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# Analysis of topical dosing and administration effects on ocular drug delivery in a human eyeball model using computational fluid dynamics

# Hang Yi, Yu Feng<sup>\*</sup>, Heather Gappa-Fahlenkamp

School of Chemical Engineering, Oklahoma State University, Stillwater, OK, 74078, USA

#### ARTICLE INFO

## ABSTRACT

Keywords: Computational fluid dynamics (CFD) Ocular drug delivery Drug diffusion and elimination Administration frequency and interval Therapeutic efficacy and safety Predicting the spatial and temporal drug concentration distributions in the eyes is essential for quantitative analysis of the therapeutic effect and overdose issue via different topical administration strategies. To address such needs, an experimentally validated computational fluid dynamics (CFD) based virtual human eye model with physiologically realistic multiple ophthalmic compartments was developed to study the effect of administration frequency and interval on drug concentration distributions. Timolol was selected as the topical dosing drug for the numerical investigation of how administration strategy can influence drug transport and concentration distribution over time in the human eye. Administration frequencies employed in this study are 1-4 times per day, and the administration time intervals are  $\Delta t = 900$  s, 1800 s, and 3600 s. Numerical results indicate that the administration frequency can significantly affect the temporal timolol concentration distributions in the ophthalmic compartments. More administrations per day can prolong the mediations at relatively high levels in all compartments. CFD simulation results also show that shorter administration intervals can help the medication maintain a relatively higher concentration during the initial hours. Longer administration intervals can provide a more stable medication concentration during the entire dosing time. Furthermore, numerical parametric analysis in this study indicates that the elimination rate in the aqueous humor plays a dominant role in affecting the drug concentrations in multiple ophthalmic compartments. However, it still needs additional clinical data to identify how much drugs can be transported into the cardiac and/or respiratory systems via blood circulation for side effect assessment.

## 1. Introduction

Developing an effective ocular drug delivery system is challenging since there are still many unanswered fundamental questions related to the etiology of ocular diseases and the optimal pathways of drug delivery to treat specific ocular diseases [1,2]. Specifically, there are knowledge gaps such as (1) the lack of ocular drug pharmacokinetics (PKs) knowledge due to the inability of sampling posterior segment tissues in humans; (2) the unknown ocular safety profile of materials used in sustained release systems; and (3) the limited availability of preclinical models that allow precise scale-up and/or translation from tissue engineering and animal studies to human studies. Therefore, to improve the fundamental understanding on how to optimize the ocular drug delivery system to maintain the drug concentration in designated ophthalmic compartments at a desired level, in-depth knowledge of the transport phenomena and interactions between drugs and eyes is needed.

Topical ophthalmic dosing and intravitreal (IVT) injection are the two commonly used methodologies to deliver medications into the eyes to treat a variety of visionary ailments or disorders [1,3,4]. Although IVT has the advantage of delivering the drug to the targeted local compartment [2,5,6], it has several limitations. For example, the injected drugs are often cleared relatively fast in tissues, so that sometimes medications are difficult to reach the designated drug delivery sites, e.g., outer retinal layers, iris, choroid, and sclera [1,7-10]. Moreover, frequent IVT injections/implants often lead to vision impairments, i.e., infection, inflammation, and contact cataract, which may cause more severe side effects than standard treatments [2,11]. Compared with IVT, topical ophthalmic delivery uses eve drops and offers the most widely preferred noninvasive and patient compliant strategy for drug administration. By topical administration, drugs can transport from the cornea to other ophthalmic compartments via convection and diffusion. It has been claimed that topical ophthalmic delivery is preferred to treat anterior segment diseases [2,12-16].

In the past decades, experimental studies have been done to

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<sup>\*</sup> Corresponding author. 420 Engineering North, Stillwater, OK, 74078, USA. *E-mail address:* yu.feng@okstate.edu (Y. Feng).

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| Acronym<br>AH<br>CFD<br>IOP<br>IVT<br>NIH<br>PKs<br>UDF<br>UDS                                    | clature<br>Aqueous humor<br>Computational fluid dynamics<br>Intraocular pressure<br>Intravitreal injection<br>National Institutes of Health<br>Pharmacokinetics<br>User-defined function<br>User-defined scalar  |  | Drug diffusivity coefficient in chambers, $m^2s^{-1}$<br>Drug diffusivity coefficient in lens, $m^2s^{-1}$<br>Drug diffusivity coefficient, $m^2s^{-1}$<br>Drug diffusivity coefficient in vitreous body, $m^2s^{-1}$<br>Elimination rate in chambers, $s^{-1}$<br>Elimination rate in cornea, $s^{-1}$<br>Elimination rate in lens, $s^{-1}$<br>Elimination rate in vitreous body, $s^{-1}$<br>Administration number per day<br>Source term in chambers |  |
|---|--|--|--|--|
| UDS<br>Symbols<br>C<br>C <sub>0</sub><br>C/C <sub>0</sub><br>Cl <sub>a</sub><br>D <sub>cham</sub> | User-defined scalar<br>Drug concentration, $\times 10^3$ kg m <sup>-3</sup><br>Initial drug concentration, $\times 10$ kg of solute per m <sup>-3</sup> of<br>solution<br>Normalized drug concentration<br>Elimination rate, $\times \frac{10^9}{60}$ m <sup>3</sup> s <sup>-1</sup><br>Drug diffusivity coefficient in cornea, m <sup>2</sup> s <sup>-1</sup> | n<br>S <sub>cham</sub><br>S <sub>corn</sub><br>S <sub>j</sub><br>S <sub>lens</sub><br>S <sub>vitr</sub><br>t<br>t<br>Δ t | Source term in chamber per day<br>Source term in cornea<br>Source term in region j<br>Source term in crystalline lens<br>Source term in vitreous body<br>Physical time, s<br>Time step size or administration time interval, s   |  |

