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Computer modeling of drug delivery in the anterior human eye after subconjunctival and episcleral implantation

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ABSTRACT

Recently, subconjunctival and episcleral implants have been proposed in the treatment of anterior eye diseases. In order to improve the delivery efficacy, it is important to understand the transport process of the implanted drugs. A 3D computational model, which includes heat transfer, aqueous humor (AH) flow, as well as diffusive and convective transport of the drug concentration, is developed to study the temporal and spatial evolution of the drug in the anterior segment of a human eye after subconjunctival and episcleral implantation, with a focus on drug delivery to three targets: iris, lens, and trabecular meshwork (TM). The release rate of the implanted drug is based on experimental data and effects of implantation location, eye orientation, and AH flow are investigated. Our numerical results indicate that subconjunctival implantation is more effective than episcleral implantation for drug delivery to all the three targets, and the accumulative amount of drug delivered to the three targets is larger in the horizontally-facing eye than in the up-facing eye. Implantation at the 12 o'clock circumferential position is the most effective for drug delivery to iris and lens, and the 3 o'clock position is the most effective for drug delivery to TM. This study may help to better understand the delivery process of implanted drugs in the anterior human eye, and improve delivery efficacy for clinical treatment of anterior eye diseases.

1. Introduction

Effective delivery of ophthalmic drugs to the targeted ocular tissues has been challenging due to the various physiological and anatomical barriers [1]. According to its target locations, drug delivery in the human eye can be generally divided into anterior and posterior segment delivery. Clinically, topical ocular drug administrations are the most widely used treatment for diseases in the anterior eye, such as glaucoma [2], cataract [2], iritis [3] and postoperative inflammation [4]. Meanwhile, common measures for posterior eye diseases treatment include implantation in episclera [5], injection in the vitreous [6], and intravitreal implantation [7]. Currently, drug delivery in the anterior eye is still challenging, due to low bioavailability of topical administration and anatomical/physiological barriers in the anterior eye, including nasolacrimal drainage [8–10], clearance from the blood vessels in the conjunctiva [10], tissue barrier of corneal epithelium [11–13], and protection against the entry of xenobiotics [10]. As a result, less than 5% of topically applied therapeutic agent can pass through the cornea and enter AH, and even less drug can reach its target tissue [14]. On the other hand, high doses of drug can be harmful to eye tissues because of the narrow therapeutic window of therapeutic agent [15]. Recently, biodegradable subconjunctival implant has been proposed in clinical trials to treat primary open angle glaucoma (POAG) and ocular hypertension [16], and episcleral implant has also been found to be effective with long duration in the treatment of keratoconjunctivitis sicca [17] and in rejection prevention of high-risk corneal transplantation [18]. However, it is still a challenge to accurately understand the delivery process of implanted drugs, mainly due to the difficulty in experimentally measuring drug distribution in the eye. On the other hand, numerical models can provide a comprehensive description of temporal-spatial evolution of drug concentration inside the human eye, and help to promote drug delivery efficiency.

There have been extensive numerical studies on posterior-segment drug delivery. Friedrich et al. [19] developed a finite element model to predict drug distribution in the vitreous humor, and found that location of the intravitreal injection had an obvious effect on the drug distribution. Missel [20] proposed a 3D model to numerically study influences of hydraulic flow and vascular clearance on intravitreal drug delivery. Park

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et al. [21] developed a 3D model to numerically simulate the drug transport process after intravitreal injection and controlled release implant, and concluded that intravitreal implant could reduce the peak drug concentration and increase the duration of drug release. Kavousanakis et al. [22] numerically studied drug delivery from an episcleral implant to tissues in the posterior eye.

The anterior-segment drug delivery after topical ocular drug administrations has also been investigated by numerical simulation. Wyatt and Lustgarten [23] investigated the pharmacokinetics and AH flow with focal application of mydriatics at the limbus, and developed a 2D computational model to study drug delivery after inferior limbus applications [24]. Avtar and Tandon [25] established a numerical model to simulate the drug transport process in the anterior eye after topical application. Lin and Yuan [26] developed a 2D computational model to probe the drug transport process of topically applied ethacrynic acid which is a potential medication to treat POAG. Ferreira et al. [27] proposed a 1D model to study the drug delivery process in the anterior chamber after topical application of a medicated lens. Recently, Chen et al. [28] numerically investigated the drug delivery process after topical application with a 3D computational eye model, and suggestions of clinical applications were proposed. However, to the best of our knowledge, there has been no computational model and numerical study on the drug delivery after implantation in the anterior eye, and effects of implantation location, eye orientation, as well as the AH flow, on the delivery efficacy, need to be investigated. Niazi et al. [29] developed a 3D numerical model which provided estimation of the AH flow and shear stress on the cornea in a human eye with implanted intraocular lens, but this model does not consider drug transport from the intraocular lens although drug-eluting intraocular lenses have been reported [30].

