (5.0 µm, 2.1 mm × 150 mm; Waters, Milford, Massachusetts, USA) using a Waters 2690 separations module, with the column oven maintained at 40°C and an injection volume of 10 µL. The mobile phase consisted of (A) 0.1% formic acid in water and (B) 0.1% formic acid in acetonitrile, at a constant flow rate of 0.4 mL/min under the following gradient elution: 40% B at 0.0 min, held until 3.0 min, increased to 90% B at 3.5 min, held at 90% B until 6.0 min, returned to 40% B at 6.1 min, and held until 11.0 min. The detection wavelength was 260 nm and the calibration range was 1–100 µg/mL. Drug amounts were calculated by multiplying the quantified concentration by the corresponding volume of the medium or lens extract. The in vivo release amount was calculated by subtracting the residual amount in the retrieved lens from the amount loaded. The in vitro and in vivo release percentages were expressed as the released amount divided by the total amount, calculated as the sum of the released and residual amounts.

## 2.6. Non-compartmental analysis

Lifitegrast concentrations in plasma and ocular tissues were determined by a previously reported LC-MS/MS method [26]. Analysis was performed on an Agilent 1290 Infinity II UHPLC system coupled with an Agilent 6495C triple-quadrupole mass spectrometer (Agilent Technologies, Santa Clara, California, USA). Ocular tissues were homogenized with water at a concentration of 0.1 g/mL. The calibration range was 0.5–500 ng/mL for all matrices. Samples exceeding the upper limit of quantification were diluted with blank matrix prior to analysis. Concentrations for solid tissues (cornea, conjunctiva, and sclera) are

reported as µg/g or ng/g. Quality control samples were analyzed prior to and following each analytical run, and all runs met the acceptance criteria.

Pharmacokinetic parameters of lifitegrast were calculated by non-compartmental analysis with Phoenix WinNonlin (version 8.3.4; Certara, Princeton, New Jersey, USA). Parameters for plasma were obtained by a two-stage approach, in which individual parameters were calculated from individual plasma concentrations and then averaged. Parameters for ocular tissues were obtained by a naïve-pooled approach, in which parameters were calculated from mean concentrations at each time point, since tissue sampling was destructive. The parameters included the maximum concentration ( $C_{max}$ ), the time to reach  $C_{max}$  ( $T_{max}$ ), and the area under the concentration–time curve from time zero to the last observation time point ( $AUC_{last}$ ). Relative ocular tissue exposure in the lens groups was expressed as the dose-normalized tissue exposure ratio, calculated as the ratio of dose-normalized  $AUC_{last}$  to that of the eye drop group.

## 2.7. Population pharmacokinetic modeling

A pharmacokinetic model integrating drug input from the lens, precorneal elimination, and corneal absorption and elimination was developed to quantify the effect of lens application on the ocular pharmacokinetics of lifitegrast (Fig. 2). Population-based analysis was applied to the sparsely sampled ocular tissue data using the stochastic approximation expectation maximization algorithm in Monolix (version 2023R1, Lixoft, Saclay, France). Model parameters were estimated by simultaneously fitting in vitro drug release, in vivo drug remaining in the lens, and corneal concentrations obtained after eye drop and chamber- and surface-loaded lens administration.

For the chamber-loaded lens, the fraction released following a lag time ( $T_{lag,CLL}$ ) was described by the Weibull function, which represents the shape and scale of release as separate parameters, allowing the two to be compared directly between in vitro and in vivo conditions:

$$F(t) = 1 - \exp \left[ -(t/\tau)^\beta \right]$$

1

where  $\tau$  is the scale parameter corresponding to the time at which 63.2% of the drug is released, and  $\beta$  is the shape parameter. The fraction remaining in the lens is therefore given by Eq. 2, and differentiation of each side with respect to time gives Eqs. 3 and 4:

$$X_{lens}/X_{lens,0} = 1 - F(t) = \exp \left[ -(t/\tau)^\beta \right]$$

2

$$d/dt (X_{lens}) = -k_{release}(t) \bullet X_{lens}$$

3

$$k_{release}(t) = (\beta / \tau) \bullet (t / \tau)^{\beta - 1}$$

4

where  $X_{lens}$  is the amount of drug remaining in the lens at time  $t$ ,  $X_{lens,0}$  is the initial amount of drug in the lens, and  $k_{release}(t)$  is the time-dependent release rate constant. If  $\beta$  is less than 1,  $k_{release}(t)$  approaches infinity as  $t$  approaches 0, a mathematical property of the Weibull function rather than a physically realistic release rate. To avoid this divergence at  $t = 0$ , a time offset (0.0001 h) was added when evaluating  $k_{release}(t)$ .

For the surface-loaded lens, drug input was described as the sum of two components, a burst and bidirectional partitioning. A fraction of the loaded dose ( $F_{burst}$ ) was assigned directly to the precorneal site as an initial input. The remaining fraction of the loaded dose ( $1 - F_{burst}$ ) on the lens surface underwent bidirectional partitioning with the precorneal site, described by reversible first-order rate constants for transfer from the lens to the precorneal site ( $k_{lens,out}$ ) and from the precorneal site back to the lens ( $k_{lens,in}$ ). The chamber-loaded lens released drug as a single release process, without a burst component ( $F_{burst} = 0$ ), following the Weibull function. Drug input, absorption, and elimination were described by the following equations:

$$X_{lens,0} = Dose_{lens} \bullet (1 - F_{burst})$$

5

$$X_{pc,0} = Dose_{eye\ drop} \text{ (eye drop) or } Dose_{lens} \bullet F_{burst} \text{ (lens) (6)}$$

$$d/dt (X_{lens}) = -k_{release}(t) \bullet X_{lens} \text{ (7A, chamber-loaded lens)}$$

$$d/dt (X_{lens}) = -k_{lens,out} \bullet X_{lens} + k_{lens,in} \bullet X_{pc} \text{ (7B, surface-loaded lens)}$$

$$d/dt (X_{pc}) = -k_a \bullet X_{pc} - k_{el,pc} \bullet X_{pc} + k_{release}(t) \bullet X_{lens} \text{ (8A, chamber-loaded lens)}$$

$$d/dt (X_{pc}) = -k_a \bullet X_{pc} - k_{el,pc} \bullet X_{pc} + k_{lens,out} \bullet X_{lens} - k_{lens,in} \bullet X_{pc} \text{ (8B, surface-loaded lens)}$$

$$d/dt (X_{cornea}) = k_a \bullet X_{pc} - k_{el,cornea} \bullet X_{cornea}$$

9

where  $X_{pc,0}$  is the initial amount of drug at the precorneal site,  $X_{pc}$  and  $X_{cornea}$  are the amount of drug at the precorneal site and in the cornea, respectively,  $k_a$  is the absorption rate constant from the precorneal site into the cornea,  $k_{el,pc}$  and  $k_{el,cornea}$  are the apparent elimination rate constants at the precorneal site

and in the cornea, respectively,  $Dose_{lens}$  and  $Dose_{eye\ drop}$  are the administered doses for lens and eye drop groups, respectively,  $F_{burst}$  is the fraction of  $Dose_{lens}$  released via the burst pathway. Corneal concentrations were obtained by dividing  $X_{cornea}$  by an average corneal weight (0.077 g) determined in this study.

Drug input from the lens was assumed to occur only during lens application. Over this period, the absorption rate constant from the precorneal site to the cornea ( $k_a$ ), the lag time for absorption from the precorneal site to the cornea ( $T_{lag}$ ), and precorneal and corneal elimination ( $k_{el,pc}$  and  $k_{el,cornea}$ ) were set as categorical covariates on formulation to allow different values in the lens groups relative to the eye drop group. Following lens removal, elimination was described by the eye drop parameters, except for  $k_{el,cornea}$  of the surface-loaded lens group. Residual lens-associated drug was removed, and lens–precorneal partitioning for the surface-loaded lens and drug release from the chamber-loaded lens were discontinued; drug already present at the precorneal site and in the cornea was retained as the initial condition for this post-removal phase.

Whether  $\tau$ ,  $\beta$  and the absorption and elimination parameters differed between conditions (in vitro vs. in vivo) and formulations (eye drop vs. chamber-loaded lens vs. surface-loaded lens) was determined by likelihood ratio test based on the objective function value (OFV), parameter precision, and prediction distributions. Between-subject variability was described using log-normal distributions for all parameters except  $F_{burst}$  for which a logit-normal distribution was applied to constrain individual estimates within the interval (0, 1) through a logistic transformation. A proportional residual error model was used for corneal concentrations and residual drug in the lens, and an additive model for in vitro release. Five hundred Monte Carlo simulations were performed to internally validate the developed population pharmacokinetic model using Berkeley Madonna (version 8.3.11, Berkeley, California, USA). The percentiles of the simulated data were visually compared with observed corneal concentrations following eye drop and chamber- and surface-loaded lens administration. The median (10th–90th percentile) of corneal  $C_{max}$  and AUC derived from the model was also compared with the corresponding parameters obtained by the naïve-pooled approach.

Human corneal concentrations were predicted from rabbit corneal concentrations, by scaling the absorption rate constant from precorneal site to cornea ( $k_a$ ) and the corneal weight ( $WT_{cornea}$ ), based on differences in corneal surface area and volume between rabbits and humans [20]. Since the corneal permeability coefficient for lifitegrast has not been characterized across species,  $k_a$  was assumed to scale with the corneal surface area-to-volume ratio, and  $WT_{cornea}$  was assumed to scale with corneal volume. Corneal surface area and volume were 1.55 cm<sup>2</sup> and 0.0887 mL in rabbits, and 1.04 cm<sup>2</sup> and 0.077 mL in humans, obtained from the literature [27, 28]. Using this exploratory translational model, inter-species differences in corneal pharmacokinetics were estimated, and an eye-drop-equivalent lens dose was derived based on AUC equivalents. Interspecies scaling and human simulations were performed for the eye drop and chamber-loaded lens groups only. For the surface-loaded lens, the

terminal elimination phase could not be reliably characterized due to the marked decline in corneal concentration observed between 8 and 12 h, precluding extrapolation to a 24 h human dosing interval.

