International Journal of Heat and Mass Transfer 85 (2015) 356–366

Contents lists available at ScienceDirect

International Journal of Heat and Mass Transfer

journal homepage: www.elsevier.com/locate/ijhmt

Numerical investigation of topical drug transport in the anterior human eye

Han Chen [a,b,*], Feng Zhang [a], Yukan Huang [c], Jiankang Wu [a]

[a] Department of Mechanics, Huazhong University of Science and Technology, Wuhan 430074, China
[b] State Key Laboratory of Digital Manufacturing Equipment and Technology, Huazhong University of Science and Technology, Wuhan 430074, China
[c] Department of Ophthalmology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

ARTICLE INFO

Article history:
Received 17 October 2013
Received in revised form 15 December 2014
Accepted 31 January 2015

Keywords:
Drug delivery
Eye
Anterior chamber
Aqueous humor
Natural convection
Heat transfer

ABSTRACT

Anterior eye diseases are commonly treated by topically applied drugs in the form of eye drops or ointment. In order to assess the effectiveness of topical drug administration, it is crucial to understand temporal evolution and spatial distribution of the drug in the anterior eye. In this paper, a numerical model of topical drug transport in the anterior human eye is developed, which is coupled with heat transfer and fluid flow in the anterior eye. Spatio-temporal evolution of drug concentration is then investigated numerically, with an emphasis on the drug concentration at three targets: the trabecular meshwork (TM), iris and lens. The results show that after the drug diffuses across the cornea, convection by the aqueous humor (AH) flow is the dominant mechanism of transport of topically applied drugs in the anterior human eye, which is due to temperature difference across the eye. Effects of eye orientation and ambient temperature are also analyzed. Ambient temperature is found to play an important role in the transport of topically applied drugs to various target tissues in the anterior eye. With the increase of ambient temperature, the peak concentration at the target first decreases, and then increases, and the minimum value is reached when ambient temperature is close to the body core temperature. Eye orientation is found to influence the maximum drug concentration at different targets, as well as the time it takes to reach the maximum. The results may help to understand the drug transport process in the anterior human eye, and provide guidelines of drug administration in order to improve the delivery efficacy.

1. Introduction

Drug delivery to the eye can be broadly classified according to the target locations, namely anterior and posterior segments (Fig. 1). Accessibility of the exposed corneal surface renders it a convenient site for the administration of ophthalmic medications, and topical drug application has been the most natural choice for the treatment of eye diseases, especially anterior segment eye diseases such as glaucoma [1], cataract [1] and iritis [2]. Currently, more than 90% of the marketed ophthalmic medications are applied topically in the form of eye drops or ointment [3]. Posterior eye diseases usually require high vitreal drug concentrations, and it is more difficult for topically applied drugs to reach the vitreous body. Therefore, drug delivery to the posterior eye is usually implemented clinically by other means such as transscleral delivery [4], intravitreal injection/implant [5], and vitreous substitution [6].

Currently, the efficacy of topically applied drugs in the treatment of anterior eye diseases is mainly limited by the difficulties in delivering enough doses to the target tissues, including loss on the ocular surface due to tear dilution and turnover [7], and physiological barriers [8] such as the corneal and sclera epithelial layers. It has been shown that less than 5% of the drug dose penetrates the cornea and reaches the aqueous humor (AH) in the anterior chamber [9]. After penetrating into the AH, a smaller portion of the drug can actually reach its target tissue. On the other hand, many of these ophthalmic drugs have a narrow therapeutic window and high drug doses required to overcome the poor drug availability may result in severe toxicity in eye tissues [10]. Therefore, appropriate drug usage is important and understanding of the transport process of topically applied drugs becomes crucial. To date, a direct and non-invasive measurement of spatio-temporal distribution of drug concentration in the eye is still practically impossible, and numerical models can be useful tools in understanding the ocular drug delivery process and predicting local drug concentration in the anterior eye.

* Corresponding author at: Department of Mechanics, Huazhong University of Science and Technology, Wuhan 430074, China.
E-mail address: hanchen@hust.edu.cn (H. Chen).

http://dx.doi.org/10.1016/j.ijheatmasstransfer.2015.01.142
0017-9310/

Nomenclature

c	specific heat (J kg^{-1} K^{-1})
C	ECA concentration (μM)
D	diffusion coefficient (m^2 s^{-1})
$\vec{g}$	gravitational acceleration (m s^{-2})
h	heat transfer coefficient (W m^{-2} K^{-1})
k	thermal conductivity (W m^{-1} K^{-1})
T	temperature (K)
$\vec{v}$	velocity vector (m s^{-1})

Greek symbols

β	volume expansion coefficient (K^{-1})
E	evaporation rate (W m^{-2})
μ	dynamic viscosity (kg m^{-1} s^{-1})
ρ_0	reference density (kg m^{-3})
σ	the Stefan–Boltzmann constant (W m^{-2} K^{-4})

