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Computational modeling of drug distribution in the posterior segment of the eye: Effects of device variables and positions

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ABSTRACT

A computational model was developed to simulate drug distribution in the posterior segment of the eye after intravitreal injection and ocular implantation. The effects of important factors in intravitreal injection such as injection time, needle gauge and needle angle on the ocular drug distribution were studied. Also, the influences of the position and the type of implant on the concentration profile in the posterior segment were investigated. Computational Fluid Dynamics (CFD) calculations were conducted to describe the 3D convective-diffusive transport. The geometrical model was constructed based on the human eye dimensions. To simulate intravitreal injection, unlike previous studies which considered the initial shape of the injected drug solution as a sphere or cylinder, the more accurate shape was obtained by level-set method in COMSOL. The results showed that in intravitreal injection the drug concentration profile and its maximum value depended on the injection time, needle gauge and penetration angle of the needle. Considering the actual shape of the injected solution was found necessary to obtain the real concentration profile. In implant insertion, the vitreous cavity received more drugs after intraocular implantation, but this method was more invasive compared to the periocular delivery. Locating the implant in posterior or anterior regions had a significant effect on local drug concentrations. Also, the shape of implant influenced on concentration profile inside the eye. The presented model is useful for optimizing the administration variables to ensure optimum therapeutic benefits. Predicting and quantifying different factors help to reduce the possibility of tissue toxicity and to improve the treatment efficiency.

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1. Introduction

Posterior segment diseases are important causes of visual impairment [1]. It is difficult to deliver adequate levels of drug to the posterior segment to have an effective treatment because of different anatomical and physiological barriers that inhibit drug transport. Geroski and Edelhaiser [2] expressed four methods of drug delivery to the posterior segment including topical, systemic, intraocular and periocular administration. The traditional topical route is inefficient and does not yield therapeutic drug levels in the posterior segment of the eye. Although, systemic administration can deliver drugs to the posterior eye, the large necessary systemic doses are often associated with side effects and toxicity [3–5]. Intraocular delivery involves placing the drug into the vitreous humor or different layers of the eyeball such as subretinal space, whereas in periocular delivery the drug is inserted out of the eyeball by implantation or injection. Periocular drug delivery using sub-Tenon's, subconjunctival, peribulbar and retrobulbar injections or placement of controlled release devices, provides safer and less invasive methods than intravitreal therapy and also offers exciting potential for localized, sustained drug delivery [2,6]. However, this method is less efficient compared to intravitreal therapy, because drug molecules must transit through numerous static, dynamic, and metabolic barriers to reach the posterior segment [7].

Many drugs used for ocular treatment have a narrow concentration window of effectiveness and may be toxic at higher concentrations [8]. Also, the concentration of some drugs that are non-toxic when injected to the normal eye, may become toxic if used to treat a vitrectomized eye [9]. Therefore, to avoid tissue toxicity and to obtain therapeutic benefits during treatment it is necessary to predict how drug is distributed within the eye. Also, several factors in intravitreal injection or ocular implantation affect local drug concentrations, that these effects should be determined properly to achieve precise drug level at target tissues.

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So far, several computational models have been developed to simulate drug distribution in the vitreous humor [10–21]. Some studies developed a transport model following intravitreal injection from a point source [10–15,17,18,20] while the others simulated drug administration by an intraocular or periocular implant [15,16,19]. Early models considered only diffusion, but later ones considered both diffusion and convection produced by the aqueous humor flow through the vitreous.

In this work, a computational model was developed for both periocular and intraocular drug delivery. The presented model is close to Balachandran and Barocas model [22] with more accurate geometry. The choroid and sclera layers were considered separately, while in the previous model these layers were assumed into one entity. However, the choroidal layer consists of blood vessels, while the sclera is a vascular that leads to different characteristics. The effects of important parameters in intravitreal injection such as injection time, needle gauge and needle angle were investigated. In this regard, unlike previous studies, a more accurate shape for the injected drug solution was obtained and used in simulations. Also, the influences of the position and type of implant on the concentration profile were studied.