### 3. Results

#### 3.1. Ocular irritation test

The ocular irritation of the controls (DPBS and BKC) and test articles (lifitegrast alone, lens loading solution, and HPMC) in a reconstructed human cornea-like epithelium model is summarized in Table 1. Negative and positive controls resulted in cell viabilities of 100.00% and 6.65%, respectively, confirming the validity of the assay. Lifitegrast alone at 25–100 mg/mL was classified as non-irritant, with cell viabilities of 99.30–109.80%. The lens loading solution, containing 40 mg/mL of lifitegrast and 3 mg/mL of sodium thiosulfate pentahydrate, resulted in a viability of 99.75% and was classified as non-irritant. HPMC was tested at 10 mg/mL, the highest concentration allowed by its viscosity. It resulted in a viability of 128.20% and was also classified as non-irritant.

Table 1  
Ocular irritation of lifitegrast alone, lens loading solution, and HPMC in a reconstructed human cornea-like epithelium model. Viability was expressed as mean  $\pm$  SD (n = 2)

| Test article                                     | Concentration (mg/mL) | Viability (%)     | Classification |
|--------------------------------------------------|-----------------------|-------------------|----------------|
| DPBS (negative control)                          | -                     | 100.00 $\pm$ 4.81 | -              |
| BKC (positive control)                           | 50 (5% w/v)           | 6.65 $\pm$ 0.49   | -              |
| Lifitegrast (alone)                              | 25                    | 99.30 $\pm$ 7.80  | Non-irritant   |
|                                                  | 50                    | 108.50 $\pm$ 3.30 | Non-irritant   |
|                                                  | 75                    | 109.80 $\pm$ 6.90 | Non-irritant   |
|                                                  | 100                   | 102.40 $\pm$ 1.20 | Non-irritant   |
| Lifitegrast (lens loading solution) <sup>a</sup> | 40                    | 99.75 $\pm$ 1.20  | Non-irritant   |
| HPMC                                             | 10                    | 128.20 $\pm$ 5.30 | Non-irritant   |

<sup>a</sup> Lens loading solution contained 40 mg/mL lifitegrast and 3 mg/mL sodium thiosulfate pentahydrate in 20 mM disodium hydrogen phosphate adjusted to pH 7.4 with 1 M NaOH.

#### 3.2. In vitro and in vivo drug release

In vitro and in vivo drug release profiles of lifitegrast from the chamber-loaded and surface-loaded lenses are shown in Fig. 3. In vitro, the chamber-loaded lens released approximately 15% of the dose by 0.5 h, followed by a slower increase to a final release of approximately 50% at 6 h. In vivo, the chamber-loaded lens showed a similar initial release (18% at 0.5 h) but reached a higher final release of 68% at 6 h. Direct comparison of the release profile between in vitro and in vivo data was limited since drug remaining in

the chamber-loaded lens in vivo was determined at only three time points (0.5, 2, and 6 h); the in vivo release pattern was further characterized by pharmacokinetic modeling. The surface-loaded lens exhibited a high initial burst of approximately 60% at 0.25 h but release then increased only gradually from 1 h to a final release of 80% at 6 h.

### 3.3. Non-compartmental pharmacokinetic analysis

The average concentration–time profiles of lifitegrast in plasma and ocular tissues following ophthalmic administration are shown in Fig. 4. The corresponding pharmacokinetic parameters are summarized in Table 2.

Following eye drop instillation, plasma concentrations of lifitegrast reached a  $C_{\max}$  of  $18.33 \pm 13.47$  ng/mL at 0.25 h and declined below the limit of quantification after 2 h. In contrast, plasma concentrations in both lens groups remained detectable and exhibited a relatively stable plateau throughout the 6 h period of lens wear. Following lens removal at 6 h, plasma concentrations declined rapidly. Using reported intravenous data from our previous study [26], absolute bioavailability was calculated at  $5.30 \pm 3.47\%$  for the eye drop,  $27.80 \pm 10.34\%$  for the chamber-loaded lens, and  $25.70 \pm 8.92\%$  for the surface-loaded lens.  $T_{\max}$  also differed markedly between the two lens formulations: the chamber-loaded lens reached  $C_{\max}$  at  $2.38 \pm 2.50$  h ( $16.87 \pm 2.20$  ng/mL), whereas the surface-loaded lens reached  $C_{\max}$  at  $0.44 \pm 0.13$  h ( $72.16 \pm 21.32$  ng/mL). This difference reflects the in vivo release behavior of the two lenses, with the surface-loaded lens showing an initial burst release, in contrast to the more gradual release from the chamber-loaded lens over the 6 h period.

Ocular tissue concentrations obtained after eye drop instillation reached  $C_{\max}$  at 0.5 h, the earliest sampling time, and declined thereafter. Ocular exposure was similar between cornea and conjunctiva (AUC ratio = 1:1). Given the limited number of sampling points (three per matrix), comparisons of ocular pharmacokinetics between formulations are based primarily on interpretation of the pharmacokinetic parameters, rather than on the concentration–time profiles. Following chamber-loaded lens application, the corneal and aqueous humor concentrations increased gradually to 6 h, consistent with the sustained release from the lens. In contrast, conjunctival and scleral concentration profiles did not follow this pattern. Compared with the eye drop, corneal AUC increased 3-fold with chamber-loaded lens application, with comparable fold-increases observed in sclera and aqueous humor. The AUC ratio of cornea to conjunctiva also increased from 1:1 to 2:1, indicating a shift in distribution toward the cornea. Following surface-loaded lens application,  $T_{\max}$  values differed among the four tissues: 1 h in cornea, 0.5 h in conjunctiva and sclera, and 4 h in aqueous humor. Compared with the eye drop, dose-normalized AUC increased 111-fold in the cornea and 321-fold in aqueous humor. The AUC ratio of cornea to conjunctiva was approximately 32:1, the highest among the three formulations.

Table 2  
Pharmacokinetic parameters of lifitegrast in plasma and ocular tissues following ophthalmic administration in rabbits

| Matrix <sup>a</sup> | Parameter                                          | Eye drop<br>(0.4 mg/eye) | Chamber-loaded lens<br>(0.4 mg/eye) | Surface-loaded lens<br>(1.25 mg/eye) |
|---------------------|----------------------------------------------------|--------------------------|-------------------------------------|--------------------------------------|
| Plasma              | T <sub>max</sub> (h)                               | 0.25 ± 0.00              | 2.38 ± 2.50                         | 0.44 ± 0.13                          |
|                     | C <sub>max</sub> (ng/mL)                           | 18.33 ± 13.47            | 16.87 ± 2.20                        | 72.16 ± 21.32                        |
|                     | AUC <sub>last</sub> (ng·h/mL)                      | 14.18 ± 9.29             | 74.36 ± 27.67                       | 214.78 ± 74.54                       |
|                     | BA (%) <sup>b</sup>                                | 5.30 ± 3.47              | 27.80 ± 10.34                       | 25.70 ± 8.92                         |
| Cornea              | T <sub>max</sub> (h)                               | 0.50                     | 6.00                                | 1.00                                 |
|                     | C <sub>max</sub> (µg/g)                            | 1.58                     | 2.84                                | 887.75                               |
|                     | AUC <sub>last</sub> (µg·h/g)                       | 6.83                     | 20.51                               | 2,377.59                             |
|                     | Dose-normalized exposure ratio (fold) <sup>c</sup> | 1.00                     | 3.00                                | 111.43                               |
| Conjunctiva         | T <sub>max</sub> (h)                               | 0.50                     | 0.50                                | 0.50                                 |
|                     | C <sub>max</sub> (ng/g)                            | 1,434.08                 | 1,623.83                            | 33,725.00                            |
|                     | AUC <sub>last</sub> (ng·h/g)                       | 7,183.42                 | 10,744.12                           | 73,664.64                            |
|                     | Dose-normalized exposure ratio (fold) <sup>c</sup> | 1.00                     | 1.50                                | 3.28                                 |
| Sclera              | T <sub>max</sub> (h)                               | 0.50                     | 6.00                                | 0.50                                 |
|                     | C <sub>max</sub> (ng/g)                            | 219.85                   | 397.45                              | 13,990.00                            |
|                     | AUC <sub>last</sub> (ng·h/g)                       | 1,015.10                 | 2,653.77                            | 39,343.38                            |
|                     | Dose-normalized exposure ratio (fold) <sup>c</sup> | 1.00                     | 2.61                                | 12.40                                |
| Aqueous humor       | T <sub>max</sub> (h)                               | 0.50                     | 6.00                                | 4.00                                 |
|                     | C <sub>max</sub> (ng/mL)                           | 21.39                    | 79.29                               | 21,350.00                            |

<sup>a</sup> Parameters for plasma are presented as the mean ± SD (n = 4); parameters for ocular tissues are single values obtained by a naïve-pooled approach (section 2.6)

| Matrix <sup>a</sup>                                                                                                                                                          | Parameter                                          | Eye drop<br>(0.4 mg/eye) | Chamber-loaded lens<br>(0.4 mg/eye) | Surface-loaded lens<br>(1.25 mg/eye) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|--------------------------|-------------------------------------|--------------------------------------|
|                                                                                                                                                                              | AUC <sub>last</sub> (ng·h/mL)                      | 143.01                   | 577.86                              | 143,455.50                           |
|                                                                                                                                                                              | Dose-normalized exposure ratio (fold) <sup>c</sup> | 1.00                     | 4.04                                | 321.00                               |
| <sup>a</sup> Parameters for plasma are presented as the mean ± SD (n = 4); parameters for ocular tissues are single values obtained by a naïve-pooled approach (section 2.6) |                                                    |                          |                                     |                                      |

<sup>b</sup> Absolute bioavailability (BA) was calculated as  $(AUC_{last,topical} \times Dose_{iv}) / (AUC_{inf,iv} \times Dose_{topical}) \times 100$  using the total dose per rabbit and intravenous data obtained from our previous study [26].

