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Computational modeling of drug delivery to the posterior eye

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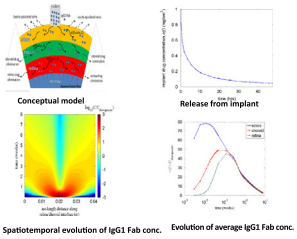
HIGHLIGHTS

- An anatomically and physiologically correct model of the human eye was validated.
- Spatiotemporal evolution of an ocular drug for macular degeneration was obtained.
- Drug delivery from an episcleral implant compared well to intravitreal injection.

GRAPHICAL ABSTRACT

Delivery of anti-VEGF drug, IgG1 Fab, from an episcleral implant to the posterior eye for treatment of age-related macular degeneration.



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ABSTRACT

Simulations of delivery of IgG1 Fab, an anti-vascular epithelial growth factor (VEGF) macromolecular drug for the treatment of age-related macular degeneration (AMD), from an episcleral thermally responsive-poly(N-isopolyacrylamide) (NIPAM)-gel implant, are made to evaluate the effectiveness of sustained delivery.

The model of the human eye used in the above simulations is validated as far as its anatomical and physiological features by the agreement observed in comparing results of simulations of intravitreal fluorescein delivery with relevant experimental data.

Simulations of IgG1 Fab delivery from an episcleral NIPAM-gel implant to the posterior eye, with the previously validated anatomically and physiologically correct model of the human eye, show that drug therapeutic levels in the posterior eye are sustained for 8 weeks similarly to those associated with intravitreal injection of IgG1 Fab. Thus, delivery of the macromolecular anti-VEGF drug IgG1 Fab from an episcleral NIPAM-gel implant seems to be a viable alternative to more invasive, risk-related delivery by intravitreal injection, as effective and sustainable as the latter.

1. Introduction

Posterior eye diseases include a variety of diseases such as glaucoma, retinopathy, and age-related macular degeneration (AMD). AMD results from uncontrolled expression of the vascular endothelial growth factor (VEGF), which is responsible for neovascularization, and involves cell proliferation and uncontrolled growth in blood vessels leading to leaking of blood and proteins, scarring of the macula region, and, eventually, irreversible loss of vision.

AMD is treated primarily with anti-VEGF macromolecular drugs such as ranibizumab, a recombinant monoclonal antibody (mAb), IgG1 Fab fragment with molecular weight (MW) 49 kDa, administered by intravitreal (IVT) injection (Oleijnik and Hughes, 2005). Interestingly, its full-size counterpart, bevacizumab, IgG1 with MW 149 kDa, which is approved for treatment of solid tumors, has also demonstrated efficacy in treatment of AMD, which raises questions about antibody pharmacology and biodistribution as well as cut-off drug molecular weight for retina penetration (Steinbrook, 2006). The anti-VEGF antibodies at therapeutic doses act by suppressing completely neovascularization triggered by expression of VEGF.

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Delivery of ocular drugs through IVT injections or local implants poses a challenge because of the presence of physiological and anatomical barriers, e.g., blood-retina barrier (BRB), and, in several cases like that of AMD, the use of macromolecular active pharmaceutical ingredients (API). A less invasive, less risky system of delivery involves transcleral delivery from thermally responsive hydrogels of poly(N-isopropyl acrylamide) (NIPAM), placed on the sclera close to the optical nerve (Ninawe et al., 2010).

Because many of the drugs for posterior eye diseases have a narrow therapeutic concentration window, it is important to be able to predict the fate of the drug in the tissues of the posterior eye in order to have an effective delivery system. Accurate predictions of ocular drug clearance are made with the help of mathematical models that honor the anatomy of the eye and incorporate physiological properties and processes that determine the evolution of drug distribution in the eye. As early as 50 years ago, simple mathematical models predicted a linear relationship between the rate of egress of material from the vitreous humor and the ratio of average concentrations in the aqueous and vitreous humor (Maurice, 1959), which still continues to be valid. Computational models are validated with experimental data (Palestine and Brubaker, 1981; Dalgaard and Larsen, 1990; Lund-Andersen et al., 1985; Engler et al., 1994) and used for allometric scaling in order to predict the experimental outcome in one species from that of another (Missel, 2012).

In a paper published in this journal (Ninawe et al., 2010), release of IgG1 Fab from an episcleral hydrogel has been modeled and transcleral delivery of this drug to the posterior eye has been simulated with a compartmental model. The drug release model, which is quite accurate, showed that most of the drug dose, close to 70%, is released by convection in the first 8 h after administration. On the other hand, simulations made with a compartmental model, which idealizes the sclera, choroid and retina tissues as continuously stirred, completely mixed compartments, have shown that sustained delivery times of 8 weeks, during which drug concentrations in the choroid exceed 150 mg/l, the concentration resulting in total inhibition of neovascularization, are achieved with monthly doses of 1 and 0.5 mg.