investigate underlying mechanisms of transport phenomena, PKs, bioavailability, and safe dosage limit of the drug administered in animal eyes [1-3,16-24]. Specifically, Owen et al. [24] found moxifloxacin had the highest levels of antibiotic in ocular tissues using rabbit models in vivo to project human eye response. Donnefeld et al. [18] tested concentrations of three drugs in human aqueous humor (AH) in the anterior chamber after topical ocular application, while the counterparts in the other compartments of an eye were not taken into consideration. Other in vivo and/or in vitro studies were summarized by several review papers [1-3,8,16,17,25-39]. However, no experimental studies have tracked the spatial and temporal variations of the drug concentrations in multiple compartments of human/animal eyes, i.e., cornea, lens, anterior chamber, posterior chamber, and/or vitreous body. In addition, no physiologically realistic model of human eyeball exists either in vitro or in vivo due to ethical reasons. As a result, unfortunately, the protocol for the translation of animal ophthalmic models to humans is still elusive. The deficiency in animal studies and in vitro studies are due to the limits in operational flexibilities, research cost, and imaging resolutions of the experimental methods. To address the above-mentioned gaps, computational fluid dynamics (CFD) based methods have been employed to predict the drug delivery process in eye models [40-48]. Specifically, CFD provides an accessible and noninvasive approach to simulate the transport of drugs as a function of both space and time explicitly based on the conservation laws [40]. Using physiologically-based eye geometries, CFD models can aid in identifying major translational knowledge gaps and provide a platform for optimizing and evaluating potential solutions for the best therapeutic outcome. The CFD approach offers several advantages, including the ability to: (1) study a system or phenomenon at different length and time scales in an eye model, (2) perform analysis of varied conditions, i.e., different drugs with corresponding diffusivity coefficients in the ocular compartments, (3) evaluate critical situations that can be investigated in a noninvasive way, and (4) carry out cost-effective studies that can speed up the development of an effective ocular drug delivery system can be evaluated over a long time. Edwards and Prausnitz [48] derived a model from fiber matrix theory to predict the permeability of the fibrous eye tissues. They found the factors, i.e., tissue hydration, tissue thickness, the size, and volume fraction of proteoglycans, which play significant roles in controlling the diffusion rates across the sclera and stroma. Fung et al. [47] simulated the drug delivery of the therapeutic contact lens in the treatment of glaucoma with a simplified two dimensional (2D) model using finite element method, and the results showed that the contact lens could deliver a sufficient amount of timolol maleate with higher efficiency than eye

drops. Datta and Rakesh [44] employed COMSOL Multiphysics (COM-SOL Inc., Stockholm, Sweden) to reproduce and extend the work of Fung et al. [47]. They observed that more drugs into the eye from the lens could lead to an increase of diffused drugs into the AH. Zhang et al. [46] developed a mathematical model with parametric investigations for topical drug delivery across the cornea to the anterior chamber, which can be meaningful to predict different solutes transport kinetics and bioavailability in diseased eyes. Chaudhuri et al. [45] found that concentrations of timolol predicted using GastroPlus (Simulations Plus Inc., Lancaster, CA) show good agreements with the concentrations in ophthalmic compartments measured in vivo. Ferreira et al. [43] studied AH flow characteristics with high intraocular pressures to represent pathologic situations using COMSOL Multiphysics. Recently, Loke et al. [42] also performed numerical simulations using COMSOL Multiphysics and found that segmental outflow and eye orientation can affect the ocular drug delivery system significantly. Missel and Sarangapani [41] employed a CFD model to trace the concentrations of three topical dosing drugs in a simplified rabbit eye model. They claimed that their simulation results match the experimental data well for most of the anterior compartments. However, improvements are still needed to predict temporal and spatial drug concentration distributions in the vitreous body and lens, which are currently challenging to be measured using in vitro and in vivo studies.

There are still many vital questions that have not been answered, e. g., (1) The mixing of drug solution with the dynamics of blinking and absorption into the eyelid tissue has not been considered in previous CFD simulations. Does this factor affect the drug transport the different ocular compartments significantly? (2) Can the simplified animal models reflect the transport behaviors of topical dosing drugs in real human eyes, since the differences in anatomy and physiology exist between human and animal eye? (3) How to find a strategy to enhance the ocular bioavailability with topical drop administration using the CFD method, as it is difficult to achieve therapeutic drug concentration into posterior segment*via* topical instillation? (4) Can the uniform drug diffusion coefficient in the whole eyeball system reflect the drug dosing administration in reality?

To partially address the above-mentioned questions, the objectives of this study are to quantify the effects of topical administration frequency and interval on the spatial and temporal drug concentration distributions in multiple ophthalmic compartments of a three dimensional (3D) human eye model. Specifically, an experimental validated virtual human eye model was built with multiple compartments (i.e., cornea, anterior and posterior chamber, crystalline lens, and vitreous body) to

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study the process of topical drug dosing administration. As an representative hydrophilic medication to treat lower intraocular pressure (IOP) and hypertension, timolol was selected as the topical dosing drug for the numerical investigation of how administration strategy can influence the drug diffusion and elimination over time in the human eye [49]. Specifically, administration frequencies employed in this study are 1–4 times per day. The administration time intervals are  $\Delta t = 900$  s, 1800 s, and 3600 s. The modeling framework and simulation results in this study are expected to enhance public health by improving regulatory confidence, speed, and efficiency in the approval process for new and generic ophthalmic drug products and decreasing costs to the public. The non-invasive and cost-effective high-fidelity *in silico* tool developed in this study is also generalized and can be revised to estimate the efficacy and safety of other topical dosing drugs, e.g., pilocarpine [50] and moxifloxacin [24,51].