<sup>c</sup> Dose-normalized tissue exposure ratio compares tissue AUC<sub>last</sub> per administered dose with the eye drop as a reference. It is an exposure-based index, not the fraction of the administered dose absorbed into the tissue. AUC<sub>last</sub> was calculated over 0–8 h for the eye-drop group and 0–12 h for the lens groups; the dose-normalized ratios therefore compare exposure over different observation periods.

### 3.4. Population pharmacokinetic modeling

The population pharmacokinetic model was developed by simultaneously fitting in vitro drug release, in vivo drug remaining in the lens, and corneal concentrations obtained after eye drop and chamber- and surface-loaded lens administration. Prediction distributions and parameter estimates are shown in Fig. 5 and Table 3, respectively. The prediction distributions adequately captured the observed data. Among the fixed effect parameters with estimable standard errors, the relative standard errors (RSE) ranged from 0.174% to 32.5%. Standard errors for the fixed effect could not be estimated for the lag time for drug release from the chamber-loaded lens ( $T_{lag,CLL}$ ) and the transfer rate constant from the precorneal site to the surface-loaded lens ( $k_{lens,in}$ ).

For the chamber-loaded lens, the shape parameter ( $\beta$ ) was estimated at 0.54, and the scale parameter ( $\tau$ ) was 13.28 h in vitro and 5.06 h in vivo, approximately 2.6-fold higher in vitro than in vivo. Separation of  $\tau$  between in vitro and in vivo conditions significantly improved the model fit ( $\Delta OFV = 32$ ,  $p < 0.05$ ), whereas separation of  $\beta$  did not ( $\Delta OFV = 3$ ,  $p > 0.05$ ); the individually estimated  $\beta$  values were also numerically similar (0.53 and 0.52 for in vitro and in vivo, respectively). A common shape parameter was therefore retained, as separate values did not improve the fit sufficiently to justify the additional parameter. Corneal absorption rate from the precorneal site was slow, with  $k_a$  estimated at  $2.10 \cdot 10^{-3} \text{ h}^{-1}$ . The model estimated a lower apparent precorneal elimination ( $k_{el,pc}$ ) during lens wear, from 4.64 to  $2.19 \text{ h}^{-1}$  (a 53% decrease). Following chamber-loaded lens application, apparent corneal elimination rate constant ( $k_{el,cornea}$ ) decreased from 0.23 to  $0.079 \text{ h}^{-1}$  (a 66% decrease), relative to the eye drop group. The fraction of drug absorbed into the cornea, calculated as  $k_a / (k_a + k_{el,pc})$ , increased from 0.045% in the

eye drop to 0.096% during lens wear, indicating that the reduced elimination during lens wear increased the amount of drug reaching the cornea. These fractions represent the proportion of drug at the precorneal site that is absorbed into the cornea, and do not represent the fraction of the total loaded lens dose absorbed into the cornea.

Following surface-loaded lens application, the model assigned 62% of the loaded dose ( $F_{\text{burst}}$ ) to a burst pathway. The remaining fraction of the loaded dose ( $1 - F_{\text{burst}}$ ) on the lens surface was partitioned bidirectionally with the precorneal site during lens wear, with first-order rate constants of  $0.14 \text{ h}^{-1}$  ( $k_{\text{lens,out}}$ ) and  $0.12 \text{ h}^{-1}$  ( $k_{\text{lens,in}}$ ). Separating  $k_{\text{el,pc,lens}}$  into distinct values for the chamber-loaded and surface-loaded lens groups did not significantly improve the model fit ( $\Delta\text{OFV} = 3$ ,  $p > 0.05$ ), and the RSEs of the separated estimates could not be reliably determined. Accordingly, a single shared  $k_{\text{el,pc,lens}}$  value was retained for both lens types. In contrast to the chamber-loaded lens, apparent corneal elimination ( $k_{\text{el,cornea}}$ ) for the surface-loaded lens increased from 0.23 to  $0.56 \text{ h}^{-1}$  relative to the eye drop. Corneal absorption rate from the precorneal site was markedly higher ( $k_{\text{a,SLL}} = 0.36 \text{ h}^{-1}$ ) than the value shared by the eye drop and chamber-loaded lens ( $k_{\text{a}} = 2.10 \cdot 10^{-3} \text{ h}^{-1}$ ), corresponding to a 14% fraction of drug at the precorneal site entering the cornea compared with 0.045% for the eye drop. The absorption lag time also increased from  $3.90 \cdot 10^{-2} \text{ h}$ , shared by the eye drop and chamber-loaded lens, to 0.21 h for the surface-loaded lens, possibly reflecting the increased viscosity of the HPMC-containing solution.

Following five-hundred Monte Carlo simulations, model predictions were visually compared with observations following eye drop, chamber-loaded, and surface-loaded lens administration in Fig. S1. The median and 10th–90th percentile range of corneal pharmacokinetic parameters obtained after ophthalmic administration were compared with the pharmacokinetic parameters obtained by the naïve-pooled approach in Table S1. The model described the overall corneal concentration-time profiles, although it did not reproduce the local increase between 2 and 4 h in the surface-loaded lens group. Model-derived pharmacokinetic parameters were compared descriptively with the naïve-pooled estimates.

Model simulations of corneal exposure following single-dose and repeated-dose administration of eye drop and chamber-loaded lens in rabbits and humans are shown in Fig. 6 and Table 4. Based on differences in corneal surface area and volume,  $k_{\text{a}}$  and  $\text{WT}_{\text{cornea}}$  in humans were approximately 77% and 87% of the corresponding rabbit values, respectively. For both the eye drop and chamber-loaded lens formulations, the population mean  $C_{\text{max}}$  and AUC in humans were approximately 11% lower than in rabbits (Fig. 6A, B). Over the 144–168 h simulation interval, the median corneal AUC was 15,627.80 ng·h/g for the 0.33 mg/eye once-daily chamber-loaded lens regimen and 15,776.35 ng·h/g for the 0.4 mg/eye twice-daily experimental eye-drop regimen. The corresponding median trough concentrations were 26.89 and 131.09 ng/g, respectively.

Table 3

Population pharmacokinetic parameter estimates of drug input, precorneal elimination, and corneal absorption and elimination for lifitegrast

| Parameter                  | Description                                                                       | Unit            | Fixed effect (%RSE)          | Omega <sup>a</sup> (%RSE) |
|----------------------------|-----------------------------------------------------------------------------------|-----------------|------------------------------|---------------------------|
| $\beta$                    | Shape parameter for chamber-loaded lens                                           | -               | 0.54 (0.179%)                | -                         |
| $\tau_{\text{vitro}}$      | Scale parameter for chamber-loaded lens, in vitro                                 | h               | 13.28 (17.3%)                | 0.34 (69.5%)              |
| $\tau_{\text{vivo}}$       | Scale parameter for chamber-loaded lens, in vivo                                  | h               | 5.06 (15.1%)                 | 0.14 (67.4%)              |
| $T_{\text{lag,CLL}}$       | Lag time for drug release from lens to precorneal site for chamber-loaded lens    | h               | 0.15                         |                           |
| $F_{\text{burst}}^b$       | Fraction of dose released via burst pathway for surface-loaded lens               | -               | 0.62 (4.64%)                 | 0.26 (67.8%)              |
| $k_{\text{lens,out}}$      | Transfer rate constant from lens to precorneal site for surface-loaded lens       | $\text{h}^{-1}$ | 0.14 (20.1%)                 | 0.31                      |
| $k_{\text{lens,in}}$       | Transfer rate constant from precorneal site to lens for surface-loaded lens       | $\text{h}^{-1}$ | 0.12                         | 0.76                      |
| $k_a$                      | Absorption rate constant from precorneal site to cornea                           | $\text{h}^{-1}$ | $2.10 \cdot 10^{-3}$ (13.1%) | 0.21                      |
| $k_{a,\text{SLL}}$         | Absorption rate constant from precorneal site into cornea for surface-loaded lens | $\text{h}^{-1}$ | 0.36 (32.5%)                 | 0.36                      |
| $T_{\text{lag}}$           | Lag time for absorption from precorneal site to cornea                            | h               | $3.90 \cdot 10^{-2}$ (2.17%) | -                         |
| $T_{\text{lag,SLL}}$       | Lag time for absorption from precorneal site to cornea for surface-loaded lens    | h               | 0.21 (0.174%)                | -                         |
| $k_{\text{el,pc,ED}}$      | Apparent elimination rate constant at precorneal site for eye drop                | $\text{h}^{-1}$ | 4.64 (28.2%)                 | 0.39 (44.6%)              |
| $k_{\text{el,pc,lens}}$    | Apparent elimination rate constant at precorneal site for lens groups             | $\text{h}^{-1}$ | 2.19 (20.5%)                 | 0.39 (22.2%)              |
| $k_{\text{el,cornea,ED}}$  | Apparent elimination rate constant in cornea for eye drop                         | $\text{h}^{-1}$ | 0.23 (18.2%)                 | 0.33 (55.0%)              |
| $k_{\text{el,cornea,CLL}}$ | Apparent elimination rate constant in cornea for chamber-loaded lens              | $\text{h}^{-1}$ | $7.90 \cdot 10^{-2}$ (12.9%) | 0.15 (49.4%)              |
| $k_{\text{el,cornea,SLL}}$ | Apparent elimination rate constant in cornea for surface-loaded lens              | $\text{h}^{-1}$ | 0.56 (14.8%)                 | 0.21 (51.2%)              |

<sup>a</sup> Omega values represent between-subject variability, reported as the estimated standard deviation of the random effect on the log scale (log-normal parameters) or the logit scale (logit-normal parameter).

<sup>b</sup> For logit-normal parameter ( $F_{burst}$ ), this standard deviation cannot be interpreted as an ordinary coefficient of variation.