2. Mathematical model

2.1. Geometry of the eye

Fig. 1 shows the geometrical model adopted in the present study. The shape of the posterior segment was assumed to be spherical. Key dimensions appeared in Table 1 is based on the physiological dimensions of the human eye. The model mainly included six compartments; the retina, the choroid, the sclera, the vitreous, the lens, and the hyaloid membrane. The lens and the hyaloid membrane form a boundary between the anterior and posterior segments of the eye. Using the new geometry, the volume of the vitreous chamber is equal to 4.4 ml which is compatible with the physiological data of the normal human eye (between 4 and 5 ml) [15,23,24]. In the Balachandran and Barocas' model, the volume of the vitreous is about 2.2 ml that is far from reality. This difference indicates that the inner radius of the retina in the presented model (10.4 mm) is closer to the physiological data compared with the inner radius of the retina in Balachandran's model (8.5 mm). Only half of the eye was modeled with the symmetry plane passing through the optical axis and the center of the drug source. The optical axis passes through the back of the lens to the center of the retina.

2.2. Governing equations

To obtain drug distribution within the eye, in addition to diffusion, convective mass transport should be considered especially for large molecules [15–19,22]. Convective mass transport occurs due to the permeation of the aqueous humor through the vitreous and posterior layers. Because of the presence of collagen fibers, the vitreous was assumed to be stagnant, incompressible and porous with high porosity. Also, all layers were considered as porous mediums. For very low fluid velocity within the eye Darcy flow equation can be applied as:

$$v = -\frac{K}{\mu}\nabla P \tag{1}$$

where v is the fluid velocity vector, μ is the viscosity of the permeating aqueous humor, P is pressure and K is the permeability of the porous medium. The term K/μ is called hydraulic conductivity. It was assumed that drug distribution does not affect the aqueous flow. Assuming conservation of mass, $\nabla \cdot v = 0$, Eq. (1) becomes:

$$\frac{K}{\mu}\nabla^2 P = 0 \tag{2}$$

To model drug distribution in the vitreous the standard convection–diffusion equation was applied as:

$$\frac{\partial C}{\partial t} + v \cdot \nabla C - D_V \nabla^2 C \mp q = 0 \tag{3}$$

where C is concentration, D_V is the diffusion coefficient of the drug in the vitreous, and q is the consumption or generation rate of the drug. It was assumed that the drug is not metabolized or degraded within the eye, so the term q was set equal to zero.

Following Balachandran and Barocas [22] active transport by retinal pigment epithelium was incorporated, because its strength is comparable to the passive transport. The mass transport equation for the retinal layer was written as:

$$\frac{\partial C}{\partial t} + (v + k_{act}) \cdot \nabla C - D_R \nabla^2 C = 0 \tag{4}$$

where k_{act} represents the active mass transfer coefficient and D_R is the diffusion coefficient in the retinal layer. There are many capillaries in the choroidal layer, so the drug can move between the tissue and the blood circulatory system. Similar to the procedure used by Balachandran and Barocas [22] the mass transport equation was written as:

$$\frac{\partial C}{\partial t} + v \cdot \nabla C - D_C \nabla^2 C - \gamma(C_{bl} - C) = 0 \tag{5}$$

where C_{bl} is the drug concentration in the blood, D_C is the diffusivity in the choroid and γ is a constant to represent the rate of drug transport between the blood vessels and the choroid layer. The term $\gamma(C_{bl} - C)$ acts as a source when the drug concentration in the blood is more than ocular tissues. Sclera is an avascular layer, so the drug mass transport equation for this layer was considered as:

Table 1
Key dimensions of the human eye.

Item/reference	Dimensions (mm)
Inner radius of the retina	10.4
Retinal thickness [30]	0.1
Choroidal thickness [31]	0.25
Scleral thickness [32]	0.5
Posterior lens curvature [30,33]	6
Anterior lens curvature [30,33]	11
Lens thickness [30,33]	4
Anterior chamber length [34]	3.8
Anterior–posterior length	24.24
Distance between the lens and center of the vitreous	5.19
Hyaloid length	1.64
Vitreous volume (ml)	4.4
Hyaloid area (mm^2)	60

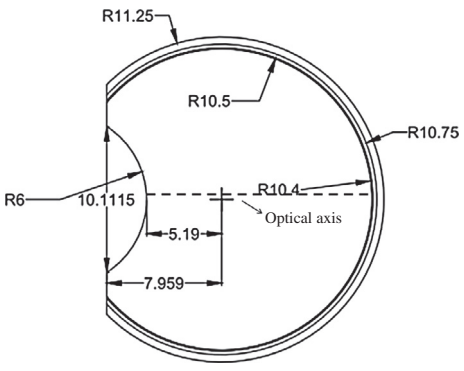

Fig. 1. Cross section view of the human eye. All dimensions are in mm.

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