#### 2. Methodology

## 2.1. Geometry and mesh

Fig. 1 presents the virtual human eyeball geometry employed in this study with the finite volume mesh details at the midplane (z = 0). Specifically, the eyeball geometry was constructed based on physiological and anatomical data documented in previous studies [52,53]. As shown in Fig. 1, The eyeball geometry consists of four major compartments: (1) the cornea region containing the cornea and sclera, (2) the anterior and posterior chamber region containing the anterior chamber, trabecular meshwork, posterior chamber, and ciliary body, (3) the crystalline lens, and (4) the vitreous body. The diameter of the eyeball is 2.67 cm. In addition, it should be mentioned that this eye model does not consider the anatomy of the ocular adnexa, i.e., lids, tear glands, tear ducts, and tear reservoirs.

Mesh details for the human eyeball model are shown in Table 1 and



Fig. 1. The human eyeball geometry and the poly-hexcore mesh details at the midplane (z = 0).

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#### Table 1

Mesh details in mesh independence test for topical dosing simulation in the human eyeball model.

| Mesh           | esh Volumetric elements |           |           |               | Volume-maximum skewness | Prism layers | Size growth rate |      |
|----------------|-------------------------|-----------|-----------|---------------|-------------------------|--------------|------------------|------|
|                | Cornea                  | Lens      | Chambers  | Vitreous body | Total                   |              |                  |      |
| Mesh 1         | 1,616,877               | 245,913   | 645,302   | 1,100,841     | 3,608,933               | 0.60         | 2                | 1.1  |
| Mesh 2 (Final) | 3,336,178               | 478,561   | 2,218,446 | 1,230,890     | 7,264,075               | 0.60         | 5                | 1.05 |
| Mesh 3         | 7,748,372               | 1,117,230 | 2,415,042 | 5,337,018     | 16,617,662              | 0.61         | 5                | 1.05 |

Fig. 1. Regions with possible high gradients of drug concentrations were discretized with refined mesh elements. The mesh independence test was performed by comparing the average drug (i.e., moxifloxacin) mass fractions in the entire eveball model and the subsidiary compartments. with a time-independent flux of moxifloxacin through the corneal surface, accordingly to experimental data [24,51]. Three poly-hexcore meshes have been generated using ANSYS Fluent Meshing 2021 R1 (ANSYS Inc., Canonsburg, PA) with different mesh sizes for the mesh independence test. Using different meshes (see Table 1), moxifloxacin mass fractions in the multiple regions (highlighted in blue) are shown in Fig. 2. It can be observed that Mesh 1 is too coarse to provide accurate results. With mesh refinement, the variations in simulated drug mass fraction are within 1.0% between Mesh 2 and Mesh 3. Thus, based on the optimal balance between computational efficiency and accuracy, Mesh 2 was selected as the final mesh for this study. Mesh 2 contains 7,264,075 elements, including five near-wall prism layers and one peel layer with a size growth ratio of 1.05.

#### 2.2. Theory

# 2.2.1. Generalized advection-diffusion equation

Assuming no rolling motion of the eyeball during and after administration, the drug transport in the eyeball is dominated by diffusion and elimination, while the convection can be neglected. Therefore, the transport process can be governed by a simplified unsteady advection-diffusion equation [40,46,47,54], i.e.,

$$\frac{\partial C}{\partial t} - D_i \nabla^2 C + S_j = 0 \tag{1}$$

$$S_j = -k_j C \tag{2}$$

where *C* is drug concentration, and *t* is time.  $D_i$  represents the drug diffusivity coefficient in the local compartments, i.e., cornea ( $D_{corn}$ ), chambers ( $D_{cham}$ ), lens ( $D_{lens}$ ), vitreous body ( $D_{vir}$ ), respectively. In

addition,  $S_j$  (i.e.,  $S_{corn}$ ,  $S_{cham}$ ,  $S_{lens}$ , and  $S_{vitr}$ ) denotes the source terms due to drug elimination in the four compartments (i.e., cornea, anterior and posterior chamber, lens, and vitreous body) with corresponding elimination rates  $k_j$  (i.e.,  $k_{corn}$ ,  $k_{cham}$ ,  $k_{lens}$ , and  $k_{vitr}$ ).

## 2.2.2. Boundary and initial conditions

Ten transient timolol drug dosing waveforms were employed as different inlet boundary conditions at the cornea surface in the eyeball model (see Fig. 3), representing different drug administration strategies in drug dosing frequencies and intervals. Based on experimentally measured drug concentrations in the tear film following topical dosing, time-dependent drug fluxes were assigned through the anterior corneal surface. Specifically, to investigate the effects of the drug dosing frequencies and intervals on timolol concentrations in the human eye, three dosing intervals (i.e.,  $\Delta t = 900$  s, 1800 s, and 3600 s) were applied with corresponding dosing frequency (i.e., 1 to 4 times per day) (see Fig. 3). As shown in Fig. 3, the one-time drug dosing drug concentration-time profile is based on experimental measurements for the timolol drug administration from previous studies [41,55]. Other waveforms were generated to investigate their effects on the drug concentrations in different ocular compartments in the eyeball model by adding the dosing intervals and times. It should be mentioned that the timolol concentration at the initial time (t = 0) has been normalized as 1 in all simulating cases. The transport of a user-defined scalar (UDS) was solved for tracking the spatial and temporal concentration distributions of the drug. Dosing administration with different initial concentrations was applied. Specifically,  $25 \,\mu l$  dose of 0.65% g/100 mL timolol maleate was considered as  $C_0 = 0.5\%$  g/100 mL for timolol [55], which has been applied by the previous study [41]. The boundaries shared by neighboring compartments were set as interfaces.

# 2.2.3. Physical properties in different ophthalmic compartments

As an example of representative hydrophilic medication, timolol was selected for this study. The concentration in the tear film decays



**Fig. 2.** Mesh independence test for the human eyeball model using the comparisons of drug mass fractions in multiple ophthalmic compartments: (a) entire eyeball, (b) cornea and sclera, (c) anterior and posterior chambers, (d) lens, (e) vitreous body.

