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EFFECT OF RETINAL PERMEABILITY ON DRUG DISTRIBUTION IN THE RABBIT EYE

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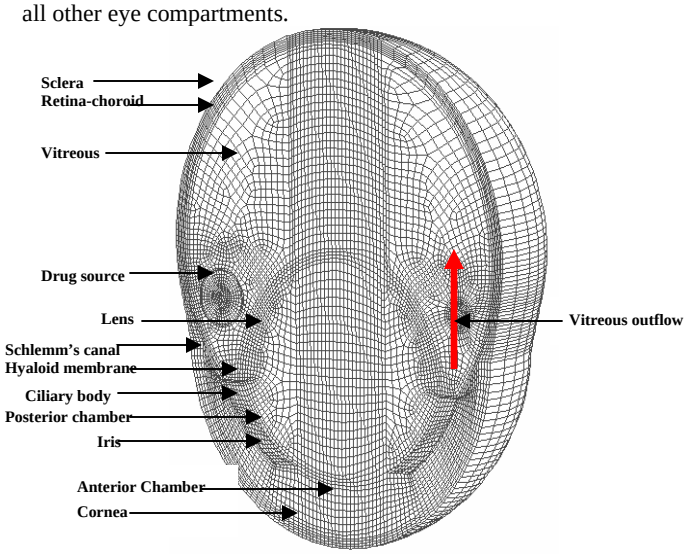
INTRODUCTION

It is important to know the drug distribution in order to treat the retinal diseases. Drug distribution and its elimination from the vitreous are determined by various factors such as retinal permeability (P), drug diffusivity (D) and convective transport by aqueous humor hydrodynamics (F). Retinal membrane, which plays an important role in the vision, is a barrier regulating the movement of particles through the membrane. The permeability of retina varies depending on its physiological state and drug characteristics such as the hydrophilicity and lipophilicity. However, the permeability of drugs through the retina is unknown for most of the drugs that are used to treat retinal diseases. These drugs have a wide range of diffusivity which influences their elimination from the vitreous. Also during extreme pathophysiological condition of the eye, there is abnormal elevation in the vitreous outflow which affects drug distribution [1, 4].

Park et.al [1] has shown the effect of drug diffusivity and convection in the vitreous on drug distribution in the rabbit eye. Friedrich et.al [2] studied the effects of permeability and diffusivity on drug distribution and elimination in the human eye. .The current study mainly focuses on the combined effect of P, D, and F on the drug distribution and elimination using a computer model of the rabbit eye. Permeability of the retina for most of the drugs usually lies between $1x10^{-5}$ cm/s (P-5, good permeation) to $1x10^{-7}$ cm/s (P-7, poor permeation) [3]. The diffusivity range for most of the drugs lies between $1x10^{-5}$ cm^2/s (D-5) and $1x10^{-7}$ cm^2/s (D-7) [2] and this study has used two extreme vitreous outflow rates 0.1 (F1) and 1 µL/min (F10) that occur during normal and diseased condition respectively.

METHOD

The 3D eye model comprises of cornea, sclera, retina-choroid, vitreous, posterior and anterior chambers, iris, ciliary processes, hyaloid membrane, lens, Schemm's canal and drug source which is shown in the Fig.1 below. Since the drug source was positioned closer to the hyaloid membrane, half of the eye was modeled, with the symmetry plane passing through the middle of drug source as well as all other eye compartments.



The Navier-Stokes equations were used to solve the flow field first and then the output of the flow was coupled with the species mass balances to calculate the drug distribution in the eye for the changing permeability and the diffusivity. The generation of aqueous humor is 2.2 µL/min [1] and two different vitreous outflow rates: 0.1 and 1 µL/min were considered for analysis respectively [1]. The mass of the

drug was chosen to be 30 µg, which was delivered in a spherical drug source of 0.1 cm radius that is administered by Intravitreal injection (IVI). The initial concentration was specified at the spherical location of the injected bolus of the drug within the vitreous. At the surface of the lens and cornea, and at all symmetric surfaces, a zero species flux boundary condition was used. Species concentration at the outer surface of the sclera is a perfect sink and thus, the concentration was set to zero to model complete clearance by the blood. The eye compartments were meshed with 8 noded hexahedral elements. To avoid distortion of elements in the eye compartments, a total of 149,761 elements were used. The Galerkin finite element method was used to solve the equations. The following table succinctly explains the complete analysis that was performed.