Table 4

Model-predicted single-dose and repeated-dose corneal exposure of lifitegrast in rabbits and humans, presented as median (10th–90th percentile) following five hundred Monte Carlo simulations

| Species                                                           | Formulation         | Regimen                          | $C_{max}$ (ng/g)                             | $C_{trough}$ (ng/g)                   | AUC (ng·h/g)                                    | $C_{avg,ss}$ <sup>a</sup> (ng/g)         |
|-------------------------------------------------------------------|---------------------|----------------------------------|----------------------------------------------|---------------------------------------|-------------------------------------------------|------------------------------------------|
| Rabbit                                                            | Eye drop            | 0.4 mg, single-dose              | 1,726.29 <sup>b</sup><br>[983.73–2,942.61]   | Not applicable                        | 9,087.42 <sup>b</sup><br>[4,226.80–17,663.34]   | Not applicable                           |
| Human                                                             | Eye drop            | 0.4 mg, single-dose              | 1,527.53 <sup>b</sup><br>[868.34–2,681.61]   | Not applicable                        | 7,551.45 <sup>b</sup><br>[3,889.21–16,333.79]   | Not applicable                           |
| Rabbit                                                            | Chamber-loaded lens | 0.4 mg, single-dose              | 2,351.75 <sup>b</sup><br>[1,312.89–4,028.73] | Not applicable                        | 20,443.00 <sup>b</sup><br>[11,791.99–34,274.82] | Not applicable                           |
| Human                                                             | Chamber-loaded lens | 0.4 mg, single-dose              | 2,113.76 <sup>b</sup><br>[1,218.56–3,742.22] | Not applicable                        | 19,028.35 <sup>b</sup><br>[10,448.46–32,924.45] | Not applicable                           |
| Human                                                             | Eye drop            | 0.4 mg, BID, 7 days <sup>c</sup> | 1,660.72 <sup>d</sup><br>[918.39–2,990.40]   | 131.09 <sup>d</sup><br>[28.70–390.83] | 15,776.35 <sup>d</sup><br>[7,385.22–30,876.50]  | 657.35 <sup>d</sup><br>[307.72–1,286.52] |
| Human                                                             | Chamber-loaded lens | 0.33 mg, QD, 7 days <sup>c</sup> | 1,731.83 <sup>d</sup><br>[990.74–3,013.80]   | 26.89 <sup>d</sup><br>[3.12–141.08]   | 15,627.80 <sup>d</sup><br>[8,930.24–27,196.50]  | 651.16 <sup>d</sup><br>[372.09–1,133.19] |
| <sup>a</sup> $C_{avg,ss}$ , average concentration at steady state |                     |                                  |                                              |                                       |                                                 |                                          |

<sup>b</sup> These parameters were derived from the 0–24 h interval of the simulated concentration–time profile.

<sup>c</sup> Neither regimen has been clinically validated; the eye-drop regimen reflects the experimental dosing used in this study rather than the approved commercial lifitegrast 5% ophthalmic solution, and the lens dose was derived from model-based AUC matching.

<sup>d</sup> These parameters were derived from the 144–168 h interval of the simulated concentration–time profile.

## 4. Discussion

The present study directly quantified ocular tissue and systemic exposure to lifitegrast following administration of eye drop and two prototype contact lens loading configurations in rabbits. Both lens formulations increased ocular exposure relative to the eye drop across all tissues examined, as well as systemic exposure. Population pharmacokinetic modeling indicated a reduction in precorneal elimination during lens wear, consistent with prolonged precorneal drug residence as a contributing factor to this increased exposure. Whereas evidence for contact lens delivery of lifitegrast has previously relied on indirect indicators, such as determination of in vitro release or tear fluid concentrations [23], the present findings are based on direct quantification of ocular tissue concentrations, supported by population pharmacokinetic modeling to explore how lens delivery affected drug absorption and elimination.

Of the ocular surface tissues (cornea and conjunctiva) examined, only the cornea exhibited a concentration profile that reflected the release pattern of the chamber-loaded lens, with a gradual increase to 6 h. This is likely attributable to the avascular nature of the cornea, as well as its more direct contact with the post-lens tear film. The conjunctiva, in contrast to the avascular cornea, has an extensive vascular supply, through which absorbed drug can be rapidly cleared into the systemic circulation [8]. Conjunctival concentrations declined more rapidly than those in the other ocular tissues in the lens groups during the later sampling period, which may reflect this vascular clearance. Differences in continued drug supply after lens removal or more rapid distribution of drug from the conjunctiva to other tissues may also have contributed. These combined factors could not be separated in this study and likely obscured the sustained-release effect of the lens in the conjunctiva.

The in vitro release test was designed to consider two features: the loading solution inside the lens is at 25°C until immediately prior to administration, and the post-lens tear film is static in nature. However, our population pharmacokinetic modeling revealed that  $\tau$  was 2.6-fold shorter in vivo (5.06 h) than in vitro (13.28 h), reflecting more rapid attainment of 63.2% release in vivo. Differences in temperature and mechanical conditions between the two settings, such as the higher ocular surface temperature (approximately 34°C [29]) relative to the in vitro condition and possible mechanical disturbance from ocular movement, may have contributed to this difference; the relative contribution of each factor, however, remains unclear.

Drug input from the two lens configurations was modeled using distinct structures reflecting their different physical modes of drug loading. In the chamber-loaded lens, drug is enclosed within an internal chamber, separated from the precorneal site by the sealing membrane. Drug was released to the precorneal site over time through the release structures, as expressed by a Weibull-type release function. In contrast, the surface-loaded lens involves drug coated directly onto the lens surface, allowing continuous and direct contact with the precorneal site. Upon contact, an initial fraction of the coating likely underwent rapid diffusion, producing the observed initial burst. The remaining drug on the lens surface then partitioned bidirectionally between the lens surface and the precorneal site throughout the

period of continuous contact; however, the standard error for the reverse-transfer rate constant ( $k_{\text{lens,in}}$ ) could not be estimated, and this reverse process was not experimentally verified.

The chamber-loaded lens supplied drug continuously over the 6 h wearing period, rather than as a single bolus. However, sustained-release does not by itself guarantee that precorneal residence was prolonged; this is supported instead by the population pharmacokinetic modeling, which estimated a marked reduction in apparent precorneal elimination ( $k_{\text{el,pc}}$ ) from 4.64 to 2.19  $\text{h}^{-1}$  during lens wear. This finding is consistent with the static nature of the post-lens tear film, isolated from the pre-lens tear film where drainage and nasolacrimal clearance normally occur [7, 9, 19]. The change in the precorneal elimination rate constant cannot be captured by non-compartmental analysis, illustrating a key advantage of population pharmacokinetic modeling in this study. Apparent corneal elimination ( $k_{\text{el,cornea}}$ ) also decreased during lens wear, from 0.23 to 0.079  $\text{h}^{-1}$ . This decrease is unlikely to reflect an intrinsic reduction in the capacity of the cornea to eliminate drug. The lower apparent corneal elimination during lens wear may instead reflect reduced back-diffusion from the cornea to the precorneal site, since the concentrated drug solution retained at the precorneal site during lens wear may reduce the concentration gradient driving force. However, the model did not separately resolve bidirectional transport between these compartments, and the contribution of back-diffusion could not be confirmed. In addition, the contribution of lens wear could not be separated from that of eyelid closure, since the closure procedures were applied only in the lens groups.

Among the three groups, the surface-loaded lens showed the greatest increase in corneal exposure relative to the eye drop, with drug exposure concentrated in the cornea to a greater extent than with the chamber-loaded lens. Three factors likely contributed to this. First, the surface-loaded lens was designed to place the drug solution near the central cornea, which may have limited exposure of the conjunctiva relative to the cornea. Second, the viscosity of the HPMC-containing solution may have further limited its spread toward the conjunctiva. Third, the higher drug concentration used for the surface-loaded lens (125 mg/mL) may have simply increased diffusion into the cornea, independent of the placement or vehicle effects described above. The relative contribution of these three factors could not be separated in the present study. The markedly higher absorption rate constant estimated for the surface-loaded lens ( $k_{\text{a,SLL}}$ ) is consistent with these same factors. Unlike the chamber-loaded lens, apparent corneal elimination increased during surface-loaded lens wear, from 0.23 to 0.56  $\text{h}^{-1}$ . Corneal concentrations attained by the surface-loaded lens were markedly higher than those of the eye drop and chamber-loaded lens at corresponding time points, ranging from approximately 17-fold to 595-fold. This higher corneal concentration would be expected to increase the flux of drug diffusing back to the precorneal site, which may explain the higher apparent elimination rate constant estimated for this formulation. This effect persisted through 12 h after application (6 h after lens removal), the last sampling time point in this study; sampling beyond this time point would be needed to determine when corneal elimination returns to a rate comparable to that of the eye drop.

Ocular tissue pharmacokinetics is inherently constrained by destructive sampling, in which each animal contributes only a single time point to the concentration–time profile. A naïve-pooled approach under these conditions may not capture the true underlying kinetics, and pharmacokinetic model-based interpretation may therefore be warranted [30]. In the present study, population pharmacokinetic modeling revealed kinetic behavior, such as changes in the apparent elimination rate constants, that non-compartmental analysis could not capture.

Pharmacokinetic modeling serves as a tool for relating drug input from a delivery system to plasma and tissue exposure, and integrating data across species can further enable prediction of human dosing and target-organ exposure [31–34]. In the present study, human corneal concentrations were predicted using only corneal surface area and volume as scaling factors, representing a preliminary form of such interspecies scaling. More sophisticated approaches for predicting human pharmacokinetics, such as allometric scaling, physiologically based pharmacokinetic modeling, and population pharmacokinetic modeling integrated with allometric scaling, have been developed and can be verified against clinical plasma data [35–37]. Ocular tissue concentrations in humans, however, cannot be similarly verified, since direct sampling of human ocular tissue is inherently limited. Since this verification has not been performed, the interspecies scaling applied in the present study should be regarded as preliminary.