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Fig. 3. Inlet conditions for timolol administration at the corneal surface with different dosing time intervals: (a)  $\Delta t = 900s$ , (b)  $\Delta t = 1800s$ , and  $\Delta t = 3600s$ .

exponentially, of which the details are discussed in Section 2.2.2. The physical properties in different ophthalmic compartments for timolol transport were obtained from previous studies [40,42,46,47,56–61], which are listed in Table 2.

#### 2.3. Numerical setup

The CFD simulations were executed using ANSYS Fluent 2021 R1 (ANSYS Inc., Canonsburg, PA). Simulations in the human eyeball for model validations were performed on a local 64-bit Dell Precision Tower 7810 with 128 GB of RAM and Intel®Xeon® Processor E5-2643 v4 3.40 GHz with 12 cores. Each simulated case took approximately 30 hours. The simulations for parametric studies were conducted on a local Dell Precision T7910 workstation (Intel®Xeon® Processor E5-2683 v4 with dual processors, 32 cores, and 256 GB RAM), and each simulated case took about 36 hours. The least-squares cell-based scheme is used for spatial discretization of gradients. The second-order scheme was employed for pressure discretization. In addition, the second-order upwind scheme was applied for the discretization of momentum and the UDS. Convergence is defined for the UDS when the root-mean-square (RMS) residual is lower than 1.0e-7.

#### 2.4. Time step independence test

Time step sizes  $\Delta t = 0.1$  s, 1.0 s, 5.0 s, and 10.0 s were employed to find the optimal time step size to balance the computational accuracy and cost in the simulations. Specifically, with the same physical diffusion time 500 s and residual convergence criterion (i.e., RMS residual < 1e-7), the differences of the spatially average timolol drug mass fraction in chambers, cornea, and the entire eyeball domain were compared by the selected four  $\Delta t$ , respectively (see Fig. 4). In Fig. 4, it can be found that the time step size  $\Delta t = 10$  s and 5s are too large to obtain accurate results. The largest relative errors among  $\Delta t = 10$  s, 5 s, and 0.1 s can reach to 2.7%, 2.5%, 2.0% in the cornea (t = 150 s), chamber region (t = 500 s), and entire eyeball model (t = 200 s), separately. The variations in

## Table 2

| Drug properties in di | ifferent ophthalmic | compartments | [40,42,46 | ,47,56–61] |
|-----------------------|---------------------|--------------|-----------|------------|
|-----------------------|---------------------|--------------|-----------|------------|

|  | Cornea       | Chambers | Lens          | Vitreous<br>body |
|--|--------------|----------|---------------|------------------|
| Density $\rho$ (kg m <sup>-3</sup> )   | 1050         | 996      | 1050          | 1000             |
| Mass Diffusivity<br>$D_i (m^2 s^{-1})$ | 1.31e-<br>10 | 7.0e-10  | 4.85e-10      | 4.85e-10         |
| Elimination rates $k_i$ ( $s^{-1}$ )   | 1.785e-<br>7 | 7.442e-4 | 2.920e-<br>03 | 2.395e-6         |

simulated average timolol mass fraction are within 0.21% between  $\Delta t=1\,$  s and 0.1 s. Therefore, considering the optimal balance between computational efficiency and accuracy,  $\Delta t=1\,$  s was selected as the final time step size for simulating the spatial and temporal evolution of drug dosing administration in the eyeball model.

## 3. Results and discussion

#### 3.1. Model validations

To validate the CFD model enhanced by the in-house user-defined functions (UDFs), the timolol concentrations in AH were compared with experimental data [60,62–64] under two numerical conditions in the human eyeball model. It is worth mentioning that the drug elimination factor due to AH production and flow was considered using a source term in this study, which has been discussed in Section 2.2.1. Specifically, UDFs have been developed for defining (1) transient drug administration profiles at the cornea, (2) compartment-specific diffusivities, and (3) compartment-specific elimination rates. The maximum rate  $Cl_a = 30 \ \mu l/min$  and minimum rate  $Cl_a = 1 \ \mu l/min$  of AH production [46,59] were employed in this study. Fig. 5 shows the comparison of the temporal evolution of the normalized timolol concentration in AH between the CFD predictions and experimental measurements after the topical dosing administration in 3 h, where  $C_0 = 0.5\%$  g of solute per 100 mL. All numerical and experimental data were normalized as  $C/C_0$ . In Fig. 5, it can be found that the timolol concentrations in CFD simulations with maximum and minimum elimination rates agree with the experimental data well from 0.25 to 1.25 h [63] and at 2.0 h [60]. Although the CFD model slightly overestimated the timolol concentration when comparing it with the experimental data at approximately 1.5 h [62,64], the relative errors are small enough for the CFD model to capture the features of temporal drug concentrations in the chambers (see the enlarged region in Fig. 5). The relative errors may be caused by the minor geometry differences and variances of metabolic elimination rates, which have been explained by the previous studies [46,59]. Specifically, the metabolic elimination rate of drugs can be several times higher than that of AH flow, as metabolism and systemic uptake by the vascular tissues of the anterior uvea constitute alternate routes of elimination. With good agreements between the numerical results and experimental data, the capability of the CFD model is validated to predict topical dosing process in this study.

#### 3.2. The effect of administration frequency on drug concentration

To investigate how the administration frequency affects the

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Fig. 4. Time step size independence test for the human eyeball model by comparing drug mass fractions in different ophthalmic compartments: (a) entire eyeball, (b) anterior and posterior chambers, and (c) cornea.