Table 1. Summary of analysis performed

F1		F10	
P-5 D-5	P-5 D-7	P-5 D-5	P-5 D-7
P-6 D-5	P-6 D-7	P-6 D-5	P-6 D-7
P-7 D-5	P-7 D-5	P-7 D-5	P-7 D-5

RESULT AND DISCUSSION

Drug distribution and elimination characteristics for different permeability (P-5 to P-7), diffusivity (D-5 and D-7) and flow rate (F1 and F10) are discussed in this section. Figures 2 and 3 show the mean concentration versus time plots for different permeability of retina to drugs with high (Fig.2) and low (Fig.3) diffusivities in the vitreous and also for two extreme flow rates. The elimination of the drug for intravitreal injection from the vitreous follows first order process. The half life ($t_{1/2}$) for the process is (ln2)/k, where k is the constant elimination rate, which is the slope of the semi log graphs shown by Fig. 2 and Fig. 3.

The $t_{1/2}$ of the drugs in the vitreous for different permeability and diffusivity values for normal (F1) and maximum vitreous outflow (F10) is calculated and listed in Table 2. Overall $t_{1/2}$ of the drug increased when the permeability and diffusivity decreased. It is observed that for F1 and high permeability (P-5), the half life increases by 14 times when diffusivity changes from D-5 to D-7. For F1 and moderate permeability (P-6) the $t_{1/2}$ increases by 1.7 times when the diffusivity changes from D-5 to D-7. This shows that moderate permeability value of $1x10^{-6}$ doesn't show a significant difference in drug elimination for different diffusivities. When the permeability decreases to P-7, the $t_{1/2}$ for both D-5 and D-7 decrease remarkably. This is because low permeability, which leads to low clearance, results in greater $t_{1/2}$. Hence the combined effect of low D and low P cause a rise in the value of $t_{1/2}$. The effect of convection on $t_{1/2}$ can be also seen from the Table. 2 and it can be observed that the combined effect of convection and permeability has a significant impact on the drug elimination, which in turn influences drug distribution in the vitreous.

This study could be used to estimate the drug distribution for 1) wide range of physicochemical properties of drugs (e.g. lipophilicity or hydrophilicity, and diffusivity of drugs), 2) normal and abnormally elevated vitreous flows during diseased condition of the eye. These results could yield essential information about the treatment protocol using IVI for targeted retinal diseases.

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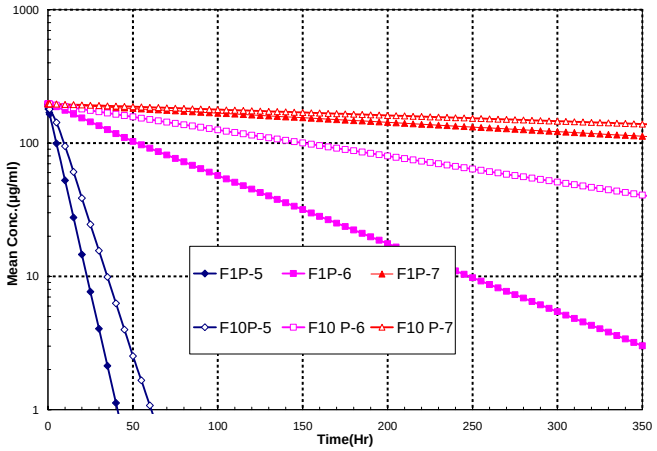

Fig.2. Mean concentration versus time in the vitreous for drugs with high diffusivity ($1x10^{-5}$ cm^2/s)

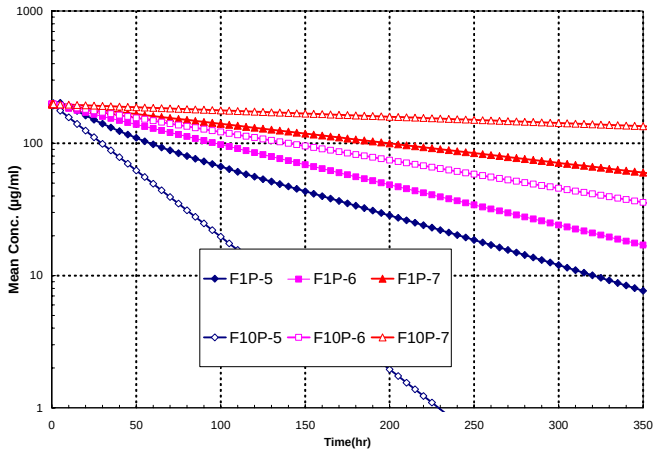

Fig.3. Mean concentration versus time in the vitreous for drugs with low diffusivity ($1x10^{-7}$ cm^2/s)

Table 2. Half life Data (hrs)

	F1		F10	
	Half life (hrs)		Half Life (hrs)	
	D-5	D-7	D-5	D-7
P-5	5.4	76.1	7.9	30.1
P-6	58.2	99.2	154.2	141.4
P-7	433.3	693.4	203.8	630.5