Subscripts

ah	aqueous humor
amb	ambient
bl	blood
cor	cornea
ref	reference

After penetrating the cornea, transport of the topically applied drug is closely related to the AH flow in the anterior chamber. Fig. 1 illustrates anatomical structures of the human eye. There are two chambers in the anterior segment of the eye, the anterior chamber (between the cornea and the iris) and posterior chamber (behind the iris and anterior to the lens). Both of these two chambers are filled with the AH, a transparent and gelatinous fluid. The AH enters the eye in the posterior chamber by secretion and ultrafiltration at the ciliary body, and flows into the anterior chamber through the pupil between the lens and iris. Most (70–90%) of the AH leaves via the trabecular meshwork (TM) while the remaining exits through the uveoscleral outflow [11]. In addition to secretion and outflow, there are various mechanisms that may be responsible for causing the AH flow, such as temperature nonuniformity, phakodenesis (vibration of the lens as the head or eye moves) and rapid eye movement during sleep. Heys and Barocas [12] and Canning et al. [13] adopted a Boussinesq model in the study of AH natural convection and explained several features observed in traumatized eyes, such as hyphemas, keratic precipitates, hypopyons, and Krukenberg's spindles. Kumar et al. [14] numerically studied AH fluid dynamics in a rabbit eye, and investigated effects of parameters such as the pupil size, eye orientation, and temperature difference across the eye. They concluded that the pupil size has little influence on the intra-ocular pressure (IOP), whose increase is believed to be the cause of glaucoma. Fitt and Gonzalez [15] conducted thorough investigation of various physical mechanisms responsible for causing AH flow, and concluded that natural convection induced by temperature difference between the corneal surface (which, under normal conditions, is exposed to the ambient environment) and interior tissues of the eye, is the dominant one.

Besides providing nutrients, the AH flow also has influences on heat and mass transport across the eye. In the early study of heat transfer in the eye [16–19], the AH was assumed to be stagnant. A 2D eye model developed by Ooi and Ng [20,21] and a 3D eye model developed by Karampatzakis and Samaras [22] considered the coupling of the AH flow and heat transfer in the eye. Their results suggested that AH natural convection has non-negligible influences on the temperature distribution in the anterior eye. Most of the research work on heat transfer in the eye has been focused on the consequences of thermal disturbances such as the extreme ambient temperature (from −10 °C to 60 °C) [23], laser-thermokeratoplasty [24], eye tumor [25], and laser surgery [26]. Excellent agreement between experimental and numerical results reported in these studies highlights the versatility of numerical modeling in the study of heat transfer in the eye.

On the numerical modeling of ocular drug delivery, posterior-segment drug delivery has aroused lots of interests [27–30]. In contrast, transport of topically applied drugs in the anterior eye has received far less attention. Avtar and Tandon [31] proposed a zero-dimensional model of drug transport in the anterior segment in which the AH was assumed to be stationary, and predicted the

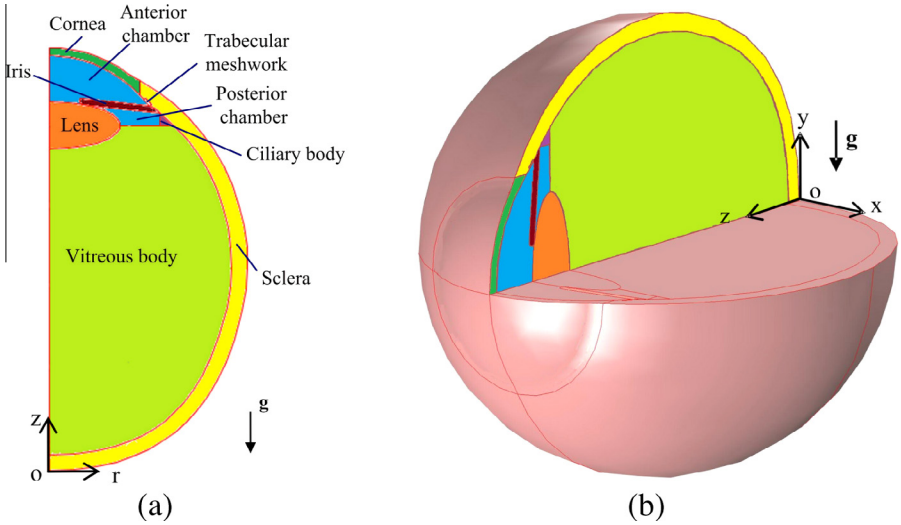

Fig. 1. Anatomical structure and numerical model of the human eye: (a) an up-facing eye and (b) a horizontally-facing eye.