**Fig. 5.** Comparisons of computational results for the timolol concentrations in a human eyeball model with experimental data ( $C_0 = 0.5\%$ g of solute per 100 mL) [60,62–64].

ophthalmic dosing administration in different compartments in the eyeball, the temporal drug concentrations  $(C/C_0)$  in different compartments were compared associated with 4 topical administration frequencies (i.e., 1 to 4 times per day in a 4-h duration) and 4 administration intervals (i.e., 900 s, 1800 s, and 3600 s). The volumetric flow rate  $Cl_a = 30 \ \mu l/min$  was used for the elimination rate due to the convection effect in the AH. The administration dosage profiles at the cornea are shown in Figs. 3 (a)-(c). The first administration started at time t = 0 s. The temporal concentration profiles in different compartments are shown in Figs. 6–8 (a)-(e). The spatial concentration distributions at different time stations are shown in Figs. 9–14 (a)-(j), where n is the number of administrations per day, and  $\Delta t$  is the administration

time interval. Overall, all four administration frequencies share similar trends initially. Specifically, timolol concentration increases in the entire eyeball rapidly after the administration and reaches the highest concentration after approximately 800 s of each administration, followed by decreased concentration due to the elimination (see Figs. 6 (a), 7 (a), and 8 (a)). Meanwhile, Figs. 6–8 manifest noticeable differences among different topical administration frequencies on the temporal timolol concentration in selected regions (i.e., entire eyeball, cornea, anterior and posterior chambers, lens, and vitreous body). It can be observed that the temporal timolol concentration with more administrations per day is higher. The resultant more dosing time durations can help maintain higher timolol levels over time in the studied medium and

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**Fig. 6.** Timolol concentration  $(C/C_0)$  profiles with different administration frequencies under the administration interval  $\Delta t = 900$  s in multiple ophthalmic compartments: (a) entire eyeball, (b) cornea, (c) chambers, (d) lens, and (e) vitreous body.



Fig. 7. Timolol concentration ( $C/C_0$ ) profiles with different administration frequencies under the administration interval  $\Delta t = 1800$  s in multiple ophthalmic compartments: (a) entire eyeball, (b) cornea, (c) chambers, (d) lens, and (e) vitreous body.



**Fig. 8.** Timolol concentration ( $C/C_0$ ) profiles with different administration frequencies under the administration interval  $\Delta t = 3600$  s in multiple ophthalmic compartments: (a) entire eyeball, (b) cornea, (c) chambers, (d) lens, and (e) vitreous body.

prolong the therapeutic action, which agrees with the conclusions in existing qualitative studies [65]. Specifically, Figs. 6 (a), 7 (a), and 8 (a) show that the average timolol concentrations in the entire eyeball with four administrations per day are 5.57e-5, 6.40e-5, and 1.90e-4 during the first 4 h with different dosing intervals (i.e.,  $\Delta t = 900$  s, 1800 s, and 3600 s), respectively. All of them are approximately 4 times higher than the single administration and higher than the other two administration frequencies. However, it is also possible that the side effects may come along with the higher concentrations in the eyeball with the overdose issue caused by the high-frequency administration strategy.

More detailed comparisons in different ophthalmic compartments

are shown in Figs. 6–8 (b)-(e). The localized comparisons are beneficial, especially on how timolol can transport from the anterior to the posterior segment of the eye, which provides important insight in decreasing IOP.

Figures 6 (b), 7 (b), and 8 (b) present temporal timolol concentrations in the cornea. It can be found the drug reaches the peak and then decreases to a low concentration rapidly after each administration, which is based on the fact that the distance between the surface of the cornea and anterior chamber is too small to maintain the drug in this local region for a long time. More details about the spatial drug distributions in the cornea region are visualized in Figs. 9–14 with specified



**Fig. 9.** Spatial timolol concentration  $(C/C_0)$  distributions under different administration frequencies and time intervals at t = 1000 s: (a) n = 1 and no interval, (b) n = 2 and  $\Delta t$  = 900 s, (c) n = 3 and  $\Delta t$  = 900 s, (d) n = 4 and  $\Delta t$  = 900 s, (e) n = 2 and  $\Delta t$  = 1800 s, (f) n = 3 and  $\Delta t$  = 1800 s, (g) n = 4 and  $\Delta t$  = 1800 s, (h) n = 2 and  $\Delta t$  = 3600 s, (i) n = 3 and  $\Delta t$  = 3600 s, (i) n = 4 and  $\Delta t$  = 3600 s.



**Fig. 10.** Spatial timolol concentration ( $C/C_0$ ) under different administration frequencies and time intervals at t = 2000 s: (a) n = 1 and no interval, (b) n = 2 and  $\Delta t$  = 900 s, (c) n = 3 and  $\Delta t$  = 900 s, (d) n = 4 and  $\Delta t$  = 900 s, (e) n = 2 and  $\Delta t$  = 1800 d (f) n = 3 and  $\Delta t$  = 1800 s, (g) n = 4 and  $\Delta t$  = 1800 s, (h) n = 2 and  $\Delta t$  = 3600 s, (i) n = 3 and  $\Delta t$  = 3600 s, (i) n = 4 and  $\Delta t$  = 3600 s.

time stations. Figs. 6 (c), 7 (c), and 8 (c) show that the timolol concentration in the chambers with 4 administrations per day is higher than the other three administration frequencies, which can increase the ocular hypotensive effect of timolol *via* reducing the AH production [66-68]. This phenomenon also can be proved directly from the spatial distributions of the timolol concentration at different time stations in Figs. 9–14, which is consistent with the findings by previous studies, i.e., topical ophthalmic delivery is preferred to treat anterior segment diseases [2,12-16]. In addition, these results may better support the clinical study that the IOP decreases in 60 min rapidly after a single administration and stays low in 2 h [65], since the drug concentration also maintains at a relatively high level (i.e., above 1.0e-4) (see Figs. 6



**Fig. 11.** Spatial timolol concentration ( $C/C_0$ ) under different administration frequencies and time intervals at t = 3800 s: (a) n = 1 and no interval, (b) n = 2 and  $\Delta t$  = 900 s, (c) n = 3 and  $\Delta t$  = 900 s, (d) n = 4 and  $\Delta t$  = 900 s, (e) n = 2 and  $\Delta t$  = 1800 s, (f) n = 3 and  $\Delta t$  = 1800 s, (g) n = 4 and  $\Delta t$  = 1800 s, (h) n = 2 and  $\Delta t$  = 3600 s, (i) n = 3 and  $\Delta t$  = 3600 s, and (j) n = 4 and  $\Delta t$  = 3600 s.