The clinical significance of the approximately 5-fold increase in dose-normalized systemic exposure observed with lens application remains uncertain. In patients receiving Xiidra® (lifitegrast ophthalmic solution 5%) twice daily, human plasma concentrations are generally very low, with quantifiable trough levels (0.55–3.74 ng/mL) detected in only 9 of 47 patients following 180–360 days of dosing [38]. Although systemic exposure following topical administration of Xiidra is low, these data do not establish a safety margin for the lens regimens studied here. Increased systemic exposure requires further evaluation. In the rabbit reproductive toxicity study cited in the label [38], adverse fetal findings occurred at the lowest tested intravenous dose (approximately 400-fold the typical human plasma exposure at the recommended ophthalmic dose), and a fetal no observed adverse effect level (NOAEL) was not identified. The prototype lenses were used to investigate drug delivery in a pharmacokinetic proof-of-concept setting, and the present findings do not establish the safety or performance of a clinical lens product. Ocular irritation testing indicated non-irritant classifications for lifitegrast and HPMC individually, at concentrations of 25–100 mg/mL and at 10 mg/mL, respectively; however, the combination of lifitegrast at 125 mg/mL with HPMC at 5 mg/mL, as used for the surface-loaded lens, was not directly tested for ocular irritation, and the safety of repeated lens wear was not evaluated.

Whether contact lens wear is beneficial or detrimental in DED remains controversial: prolonged wear of conventional lenses has been associated with worsened ocular surface symptoms, likely through disruption of the tear film and increased evaporation [39], whereas therapeutic lenses have also been used to protect and hydrate the corneal surface in severe disease [40]. This apparent contradiction may reflect differences between conventional lenses worn for vision correction and drug-loaded lenses designed for short-term, targeted delivery, as in the present study.

Eye drop-based DED treatments, including anti-inflammatory agents such as lifitegrast and cyclosporine, are limited by low ocular bioavailability, largely reflecting rapid precorneal clearance and the limited capacity of the tear film [1, 7]. Since each instillation delivers a variable fraction of drug to the precorneal site [8], therapeutic effect is often inconsistent between patients. This may lead to more frequent or excessive administration and an increased risk of adverse effects, including systemic absorption via the nasolacrimal duct [9, 41]. Compared with an eye drop, the chamber-loaded lens supplies drug gradually over the wearing period, which may reduce the burden on the limited capacity of the tear film. Combined with prolonged ocular surface residence by contact lens, as suggested by the reduction in precorneal elimination observed in this study and the longer mean residence time reported for a lifitegrast-eluting lens by Li et al. [23], this sustained delivery may offer a strategy to increase ocular drug exposure, potentially reducing variability between patients.

## 5. Conclusion

This study provided direct evidence for increased ocular exposure of lifitegrast when delivered by two prototype contact lens loading formulations, chamber-loaded and surface-loaded lenses, compared with an eye drop formulation, by quantifying lifitegrast in ocular tissues. Both lens loading configurations increased ocular tissue and systemic exposure relative to an eye drop, with the surface-loaded lens producing the greater increase. A release-linked population pharmacokinetic model with configuration-specific input structures provided an exploratory description of the observed corneal exposure profiles. A preliminary interspecies scaling of the model further suggests that a once-daily lens dose may achieve corneal exposure comparable to twice-daily eye drop administration in humans, warranting further evaluation. These findings may be associated with prolonged ocular surface residence by contact lens delivery, offering a potential strategy to overcome the pharmacokinetic limitations of conventional eye drops.

## Declarations

### Competing interests

The authors have no relevant financial or non-financial interests to disclose.

### Ethics approval

This study was approved by the Institutional Animal Care and Use Committee at HLB bioStep (formerly KNOTUS; Incheon, Republic of Korea) (approval nos. 22-KE-0310, 24-HB-0698, 24-HB-0699, and 24-HB-0713).

### Consent to participate

Not applicable

### Consent to publish

## Author Contribution

T.H.K. and H.R.K. conceived and designed the study. T.H.K. acquired funding and administered the project. W.K. and S.K. performed the investigation. W.K. and E.K. developed the software. W.J., E.K., S.K., A.L., and D.H.C. curated the data. W.K., W.J., and E.K. performed formal analysis. W.J. prepared the visualizations. A.L. and H.R.K. validated the results. A.L., H.R.K., and D.H.C. supervised the research. D.H.C. and T.H.K. contributed to methodology. W.K. wrote the original draft. H.R.K., D.H.C., and T.H.K. reviewed and edited the manuscript. All authors read and approved the final manuscript

## Acknowledgments.

This research was supported by the Ministry of Trade, Industry, and Energy [20008799] and National Research Foundation of Korea [2019R111A3A01062573].

## Data availability

The underlying datasets supporting the findings of this study are not publicly available.

## References

1. Gaudana R, Ananthula HK, Parenky A, et al. Ocular drug delivery. *AAPS J*. 2010;12:348–60. <https://doi.org/10.1208/s12248-010-9183-3>.
2. World Health Organization. World report on vision. Geneva: World Health Organization. 2019. <https://www.who.int/publications/i/item/9789241516570>. Accessed 11 Sep 2026.
3. Gayton JL. Etiology, prevalence, and treatment of dry eye disease. *Clin Ophthalmol*. 2009;3:405–12. <https://doi.org/10.2147/OPTH.S5555>.
4. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf*. 2017;15:276–83. <https://doi.org/10.1016/j.jtos.2017.05.008>.
5. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf*. 2017;15:334–65. <https://doi.org/10.1016/j.jtos.2017.05.003>.
6. Gaudana R, Jwala J, Boddu SHS, et al. Recent perspectives in ocular drug delivery. *Pharm Res*. 2009;26:1197–216. <https://doi.org/10.1007/s11095-008-9694-0>.
7. Urtti A. Challenges and obstacles of ocular pharmacokinetics and drug delivery. *Adv Drug Deliv Rev*. 2006;58:1131–5. <https://doi.org/10.1016/j.addr.2006.07.027>.
8. Santos G, Delgado E, Silva B, et al. Topical ocular drug delivery: the impact of permeation enhancers. *Pharmaceutics*. 2025;17:447. <https://doi.org/10.3390/pharmaceutics17040447>.

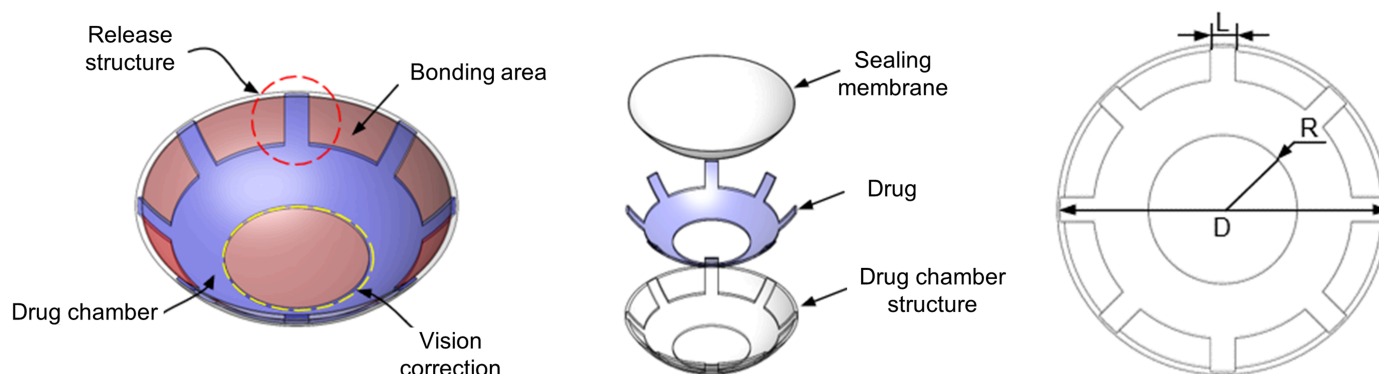
9. del Amo EM, Rimpelä AK, Heikkinen E, et al. Pharmacokinetic aspects of retinal drug delivery. *Prog Retin Eye Res.* 2017;57:134–85. <https://doi.org/10.1016/j.preteyeres.2016.12.001>.
10. Grassiri B, Zambito Y, Bernkop-Schnürch A. Strategies to prolong the residence time of drug delivery systems on ocular surface. *Adv Colloid Interface Sci.* 2021;288:102342. <https://doi.org/10.1016/j.cis.2020.102342>.
11. Maharjan P, Cho KH, Maharjan A, Shin MC, Moon C, Min KA. Pharmaceutical challenges and perspectives in developing ophthalmic drug formulations. *J Pharm Investig.* 2019;49:215–28. <https://doi.org/10.1007/s40005-018-0404-6>.
12. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. *Adv Drug Deliv Rev.* 2005;57:1595–639. <https://doi.org/10.1016/j.addr.2005.07.005>.
13. Toropainen E, Fraser-Miller SJ, Novakovic D, et al. Biopharmaceutics of topical ophthalmic suspensions: importance of viscosity and particle size in ocular absorption of indomethacin. *Pharmaceutics.* 2021;13:452. <https://doi.org/10.3390/pharmaceutics13040452>.
14. Kapanigowda UG, Nagaraja SH, Ramaiah B, et al. Improved intraocular bioavailability of ganciclovir by mucoadhesive polymer based ocular microspheres: development and simulation process in Wistar rats. *Daru.* 2015;23:49. <https://doi.org/10.1186/s40199-015-0132-7>.
15. Nair AB, Shah J, Jacob S, et al. Experimental design, formulation and in vivo evaluation of a novel topical in situ gel system to treat ocular infections. *PLoS ONE.* 2021;16:e0248857. <https://doi.org/10.1371/journal.pone.0248857>.
16. Jin L, Li X, Chen X, et al. A study on puerarin in situ gel eye drops: formulation optimization and pharmacokinetics on rabbits by microdialysis. *Int J Pharm.* 2023;642:123176. <https://doi.org/10.1016/j.ijpharm.2023.123176>.
17. Abul Kalam M, Sultana Y, Ali A, et al. Part II: enhancement of transcorneal delivery of gatifloxacin by solid lipid nanoparticles in comparison to commercial aqueous eye drops. *J Biomed Mater Res A.* 2013;101:1828–36. <https://doi.org/10.1002/jbm.a.34467>.
18. Lin MC, Graham AD, Polse KA, et al. Measurement of post-lens tear thickness. *Invest Ophthalmol Vis Sci.* 1999;40:2833–9.
19. McNamara NA, Polse KA, Brand RJ, et al. Tear mixing under a soft contact lens: effects of lens diameter. *Am J Ophthalmol.* 1999;127:659–65. [https://doi.org/10.1016/S0002-9394\(99\)00051-3](https://doi.org/10.1016/S0002-9394(99)00051-3).
20. Gause S, Hsu KH, Shafor C, et al. Mechanistic modeling of ophthalmic drug delivery to the anterior chamber by eye drops and contact lenses. *Adv Colloid Interface Sci.* 2016;233:139–54. <https://doi.org/10.1016/j.cis.2015.08.002>.
21. Pereira-da-Mota AF, Phan CM, Concheiro A Testing drug release from medicated contact lenses: the missing link to predict in vivo performance. *J Control Release.*, Mondal H, Kim HJ, Asadujjaman M et al. Enhanced therapeutic efficacy of cyclosporin A eluting hyaluronic acid contact lenses in the management of dry eye disease. *J. Pharm. Investig.* 55, 647–660 (2025). <https://doi.org/10.1007/s40005-024-00720-8>.