In the current study, drug release from the implant is modeled based on experimental data in the literature, and a 3D finite element computational model is developed based on our preliminary work in Ref. [31], and used to investigate the drug transport process in the anterior human eye. Our computational model incorporates heat transfer in both the anterior and posterior eye, secretory and natural convection flow of AH, as well as diffusive and convective transport of the drug. Subconjunctival and episcleral implantation are then compared, and influences of eye orientation and circumferential position of the implant on the delivery efficacy to some common targets are also studied.

2. The computational model

Anatomical structure of a human eye with implants is schematically shown in Fig. 1. The axisymmetric 3D eye model (Fig. 2) is established based on the 2D geometry data of an anterior human eye in Lin and Yuan's work [26] and those of a posterior eye in Ooi and Ng's work [32]. Specific geometric data are also listed in Table 1. As is shown in Fig. 2, the model includes all the important components of the eye, i.e., cornea, iris, anterior and posterior chambers, trabecular meshwork, lens, sclera, vitreous, ciliary body (CB) and the drug source, which is either the subconjunctival implant or episcleral implant. The episcleral implant consists of cyclosporine A and silicone matrix, and is a solid 0.75 inches in length, 0.08 inches in width and 0.04 inches in thickness [17]. The subconjunctival implant is assumed to be the same size as the episcleral implant, with its top and bottom surfaces in contact with sclera and conjunctiva, respectively.

In our computational model, the unsteady convection-diffusion equation below is solved to obtain the spatio-temporal variation of the drug concentration:

$$\frac{\partial C}{\partial t} + \vec{v}\cdot\nabla C = D\nabla^2 C, \tag{1}$$

where D is the diffusion coefficient, $\vec{v}$ is the AH velocity, and C is the drug concentration. Without loss of generality, ethacrynic acid [33,34] has been chosen as an example of the drug, whose physical properties are listed in Table 2.

Cumulative mean release amount of the implanted drug is modeled as an exponential function with respect to time (Fig. 3), based on the measured data of a silicone-based matrix implant [17], and is described by

$$C_{\text{cum}} = 3645.83 \times \left(1 - e^{-0.008t}\right) \times 10^{-3} \ \ (\text{g}). \tag{2}$$

In our computational model, only the bottom side of the subconjunctival/episcleral implant is considered to contribute to drug delivery to the targets. Based on Eq. (2) and assuming equal amount of release on the top and bottom surfaces, the flux boundary condition for Eq. (1) on the bottom surface of the implant is specified as

$$\text{Flux} = \frac{1.688 \times e^{-0.008t}}{A_{imp}} \times 10^{-10} \quad \left(\text{gm}^{-2}\text{s}^{-1}\right), \tag{3}$$

where $A_{\text{imp}} = 3.87 \times 10^{-5}\text{m}^2$ is the bottom surface area of the implant.

The boundary condition for Eq. (1) on the TM surface is given by

$$\vec{n}\cdot(-D\nabla C) = 0, \tag{4}$$

where $\vec{n}$ is the outward normal unit vector.

A left-right symmetry boundary condition is specified on the x = 0 plane, i.e.

$$\partial C/\partial x = 0. \tag{5}$$

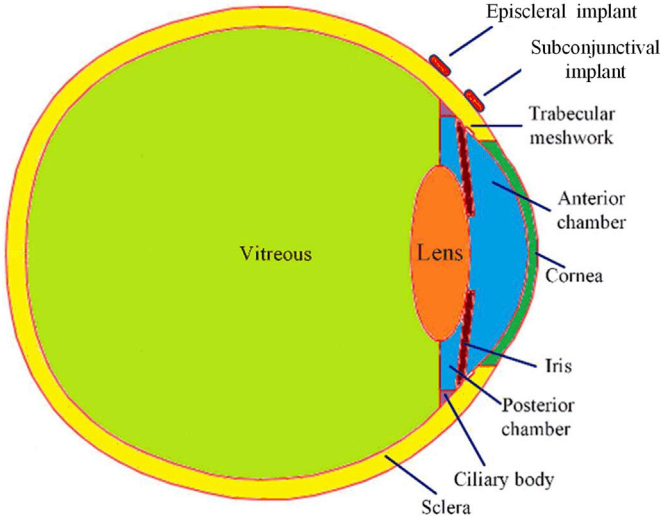

Fig. 1. Anatomical structure of a human eye with implants.

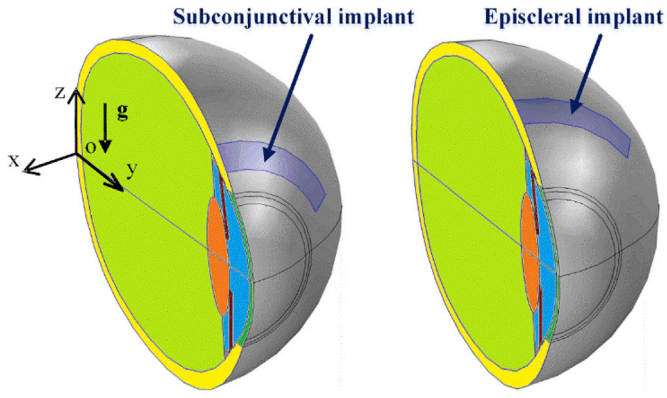

Fig. 2. Computational model of the human eye with implants.