**Fig. 12.** Spatial timolol concentration ( $C/C_0$ ) under different administration frequencies and time intervals at t = 5600 s: (a) n = 1 and no interval, (b) n = 2 and  $\Delta t$  = 900 s, (c) n = 3 and  $\Delta t$  = 900 s, (d) n = 4 and  $\Delta t$  = 900 s, (e) n = 2 and  $\Delta t$  = 1800 s, (f) n = 3 and  $\Delta t$  = 1800 s, (g) n = 4 and  $\Delta t$  = 1800 s, (h) n = 2 and  $\Delta t$  = 3600 s, (i) n = 3 and  $\Delta t$  = 3600 s, and (j) n = 4 and  $\Delta t$  = 3600 s.

(c), 7 (c), and 8 (c)) in the chambers in the first 2 h which can lead to more consistent therapeutic effect to reduce the AH pressure in the anterior regions of the diseased eye. The drug concentration then started to decrease due to the continuous diffusion and elimination and is at a relatively low concentration level (i.e., less than 1.0e-4) with a single administration. It also shows that more administration numbers per day

can help the drug keep at a relatively higher level with all administration intervals. This parametric analysis potentially provides more details as references and guidelines to the physicians/doctors to optimize the administration plan in order to reduce the IOP of diseased eyes better. The localized drug concentration distributions shown in Figs. 9–14 (a)-(j) also lead to the same observations mentioned above. In addition,



**Fig. 13.** Spatial timolol concentration ( $C/C_0$ ) under different administration frequencies and time intervals at t = 7400 s: (a) n = 1 and no interval, (b) n = 2 and  $\Delta t$  = 900 s, (c) n = 3 and  $\Delta t$  = 900 s, (d) n = 4 and  $\Delta t$  = 900 s, (e) n = 2 and  $\Delta t$  = 1800 s, (f) n = 3 and  $\Delta t$  = 1800 s, (g) n = 4 and  $\Delta t$  = 1800 s, (h) n = 2 and  $\Delta t$  = 3600 s, (i) n = 3 and  $\Delta t$  = 3600 s, and (j) n = 4 and  $\Delta t$  = 3600 s.



**Fig. 14.** Spatial timolol concentration ( $C/C_0$ ) under different administration frequencies and time intervals at t = 11000 s: (a) n = 1 and no interval, (b) n = 2 and  $\Delta t$  = 900 s, (c) n = 3 and  $\Delta t$  = 900 s, (d) n = 4 and  $\Delta t$  = 900 s, (e) n = 2 and  $\Delta t$  = 1800 s, (f) n = 3 and  $\Delta t$  = 1800 s, (g) n = 4 and  $\Delta t$  = 1800 s, (h) n = 2 and  $\Delta t$  = 3600 s, (i) n = 3 and  $\Delta t$  = 3600 s, and (j) n = 4 and  $\Delta t$  = 3600 s.

it is interesting that high local concentrations can be found at the corners near the interface between the cornea and anterior chambers (see Figs. 11 (b), 12 (b), 12 (e), 13 (a)-(e), and 14 (a)-(h)). The detention of the drug at those regions is due to the lower elimination rate in the cornea than in the anterior chambers (see Table 2).

As shown in Figs. 6 (d), 7 (d), and 8 (d), the concentration in the lens

reaches peaks after 1 h with a single administration. More administrations can not only increase the highest drug concentration but also can prolong the time duration with a relatively high drug concentration in the lens. The administration with n = 4 and  $\Delta t = 3600 \text{ s}$  (see Fig. 8 (d)) can generate the evenest drug concentration level in the lens during the first 4 h. The average concentration is higher than 3.0e-5. It also can be

# observed that timolol concentration keeps increasing for all investigated simulations in the vitreous body during the first 4 h (see Figs. 6 (e), 7 (e), and 8 (e)), and more administration numbers can prolong the timolol concentrations in a relatively high level than cases with fewer administration per day. Such observations also indicate that higher administration frequency can potentially enhance the drug delivery to the posterior segment of the eye, while the peak concentration needs to be closely monitored to avoid overdose issues and the induced side effect. The simulation results can provide some information for these patients who suffer from eye diseases in the vitreous body which are usually treated by IVT injection. Since IVT may lead to significant vision impairment, topical dosing administration with more numbers per day may be an alternative approach to treat the diseases in the vitreous body and potentially reduce the side effects to the eye.