22. Li Y, Zhou K, Yin X, et al. Lifitegrast-eluting contact lens for dry eye disease: sustained release, enhanced ocular bioavailability, and robust in vitro-in vivo correlation. *Drug Deliv Transl Res*. 2026. <https://doi.org/10.1007/s13346-026-02152-3>.
23. Perez VL, Pflugfelder SC, Zhang S, et al. Lifitegrast, a novel integrin antagonist for treatment of dry eye disease. *Ocul Surf*. 2016;14:207–15. <https://doi.org/10.1016/j.jtos.2016.01.001>.
24. Chung JK, Spencer E, Hunt M, et al. Ocular distribution and pharmacokinetics of lifitegrast in pigmented rabbits and mass balance in beagle dogs. *J Ocul Pharmacol Ther*. 2018;34:224–32. <https://doi.org/10.1089/jop.2017.0106>.
25. Kim E, Jang E, Jung W, et al. Establishment of an LC-MS/MS method for quantification of lifitegrast in rabbit plasma and ocular tissues and its application to pharmacokinetic study. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2023;1229:123892. <https://doi.org/10.1016/j.jchromb.2023.123892>.
26. Watsky MA, Jablonski MM, Edelhauser HF. Comparison of conjunctival and corneal surface areas in rabbit and human. *Curr Eye Res*. 1988;7:483–6. <https://doi.org/10.3109/02713688809031801>.
27. Naware S, Bussing D, Shah DK. Translational physiologically-based pharmacokinetic model for ocular disposition of monoclonal antibodies. *J Pharmacokinet Pharmacodyn*. 2024;51:493–508. <https://doi.org/10.1007/s10928-023-09881-9>.
28. Shah AM, Galor A. Impact of ocular surface temperature on tear characteristics: current insights. *Clin Optim*. 2021;13:51–62. <https://doi.org/10.2147/OPTO.S281601>.
29. Cho SJ, Kang DW, Kim JH, et al. Multicompartmental pharmacokinetic evaluation of enavogliflozin eye drop formulation: understanding its distribution to posterior segments. *J Pharm Investig*. 2024;54:329–43. <https://doi.org/10.1007/s40005-023-00653-8>.
30. Tran TP, Tran NP, Park JS. Pharmacokinetic modeling in drug delivery system. *J Pharm Investig*. 2026;56:127–49. <https://doi.org/10.1007/s40005-025-00792-0>.
31. Cheng CF, Jeong YS, Jusko WJ. Meta-analysis of levamisole absorption and disposition across diverse species using a minimal physiologically-based pharmacokinetic model. *J Pharm Investig*. 2026;56:171–83. <https://doi.org/10.1007/s40005-025-00770-6>.
32. Heo DG, Sanders M, de Moura VCN, et al. Dose optimization of omadacycline for the treatment of nontuberculous mycobacterial pulmonary disease (NTM-PD) using a physiologically based pharmacokinetic modeling approach. *J Pharm Investig*. 2026;56:203–15. <https://doi.org/10.1007/s40005-025-00776-0>.
33. Kang DW, Kim JH, Cho HY. Model-informed repurposing of pyronaridine for mild to moderate COVID-19: predicting target organ exposure and therapeutic potential. *J Pharm Investig*. 2026;56:1085–98. <https://doi.org/10.1007/s40005-025-00789-9>.
34. Kim J, Kim K, Lee TS, Cho H, Yoo S-D, Kim TH, Shin BS, Shin S. Prediction of the pharmacokinetics of the GLP-1 receptor agonist semaglutide in humans via a population pharmacokinetic model integrating interspecies scaling. *J Pharm Investig*. 2025;55(6):827–35. <https://doi.org/10.1007/s40005-024-00717-3>.

35. Kong JS, Seo SW, Kim T, et al. Physiologically based pharmacokinetic modeling for umbelliferone in rats and humans: impact of extrahepatic phase II metabolism and hepatic/gut first-pass extraction on oral bioavailability and systemic disposition. *J Pharm Investig.* 2026;56:185–202. <https://doi.org/10.1007/s40005-025-00767-1>.
36. Choi N, Shin BS, Shin S. Evolution of human pharmacokinetics prediction methods: from allometry to artificial intelligence. *J Pharm Investig.* 2026;56:729–48. <https://doi.org/10.1007/s40005-026-00805-6>.
37. US Food and Drug Administration. XIIDRA (lifitegrast ophthalmic solution) 5%: highlights of prescribing information. NDA 208073/S-005. Revised June 2020.
38. Fonn D. Targeting contact lens induced dryness and discomfort: what properties will make lenses more comfortable? *Optom Vis Sci.* 2007;84:279–85.
39. Akpek EK, Amescua G, Farid M, et al. Dry eye syndrome preferred practice pattern. *Ophthalmology.* 2019;126:P286–334.
40. Coursey TG, Wassel RA, Quiambao AB, et al. Once-daily cyclosporine-A-MiDROPS for treatment of dry eye disease. *Transl Vis Sci Technol.* 2018;7:24.

## Figures

### (A) Structure of the contact lens



### (B) Drug loading into the chamber

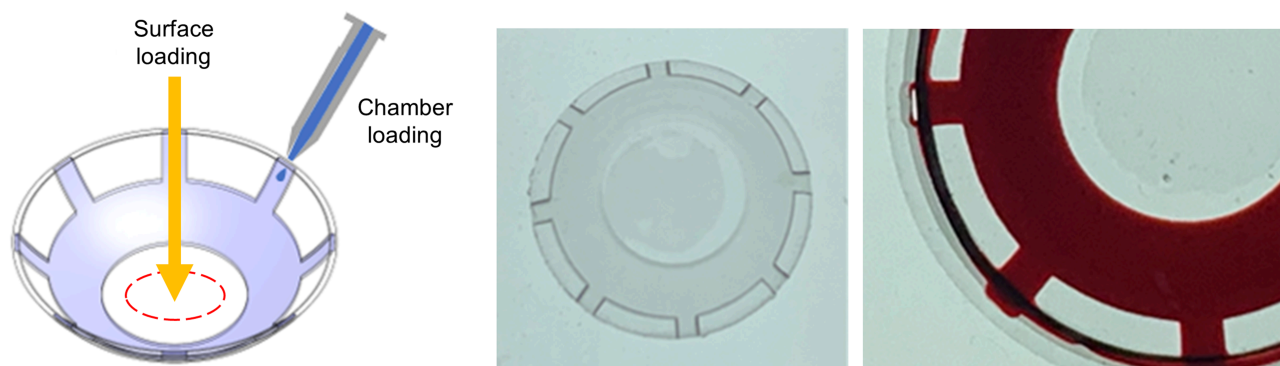


Figure 1

Design and preparation of the drug-loaded contact lens. Structure of the assembled lens, showing the drug chamber, release structures and sealing membrane (A). Loading of the drug solution into the chamber through a release structure (B)

