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Segmental aqueous humour outflow and eye orientation have strong influence on ocular drug delivery

Chai Y Loke[a], Ean H Ooi[a,b,*], Mohmed S Salahudeen[a], Norlina Ramli[c], Amir Samsudin[c]

[a] School of Engineering, Monash University Malaysia, Bandar Sunway, Selangor 47500, Malaysia
[b] Advanced Engineering Platform, Monash University Malaysia, Bandar Sunway, Selangor 47500, Malaysia
[c] Department of Ophthalmology, Faculty of Medicine, University of Malaya, Kuala Lumpur 50603, Malaysia

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ABSTRACT

The present study is motivated by the recent concerns raised over the existence of segmental outflow and its implications on ocular drug delivery. A 3D model of the human eye is developed, where hydrodynamic and mass transport analyses after eye drop instillation, are carried out. To model segmental outflow, the permeability of the trabecular meshwork (TM) is assumed to vary spatially following a rectangular function. The choice of the rectangular function is based on the results from the tracer distribution study of Chang et al., 2014. Results from the numerical simulations show that segmental outflow causes the majority of the available drugs to egress through the active region, while non-active region experiences very minimal drug exposure. This supports the experimental findings of Chang et al. Additionally, it was found that eye orientation can affect the delivery of ophthalmic drugs by influencing the aqueous humour hydrodynamics. The results obtained here suggest that there may be a need to re-evaluate the design of ocular drug delivery system by taking into consideration the effects of segmental outflow and eye orientation.

1. Introduction

Aqueous humour (AH) is a watery substance that resides in the anterior and posterior chambers of the eye. Its motion is driven primarily by thermally-induced buoyancy forces and to a lesser extent, by its production and drainage, with the velocity due to thermally driven flow being two orders of magnitude larger than that of production and drainage [1]. Aqueous humour exits the anterior chamber via the conventional and unconventional outflow pathways. The latter accounts for approximately 10% of the total outflow and its hydraulic contribution is often neglected in the hydrodynamics study of AH. The conventional outflow pathway comprises three major components, namely the trabecular meshwork (TM), the Schlemm's canal (SC) and the collector channels (CC). Glaucoma is an ocular disease that is commonly associated with an increase in the intraocular pressure (IOP). The elevation in IOP has been attributed to the rise in the hydraulic resistance inside the conventional outflow pathway, which reduces the outflow of AH and subsequently elevates the IOP. The excessive stress exerted onto the optic nerve head (ONH) by the elevated IOP can cause irreparable mechanical damage that can lead to blindness. As such, the majority of the anti-glaucoma drugs are designed to lower the IOP in order to alleviate the stress

* Corresponding author at: School of Engineering, Monash University Malaysia, Bandar Sunway, Selangor 47500, Malaysia.
E-mail addresses: ooi.ean.hin@monash.edu, ehooi@live.com (E.H. Ooi).

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on the ONH. These drugs are typically administered via eye drops, whereby the drugs diffuse from the corneal surface into the cornea and subsequently into the anterior chamber. Therefore, the flow of AH forms a major route for the delivery of anti-glaucoma drugs.

The sensitivity of the human eye to physical contact has led to the majority of the studies on AH hydrodynamics to be carried out *in silico*. To the authors' knowledge, all the existing computational models reported in the literature have assumed the flow of AH through the conventional outflow pathway to be uniform and homogeneous [1–5]. Nevertheless, several recent studies have found this not to be the case. Experimental studies carried out on human and bovine eyes *ex vivo* have demonstrated that the outflow of AH is segmental and heterogeneous, i.e. some parts of the conventional outflow pathway are active, while others are not [6–9]. This phenomenon has been attributed to the irregular distribution of CC across the conventional outflow pathway [6–8], while non-uniform distribution of pores across the inner wall endothelium of the SC has also been suggested as another cause for the observed segmental outflow [9].