## 3.3. The effect of administration time interval on drug concentration

Temporal drug concentrations  $(C/C_0)$  under three administration time intervals, i.e.,  $\Delta t = 900$  s,  $\Delta t = 1800$  s, and  $\Delta t = 3600$  s were investigated with different administration frequencies (i.e., n = 2, 3, and 4). The volumetric flow rate  $Cl_a = 30 \ \mu l/min$  was used for the elimination rate due to the convection effect in AH. Specifically, the simulation results in temporal timolol concentrations in five selected regions (i.e., entire eyeball, cornea, chamber, lens, and vitreous body) (see Figs. 15–17), and spatial timolol distributions at different time stations (see Figs. 9-14) are visualized. Specifically, Figs. 15 (a), 16 (a), and 17 (a) demonstrate that the average timolol concentration with longer administration time intervals can generate more even drug concentration in a prolonged time duration at lower concentration levels in the entire eyeball. Timolol concentration with the most prolonged time interval in this study (i.e.,  $\Delta t = 3600$  s) can keep the drug concentration higher than 1.34e-4 during the first 2, 3, and 4 h with corresponding two, three, and four administrations per day, respectively. Such a minimum drug concentration is lower than the  $C/C_0 = 1.23e$ -3 with  $\Delta t =$ 900 s and the concentration  $C/C_0 = 5.19e-4$  with  $\Delta t = 1800$  s. However, the case with the longest time interval (i.e.,  $\Delta t = 3600$  s) can remain the drug concentration above 1.34e-4 longer than the other two administration time intervals, varying with the administration numbers per day. It is also interesting to find from Figs. 15 (a), 16 (a), and 17 (a) that the longer administration time interval can reduce the variation intensity in drug concentration level after each administration. Therefore, it can be a feasible strategy for physicians if a more stable drug concentration level and longer active time are needed in the entire eyeball during the treatment.

For the cornea, it can be observed from Figs. 15 (b), 16 (b), and 17 (b) that the residence time of timolol is much lower in the cornea compartment than in other compartments in all three administration

time intervals. This is not because of the diffusivity but due to the small thickness of the cornea compartment than the other compartments. As a result, the drug can reach chambers in a short time after entering the cornea compartment. The drug concentration increases rapidly in the first 10 min after each administration, followed by decreases in the next 10 min. The drastic variations of drug concentrations are because of the thin thickness of the cornea. Specifically, the drug can enter and exit the cornea in a relatively short time period due to the short distance to diffuse, compared with other compartments. The timolol enters into the chambers to reduce IOP by keeping a relatively high drug concentration, which can be proved by previous studies that active plasma concentration is reached about 24 min after the administration of the topical agent [49,69].

For the chambers (see Figs. 15 (c), 16 (c), and 17 (c)), it is interesting to find that the trend of temporal timolol concentration in the chambers is similar to the trend in the entire eyeball with all three administration time intervals (see Figs. 15 (a), 16 (a), and 17 (a)). With  $\Delta t = 3600$  s, timolol concentration maintains between 1.34e-3 and 1.68e-2 repeatedly before the last administration. In contrast, with shorter administration time intervals (i.e.,  $\Delta t = 900$  s and  $\Delta t = 1800$  s), the maximum drug concentrations are higher in the first hour due to the fact that more drug administrations exist at the cornea, compared with longer administration time interval (i.e.,  $\Delta t = 3600$  s). The higher maximum drug concentration resulting from the shorter administration time intervals may lead to a better instantaneous therapeutic effect, but can also cause safety issues with the potential overdose problem. In addition, shorter administration time intervals (i.e.,  $\Delta t = 900$  s and  $\Delta t = 1800$  s) cannot provide a relatively high drug concentration in the chambers after the first 60 min as the longer administration time interval (i.e.,  $\Delta t = 3600$  s). Therefore, considering both drug concentration and its maintaining time, the administration interval  $\Delta t = 3600$  s may be a better choice for the patients to address the IOP issue when similar hydrophilic doses are used

Figs. 15–17 (d) and (e) present the temporal timolol concentration that developed in the crystalline lens and vitreous body, respectively. With the shortest administration time interval (i.e.,  $\Delta t = 900$  s), the timolol concentration is higher over 2 h in lens and 4 h in the vitreous body than the cases with longer administration time intervals (i.e.,  $\Delta t =$ 1800 s and  $\Delta t = 3600$  s). Such comparisons imply that topical administration with shorter time intervals and more daily administrations can facilitate drug penetration through the cornea and chambers, then the delivery to the lens and vitreous body to address the eye diseases located in the posterior eye.

## 3.4. The effects of elimination rates on drug concentration

Using one administration per day (n = 1), three volumetric flow



**Fig. 15.** Timolol concentration ( $C/C_0$ ) time profiles with different administration time intervals using 2 administrations per day in multiple ophthalmic compartments: (a) entire eyeball, (b) cornea, (c) chambers, (d) lens, and (e) vitreous body.



**Fig. 16.** Timolol concentration  $(C/C_0)$  time profiles with different administration time intervals using 3 administrations per day in multiple ophthalmic compartments: (a) entire eyeball, (b) cornea, (c) chambers, (d) lens, and (e) vitreous body.



**Fig. 17.** Timolol concentration ( $C/C_0$ ) time profiles with different administration time intervals using 4 administrations per day in multiple ophthalmic compartments: (a) entire eyeball, (b) cornea, (c) chambers, (d) lens, and (e) vitreous body.

rates, i.e.,  $Cl_a = 1$ , 21, and 30  $\mu l/min$ , representing drug elimination factors due to the convection effect in the AH, were employed to investigate the effects of elimination rates on the temporal timolol concentrations in multiple designated ophthalmic compartments (see Figs. 18 (a)-(e)). Overall, numerical results shown in Figs. 18 (b)-(d) indicate that the elimination rate has a significant impact on the temporal drug concentrations in different compartments. In addition, a higher elimination rate leads to a higher amount of timolol clearance in the chambers, resulting in fewer drugs entering the posterior regions (i.

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e., lens and vitreous body) of the eyeball.

Specifically, Fig. 18 (a) shows how the average drug concentrations developed in 3 h after the first administration in the entire eyeball under the three different elimination rates ( $Cl_a$ ). By comparing the maximum timolol concentration in the entire eyeball near physical dosing time 0.25 h, the timolol concentration of the case with  $Cl_a = 1 \ \mu l/min$  is approximately 3.0e-4 higher than the case with the maximum elimination rate  $Cl_a = 30 \ \mu l/min$ , and approximately 2.0e-4 higher than the case with elimination rate  $Cl_a = 21 \ \mu l/min$ , respectively. After t = 1.5 h, the



**Fig. 18.** Timolol concentration  $(C/C_0)$  time profiles with different elimination rates in multipleophthalmic compartments: (a) entire eyeball, (b) cornea, (c) chambers, (d) lens, and (e) vitreous body.

segment of the eye.