Experimental data on the fate of IgG1 Fab in the tissues of the posterior eye for both intravitreal (IVT) injection and delivery from a local implant do not exist. There are only clinical trials of IgG1 Fab by IVT injection (CHMP Review, 2007) which confirm that the therapeutic effects of a 1 and 0.5 mg monthly doses of anti-VEGF drug last for 8 weeks.

Although simulations of IgG1 Fab delivery from a local implant with the compartmental model produced results comparable to those of clinical trials with IgG1 Fab by IVT injection, these simulations were repeated with an anatomically and physiologically correct model similar to that used in another work (Balachandran and Barocas, 2008). As with that work (Balachandran and Barocas, 2008), the anatomical and physiological features of the model were validated by comparing the results of simulations with a number of experimental studies of fluorescein (MW = 330 Da) delivery to the posterior eye. Once the anatomically and physiologically correct model was validated, it was used for simulations of IgG1 Fab (MW = 49 kDa) delivery from a local NIPAM hydrogel implant.

2. Materials and methods

2.1. Physical model

A three-dimensional geometric model, fairly close to the model in another work (Balachandran and Barocas, 2008), consisting of spherical shells, represents the human posterior eye. A cross-section view of the geometric model is shown in Fig. 1.

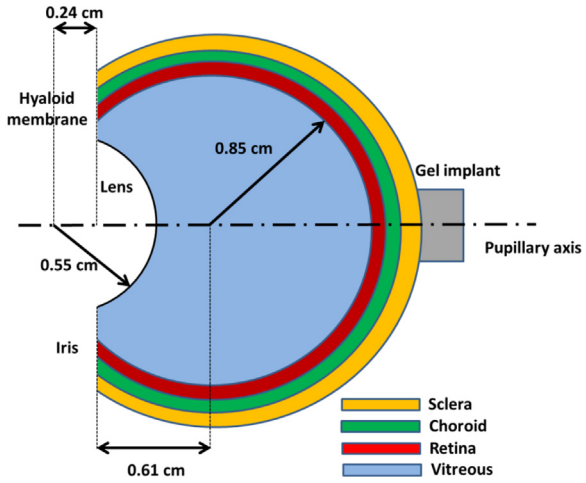

Fig. 1. Geometric model of the posterior eye together with episcleral cylindrical gel implant.

The vitreous humor can be treated as a static, incompressible porous medium and is bounded on the anterior surface by the lens and the hyaloid membrane, and the retina on the posterior surface. The hyaloid membrane, which consists of loosely packed collagen fibers and hyaluronic acid, forms a boundary between the stagnant vitreous and the flowing aqueous humor but does not act as a barrier to transport of small molecules like fluorescein. Once drugs pass through the hyaloid membrane, they are eliminated by the flowing aqueous humor (Xu et al., 2000). The aqueous humor is continuously produced by the ciliary body and drained from the anterior chamber after it passes between the iris and the lens. The lens, composed of highly compacted cellular material, is almost impermeable to drugs, and as such can be excluded from the model. In recent studies of IVT injection (Missel, 2012) has been discovered that inclusion in the model of the space of Petit, a small gap between the anterior boundary of the vitreous humor and the ciliary body, which effectively extends the aqueous humor nearly up to the most anterior portion of the retina, allows more accurate predictions of ocular drug clearance.

The retina, immediately adjacent to the vitreous humor on one side and the choroid on the other, consists of several cellular layers, some of which form the blood-retinal barrier (BRB). The BRB has two components, the retinal vascular endothelium and the retinal pigmented epithelium (RPE). Retinal blood vessels that are similar to cerebral blood vessels maintain the inner blood-ocular barrier, which consists of a single layer of non-fenestrated endothelial cells with tight junctions, impervious to tracer, to prevent passage of large molecules from capillaries of the choroid into the retina (Tsuboi, 1987). Experimental studies uncovered the difference in inward and outward permeability of the BRB and attributed the higher outward permeability to an active transport generated by the flow of the aqueous humor (Tsuboi, 1987).

2.2. Mathematical model

2.2.1. Flow model

The Darcy flow equation:

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

where $\mathbf{v}$ is the flow velocity, K is the permeability of the medium (vitreous humor) and μ the viscosity of the aqueous humor, is applied to describe the flow of the aqueous through the vitreous humor. The flow of the aqueous humor is assumed to remain