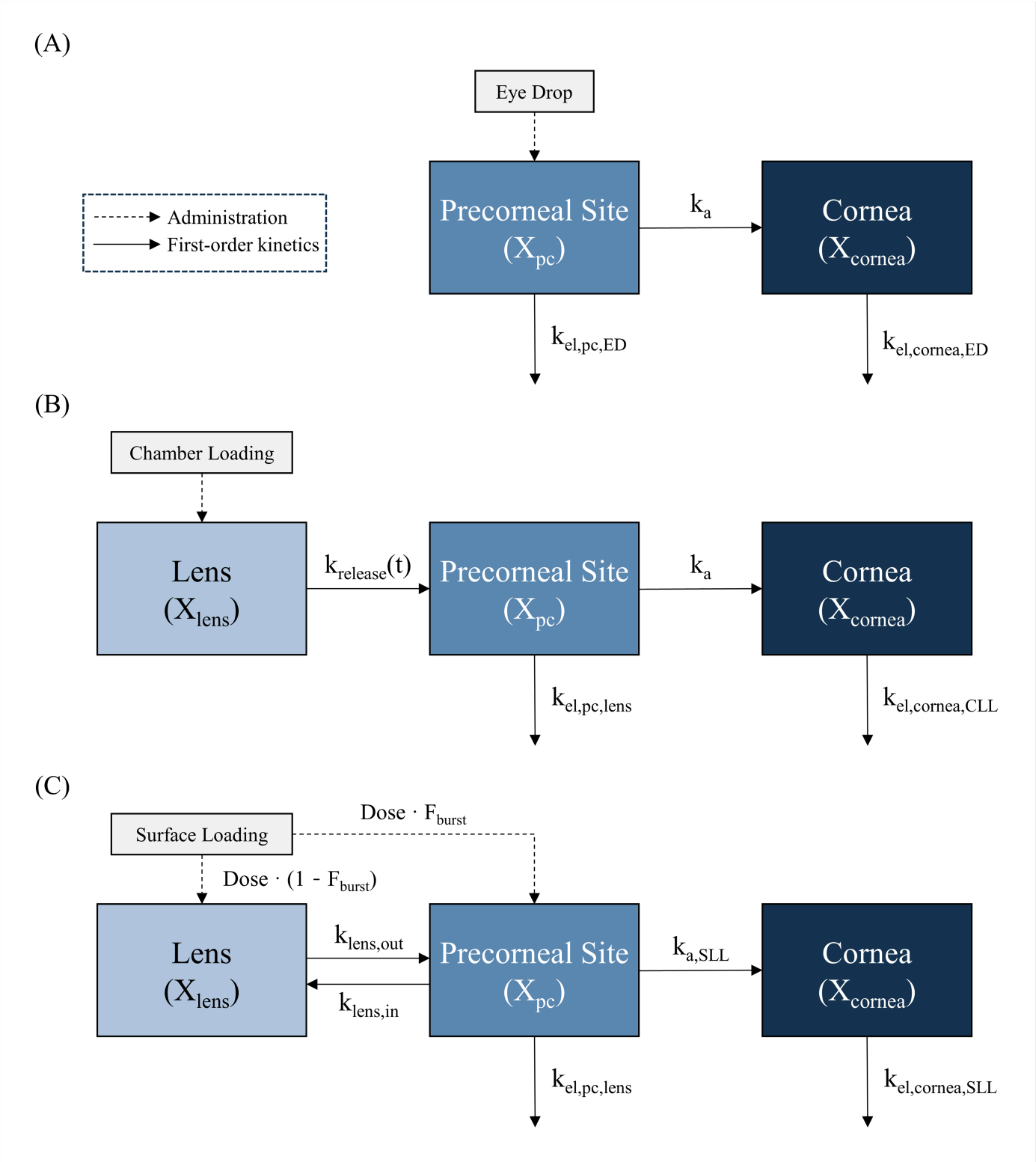


Figure 2

Structural model describing drug input, precorneal elimination, and corneal absorption and elimination of lifitegrast in rabbits following eye drop (A), chamber-loaded lens (B), and surface-loaded lens (C) application. ED, eye drop; CLL, chamber-loaded lens; SLL, surface-loaded lens

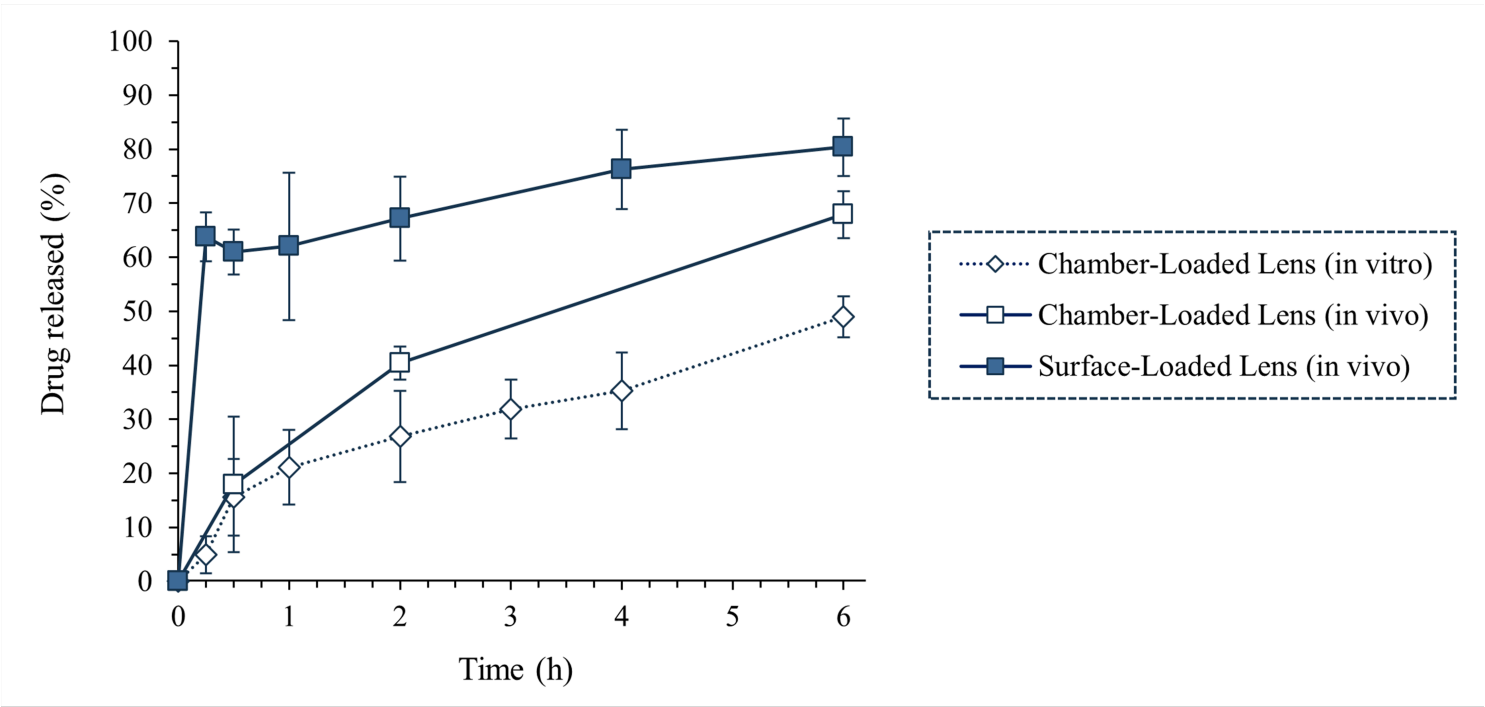
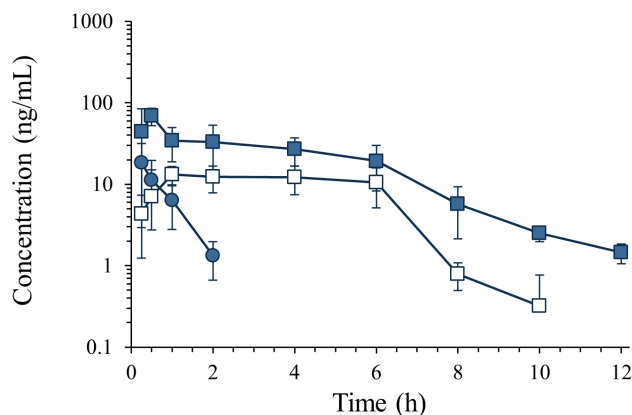


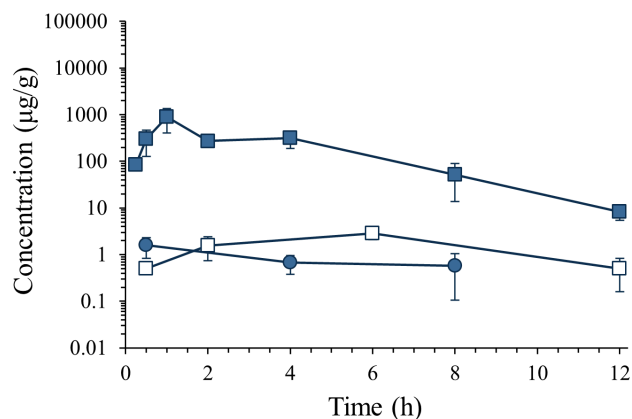
Figure 3

In vitro drug release from the chamber-loaded lens (open diamonds, dashed line) and in vivo apparent drug release from the chamber-loaded (open squares, solid line) and surface-loaded (filled squares, solid line) lenses. Data are presented as the mean  $\pm$  SD ( $n = 5$  for in vitro;  $n = 4$  per time point for in vivo, except  $n = 8$  at 6 h)

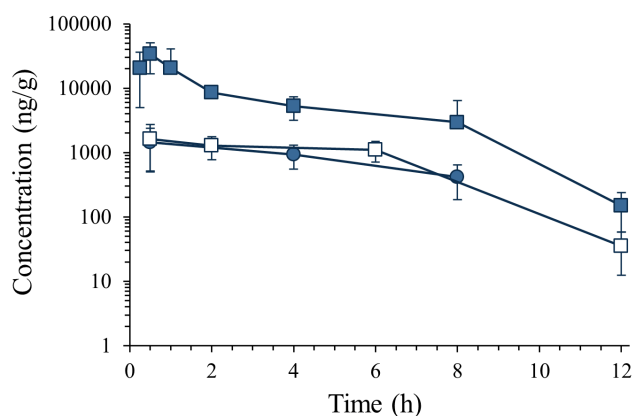
### (A) Plasma



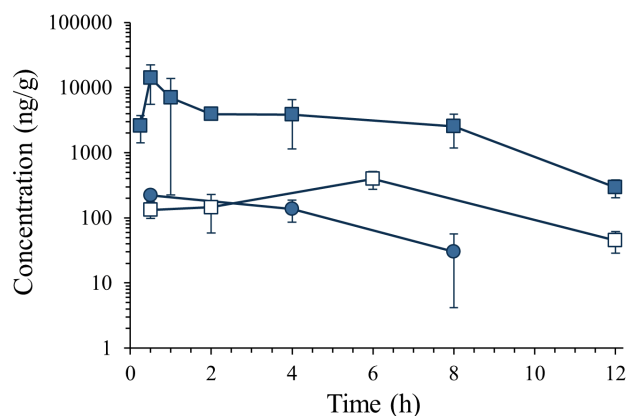
### (B) Cornea



### (C) Conjunctiva



### (D) Sclera



### (E) Aqueous humor

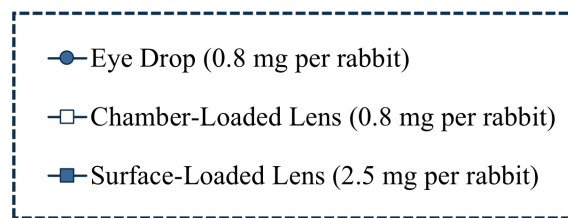
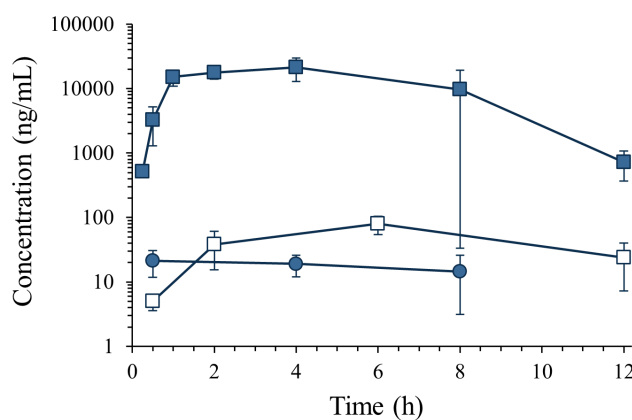