#### drug concentration of the case with $Cl_a = 1 \, \mu l / min$ increases to four times to evaluate the effects on eveballs by other hydrophilic medications, e. higher than the other two cases (i.e., $Cl_a = 21$ and $30 \,\mu l/min$ ). It also can g., pilocarpine and moxifloxacin, with related clinical inlet boundary be found that the variations of the drug concentration share the same conditions. trend in the chambers as well as in the entire eyeball (see Figs. 18 (a) and

Key conclusions are summarized as follows, i.e.,

- Administration frequency (i.e., times per day) can significantly affect the drug concentrations in the designated ophthalmic compartments. More administrations per day can maintain the drug concentration at a relatively high level in all ophthalmic compartments longer.
- A shorter administration time interval can help the drug maintain a higher concentration in shorter time duration, while a longer administration time interval can be a more balanced administration approach when a more stable drug concentration is a need in a longer time duration.
- The elimination rate in AH plays a dominant role on the drug concentration in chambers, i.e., higher elimination rate can consume more drugs in the chambers, and then further influence the drug concentrations in the lens and vitreous body.

# 5. Future work

The CFD model can be further improved by explicitly considering: (1) the flow convection due to the constant rotational motion of the eyeball; (2) the elastic deformation of the eyeball; and (3) the translocation of the drug into the blood circulation.

In addition, this study employed a uniform inlet boundary condition for topical administrations. The uniform inlet boundary condition for timolol was based on the previous study, which can be replaced by more reaslitic non-uniform spatial distributions. Also, the precorneal loss which was not considered in this study will be modeled [41]. While errors and variations caused by this assumption still need to be addressed via benchmarked experimental data for the specific drug and the corresponding temporal dosing conditions. Comparisons of the drug transport and delivery efficiency among multiple types of medications can be investigated using the CFD model developed in this study in the future.

Furthermore, for drug delivery via nanoparticles, the viscosity and particle size effect on the drug delivery efficiency to multiple ophthalmic compartments can be numerically investigated [74].

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# Ethical approval

Not required.

## Data statement

The data that support the findings of this study are available from the corresponding author upon request.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## 3.5. Therapeutic efficacy and safety of drug dosing administration

(c)). Fig. 18 shows that after the drug concentration starts to decrease, the influence of *Cl<sub>a</sub>* becomes dominant. With the lowest *Cl<sub>a</sub>*, timolol was

being eliminated slower, and the concentration can keep at a relatively

higher level (i.e., above 1.8e-4) till t = 3 h than the other cases with

higher *Cl<sub>a</sub>*. It is also worth mentioning that the drastic change of the drug concentration before t = 0.6 h is due to transient administration inlet

conditions (see Fig. 3) at the top of the cornea and the timolol diffusion

through the region between the cornea surface and anterior during this

time slot. With reaching the maximum drug concentration later than the

anterior regions of the eye (see Fig. 18 (d)) and the monotonic increasing

trend of the drug concentration in the vitreous body (see Fig. 18 (e)), the

delayed drug delivery can be observed from the anterior of the eye to the

posterior. Figs. 18 (d) and (e) also indicate that the elimination rate has a

significant effect on the drug concentration in the lens and the vitreous

body. Therefore, drugs with lower clearance rates could potentially enhance the delivery efficiency and bioavailability to the posterior

Reaching the optimal balance between therapeutic efficacy and safety is always the goal to make disease-specific and patient-specific administration plans for patients [49]. However, it is still challenging to provide quantitative evidence towards such a goal using in vitro and in vivo studies. According to the guideline provided by the National Institutes of Health (NIH), timolol eve drops are usually instilled once or twice a day at evenly spaced time intervals, while adding more or fewer administrations should be prescribed by the doctors [70]. A previous study [71] shows that the similar efficacy profile of the IOP lowering effect of 0.1% timolol compared to a 0.5% timolol in healthy volunteers was confirmed. Another study [68] demonstrates that the concentration of ophthalmic timolol (i.e., 0.1%, 0.25%, 0.5%, and 1.0%) has insignificant effects on the blood pressure, visual acuity, and pupillary diameter, it may be due to the dosing interval time was too long (12 h) to induce the adverse reactions to the eye. This phenomenon may be explained by the CFD results in this study directly. Specifically, the timolol concentration decreases rapidly in the selected medium in the eyeball in 4 h (see Figs. 6-8 and Figs. 15-17). Therefore, the drug concentration after 4 h can be even lower, and the effect should be negligible. However, recent studies still indicate that ophthalmic timolol may cause serious adverse effects with both subjective and objective aspects, such as cardiac disorders, vascular disorders, respiratory difficulties (i.e., asthma and chronic obstructive pulmonary disease), and corneal diseases [49,72,73]. The possible adverse issues are related to the dose of exposition and to the plasmatic concentration of beta-blockers, and this possibility increases rapidly after the threshold of 200 pg/mL [69,71]. Although the CFD approach can be employed to quantify how much drugs can transport through the eyeball by considering eliminations for AH convection flow and metabolic process in the eyeball, reliable clinical data are needed to calibrate or validate the CFD model on quantifying the concentration of drugs enters other tissues, i. e., cardiac and/or respiratory systems via blood circulation.

# 4. Conclusions

The effects of topical administration frequency, time interval, and elimination rate on the temporal and spatial drug concentration distributions have been investigated systematically in this study using an experimentally validated CFD approach in a 3D human eye model. The noninvasive and cost-effective high-fidelity CFD model employed in this study is promising since it has the potential to not only assess the efficiency and safety of timolol topical administration but also can be used

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