

COMPARISON OF DRUG DISTRIBUTION BETWEEN INTRAVITREAL INJECTION AND A CONTROLLED – RELEASE IMPLANT IN A RABBIT EYE

Rupak K. Banerjee

Division of Bioengineering and Physical Science
National Institutes of Health
Bethesda, MD 20892

Keyvan Keyhani

Fluent Incorporated
Evanston, IL

Brian King

Division of Bioengineering and Physical Science
National Institutes of Health
Bethesda, MD 20892

Robert J. Lutz

Division of Bioengineering and Physical Science
National Institutes of Health
Bethesda, MD 20892

Robert L. Dedrick

Division of Bioengineering and Physical Science
National Institutes of Health
Bethesda, MD 20892

Michael Robinson

National Eye Institute
National Institutes of Health
Bethesda, MD 20892

ABSTRACT

Due to physiological barriers within the eye, which limit penetration of many drugs from the systemic circulation into the vitreous, the most common method of treating retinal disease is direct intravitreal injection. However, this common procedure may be inappropriate for a wide range of drugs as it may lead to highly variable concentrations potentially causing higher toxicity for tissues inside the eye and limiting therapeutic effect.

A recent procedure is to use surgically implanted drug release device, called implant here, in the vitreous of the eye that allow controlled release of drug over a sustained period of time. For constant release of drug over 15 hours, a substantial reduction in peak drug concentration is predicted near the retina. When compared with the implant, a doubling of drug concentration would be expected for more than 3 hours near the retina for the intravitreal injection.

INTRODUCTION

Many of the drugs used for treating retinal and vitreal diseases of an eye have a narrow concentration range in which they are effective and may be toxic at higher concentrations (Forster et al. (1980), Pflugfelder (1987), Stainer et al. (1977), Tabatabay (1987), Talamo et al. (1985)). Friedrich et al. (1997) modeled the posterior part of a rabbit eye having vitreous, posterior aqueous compartment with surrounding retina layer. They showed drug distribution in the vitreous and estimated the permeability of the retina.

If the disease is to be properly treated and damage to tissues by excessively high concentrations of drug is to be avoided, then it is important to know the drug distribution following administration. Using a finite element model, we compared drug distribution in the vitreous of a rabbit eye after an intravitreal injection with that after an implant having a controlled rate of drug release.

METHOD

The model was based on the physiological dimensions of a rabbit eye, based on the cross-sections of the eye shown by Araie and Maurice (1991). The rabbit eye was chosen instead of a human eye,

as experimental data are available for confirmation of model predictions.

An eight-compartment rabbit eye having sclera, retina-choroid, vitreous humor, lens, posterior and anterior chamber, hyloid membrane, and cornea is modeled. Figure 1 shows a cross-section of the 3D eye model. Since the injection or the implant was positioned toward the hyloid membrane, half of the vitreous was modeled, with the symmetry plane passing through the middle of both the injection/implant and vitreous. Fluorescein was selected as a model compound due to available experimental data (Araie and Maurice (1991)).

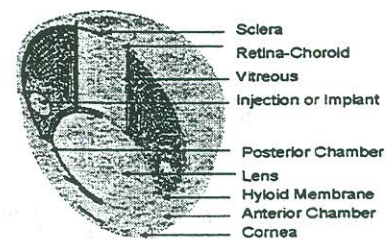


Fig. 1 Cross-section of the 3D eight-compartment rabbit eye model.

Previous studies (Araie and Maurice (1991), Friedrich et al. (1997)) concluded that fluorescein mass transfer in the aqueous occurs mainly by diffusive transport. Considering this finding and in order to maintain simplicity, the present study ignored convection. Therefore, the conservation of mass equation, used is $(\partial c / \partial t) = D \nabla^2 c$, does not include the convective term. However, at

the front of the lens there is fluid flow and hence, the washout effect of fluorescein due to convection needs further investigation.

The fluorescein mass is $30 \mu\text{g}$ delivered through a 0.1 cm radius of injection or drug implant. For the vitreal injection case, the initial condition that needs to be specified is the location and concentration of the injected fluorescein within the vitreous. In contrast, for a spherical implant, the same amount of drug is delivered with a constant flux condition over 15 hours. At the surface of the lens and cornea, and at all the symmetry surfaces, a no-flux boundary condition, $(\partial c / \partial n) = 0$, was applied, and, because the blood is a perfect sink, the concentration at the outer surface of the sclera could be set equal to zero, $c = 0$.

Retinal permeability of fluorescein is considered to be $2.6 \times 10^{-5} \text{ cm/sec}$ (Friedrich et al. (1997)). The diffusivity, $6 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$, of small molecules, such as fluorescein in the vitreous, hyloid membrane and posterior and anterior chamber, is essentially the same as in an aqueous solution (Araie and Maurice (1991)).

The eye compartments, were divided into a number of eight nodal brick elements. Approximately 120,000 elements were used for the model. FIDAP's Galarkin formulation (1999) was used to perform finite element analysis, and simulations were run on a Pentium III dual process computer.