The discovery of segmental outflow has raised some concerns on whether the non uniform AH outflow through the TM can affect the delivery of anti-glaucoma drugs. In the presence of segmental outflow, drugs that enter the anterior chamber have a tendency to flow through the active regions, while flow through the non-active regions is limited by the slower and less effective diffusion process [8]. For anti-glaucoma drugs that specifically target the conventional outflow pathway, the heterogenous drug deposition across the TM can create conditions of potentially 'over-treating' and 'under-treating' the disease, thereby affecting the efficacy of the drugs. In spite of this, there have been no reported studies on the effects of segmental outflow on the drug distribution across the anterior and posterior chambers. The majority of the computational studies carried out on ocular drug delivery have focused on the understanding of the mechanisms by which drugs transport from the corneal surface into the anterior chamber [10], the comparison between different modes of drug delivery [2,11,12], drug delivery to the posterior of the eye [13] and the development of pharmacokinetic-based models [14]. Consequently, there is a lack of understanding on how segmental outflow influences drug delivery into the ocular system.

Motivated by this, the present study seeks to investigate through a computational fluid dynamics study, the effects of segmental outflow on the hydrodynamics of AH inside the human eye and their implications on ocular drug delivery. Additionally, the effects of different eye orientation are examined to contrast the significance between segmental outflow and buoyancy-induced AH flow on the delivery of ophthalmic drugs. A three-dimensional model of the human eye is developed and simulations are carried out using the commercial finite element software COMSOL Multiphysics 5.3 ®. Flow of AH inside the anterior and posterior chambers is governed by the Navier–Stokes equations. The conventional outflow pathway is modeled as a porous medium, where the flow is described using the Stokes–Brinkman equation. Segmental outflow is modeled by assuming the permeability of the TM to be heterogeneous. A baseline permeability value is prescribed across the active regions to mimic high outflow facility, while non-active regions are assigned near zero permeability to retard outflow. To model ocular drug delivery, the most common method for delivering anti-glaucoma drugs, i.e. via topical eye drops, is considered. The present study considers only the transport of drugs within the anterior-posterior chambers and the TM, while transport into the gel-like substance of the vitreous is ignored.

2. Materials and methods

2.1. Model geometry

The three-dimensional model of the human eye developed in the present study consists of the cornea, anterior and posterior chambers, lens, vitreous, iris and sclera. The layers of the retina, choroid and sclera are modeled as a single homogeneous domain due to the relatively thin structures of the retina and the choroid [15]. The dimensions of the eye model follow closely those reported by Ooi and Ng [4]. An additional ring-like domain, 497 μm in length and 174 μm in height, is added to the outer circumference of the anterior chamber to represent the conventional outflow pathway. Since the length in the flow-wise direction of the SC and the CC are approximately two orders of magnitude smaller than the TM, the conventional outflow pathway is modeled as a homogeneous domain, which hereafter, is simply referred to as the TM. A gap of 25 μm is created between the tip of the iris and the lens to allow AH to flow from the posterior chamber into the anterior chamber. As such, the anterior and posterior chambers belong to the same piecewise-homogeneous domain. Fig. 1a shows the model of the human eye developed, where only one-half of the model is shown to illustrate the internal structures of the eye. A sagittal plane view is depicted in Fig. 1b.

2.2. The flow model

The flow model is prescribed only in the TM and the anterior and posterior chambers, as shown in Fig. 1c. Flow of AH inside the anterior and posterior chambers is assumed to be laminar and incompressible, such that the flow may be described using the Navier–Stokes equations:

$$\rho(\mathbf{u}\cdot\nabla\mathbf{u}) = -\nabla p + \mu\nabla^2\mathbf{u} + \rho\mathbf{g}, \tag{1}$$

$$\rho\nabla\cdot\mathbf{u} = 0, \tag{2}$$

where $\boldsymbol{u} = (u, v, w)$ is the velocity vector, p is pressure, ρ and μ are the density and dynamic viscosity of AH, respectively and $\mathbf{g}$ is the vector representing gravitational acceleration. For the model developed here, which represents an individual in

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