**Figure 4**

Average concentration–time profiles of lifitegrast in the plasma (A), cornea (B), conjunctiva (C), sclera (D), and aqueous humor (E) following ophthalmic administration in rabbits. Filled blue circles, eye drop (0.8 mg/rabbit or 0.4 mg/eye); open blue squares, chamber-loaded lens (0.8 mg/rabbit or 0.4 mg/eye); filled blue squares, surface-loaded lens (2.5 mg/rabbit or 1.25 mg/eye). Data are presented as the mean  $\pm$  SD. Doses for plasma were expressed as mg per rabbit ( $n = 4$  up to 2 h for eye drop, 6 h for chamber-

loaded lens, 8 h for surface-loaded lens, with  $n = 2$  thereafter for both lens groups). Doses for ocular tissues were expressed as mg per eye ( $n = 4$  eyes per time point)

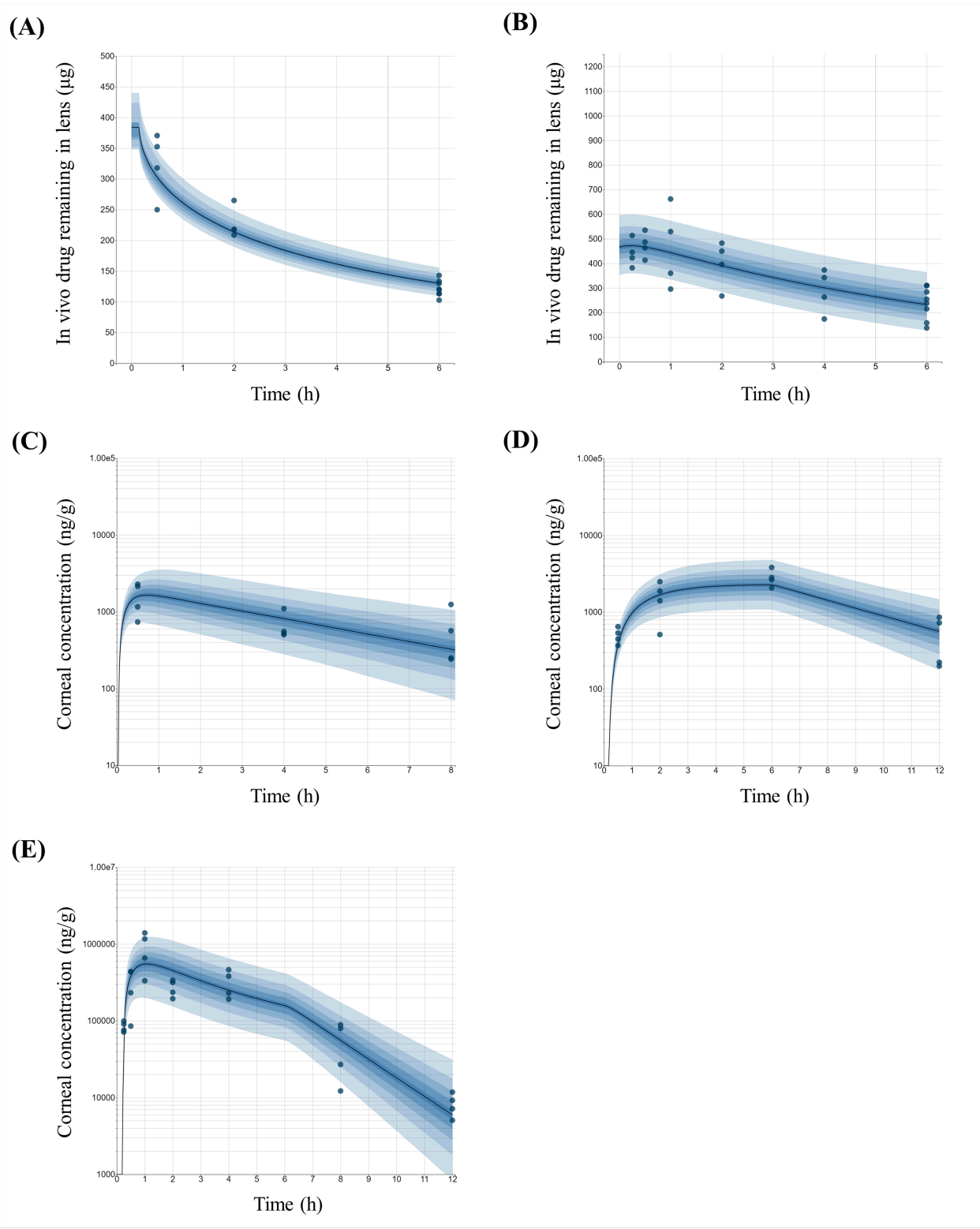


**Figure 5**

Prediction distributions for the population pharmacokinetic model of lifitegrast. In vivo drug remaining in the chamber-loaded (A) and surface-loaded (B) lenses; corneal concentrations following eye drop (C),

chamber-loaded lens (D), and surface-loaded lens (E) administration. Solid lines represent the median model prediction. Shaded areas represent the 10th–90th percentiles of the prediction distribution, based on simulated data from the final model.

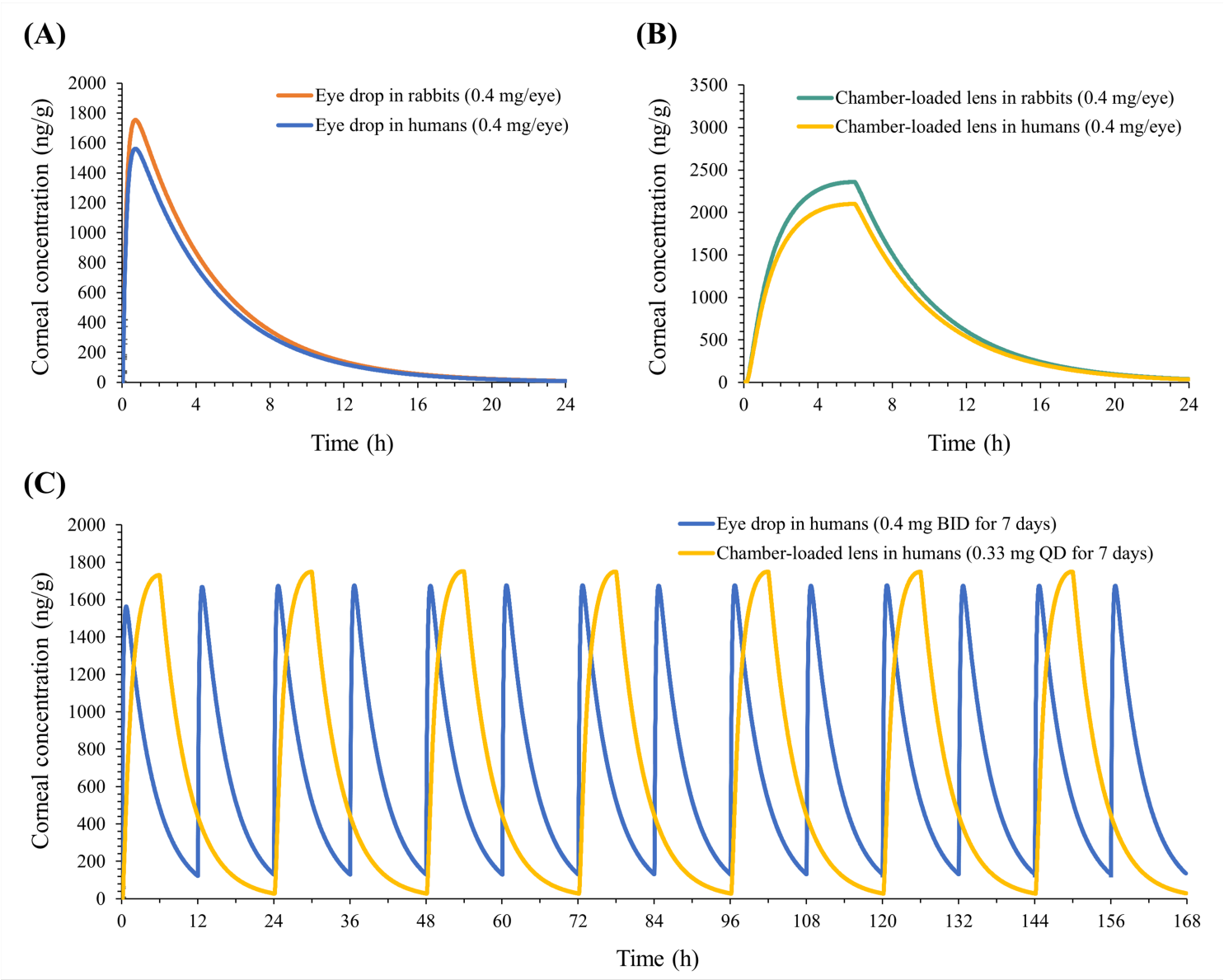


**Figure 6**

Exploratory model simulations of corneal concentration–time profiles following single-dose and repeated-dose administration of the eye drop and chamber-loaded lens in rabbits and humans. BID, twice daily; QD, once daily

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Fig.S1.tif](#)