RESULTS

Figure 2a shows the concentration profile along the symmetry axis between the lens and the retina at different times for the intravitreal injection whereas Fig. 2b shows similar concentration plots for the implant. Experimental concentration data were collected only at 15 hour for fluorescein by Araie and Maurice (1991) and were replotted (black dots) on Fig. 2a. Experimental measurements at several locations along the symmetric axis were found to be within 10% of the calculated data. Following intravitreal injection, the drug concentration near the retina quickly peaked at about 6.67 hours, whereas for the implant, the concentration gradually approached peak after 15 hours (Fig. 3). When compared with the implant, a 100% increase in drug concentration occurred for more than 3 hours (between the 5th and the 8th hour) near the retina for the intravitreal injection case. Clearly, a controlled release of the same quantity of drug over a 15-hour time period, results in a 50% reduction in drug concentration near the retina.

REFERENCES

- Araie, M., and Maurice, D. M., 1991, "The Loss of Fluorescein, Fluorescein Glucuronide and Fluorescein Isothiocyanate Dextran from the Vitreous by the Anterior and Retinal Pathways," *Exp. Eye Res.*, Vol. 52, pp. 27-39.
- FIDAP Manual (1999) Fluent Incorporated, 10 Cavandish Court, Lebanon, NH 03766, USA.
- Forster, R. K., Abbott, R. L., and Gelender, H., 1980, "Management of Infectious Endophthalmitis," *Ophthalmology*, Vol. 87, pp. 313-319.
- Friedrich, S. W., Cheng, Y-L., and Saville, B. A., 1997, "Finite Element Modeling of Drug Distribution in the Vitreous Humor of the Rabbit Eye," *Ann. Biomed. Eng.*, Vol 25, (3), pp. 303-314.
- Pflugfelder, S. C., Hernandez, E., Fliesler, S. J., Alvarez, J., Pflugfelder, M. E. and Forster, R. K., 1987, "Intravitreal Vancomycin: Retinal Toxicity, Clearance, and Interaction with Gentamicin," *Arch. Ophthalmol.* Vol. 105, pp. 831-837.

Stainer, G. A., Peyman, G. A., Meisels, H. and Fishman, G., 1977, "Toxicity of Selected Antibiotics in Vitreous Replacement Fluid," *Ann. Ophthalmol.* Vol. 9, pp. 615-618.

Tabatabay, C. A., D'Amico, D. J., Hanninen, L. A. and Kenyan, K. R., 1987, "Experimental Drusen Formation Induced by Intravitreal Aminoglycoside Injection," *Arch. Ophthalmol.* Vol.105, pp. 826-830.

Talamo, J. H., D'Amico, D. J. Hanninen, L. A. Kenyan, K. R. and Shanks, E. T., 1985, "The Influence of Aphakia and Vitrectomy on Experimental Retinal Toxicity of Aminoglycoside Antibiotics," *Am. J. Ophthalmol.* Vol.100, pp. 840-847.

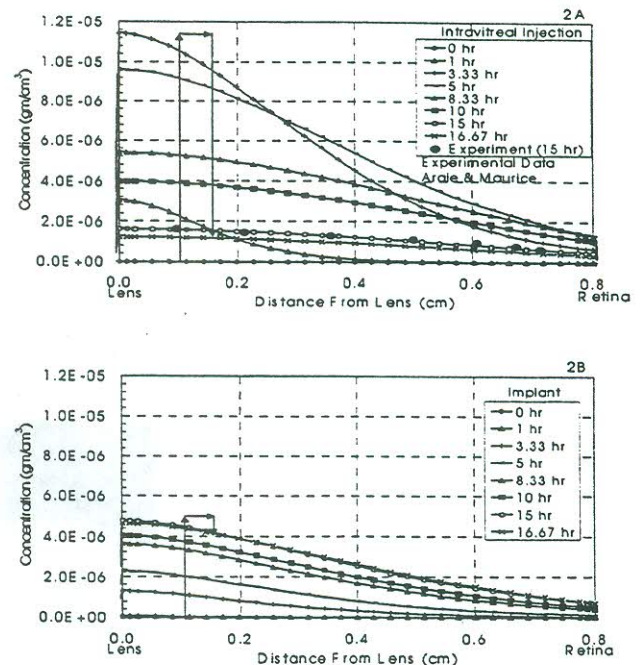


Fig. 2 Concentration profile along the symmetry axis between the lens and the retina; Fig. 2A is for intravitreal injection; Fig. 2B is for implant

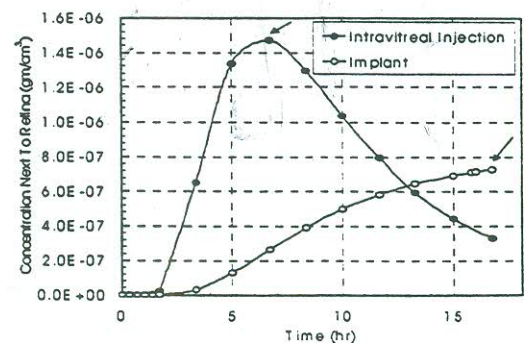


Fig. 3 Time varying concentration profile next to retina for both intravitreal injection and implant.