Effect of Retinal Permeability, Diffusivity, and Aqueous Humor Hydrodynamics on Pharmacokinetics of Drugs in the Eye

MAHESH K. KRISHNAMOORTHY, 1 JUYOUNG PARK, 1 JAMES J. AUGSBURGER, 3 and RUPAK K. BANERJEE 1, 2

ABSTRACT

Aim: Retinal permeability is one of the important parameters that determine drug distribution during diseased retinal conditions, whose effect is still unclear. Thus, the main aim of this study was to understand the influence of varying retinal permeability (P) on drug distribution under normal (F1) and elevated vitreous outflow pathophysiologic conditions (F10) for a wide variety of drug diffusivities—high: D(-5) and low: D(-7).

Method: A computational model of the rabbit eye was developed that took into account the varying effects of convection during normal and pathophysiologic conditions.

Results: High retinal permeability, P(-5), is associated with low peak macular concentration and a rapid clearance from the ocular chambers, with the retina as the major route of elimination. For low permeability, P(-7), there is very high peak macular concentration, slow elimination, and a buildup of drug concentration, which depends on vitreous outflow. The variation of t1/2 with P was found to be of linear and nonlinear trends for F1 and F10 flow cases, respectively. Moreover, for D(-5) diffusivity, there was a 1.5-fold increase and a 1.6-fold decrease in t1/2 values when the retinal permeability values were P(-5) and P(-7). On the contrary, for D(-7) diffusivity, there was a 2.5-fold decrease and a 1.4-fold increase in t1/2 values for P(-5) and P(-7), with t1/2 increasing for P(-6) during both high and low diffusivities.

Conclusions: Thus, the combined effect of variables P, D, and F are important factors that should be considered in order to determine drug dosage. This study could be used to estimate the drug distribution and elimination for (1) wide range of physicochemical properties of drugs and (2) normal and abnormally elevated vitreous flows during the diseased condition of the eye. These results could help in obtaining essential information about the treatment protocol for targeted retinal diseases while simultaneously avoiding the toxic effects of these drugs.

INTRODUCTION

POSTERIOR-SEGMENT EYE DISEASES, such as age-related macular degeneration (AMD), diabetic retinopathy, and retinitis pigmentosa, account for most cases of irreversible blindness worldwide. 1–4 A wide variety of drugs, with varying physicochemical properties, are being used to treat these diseases. A number of in vivo studies5–8 and clinical studies9,10 have been performed to

Departments of 1 Mechanical Engineering, 2 Biomedical Engineering, and 3 Ophthalmology, University of Cincinnati, Cincinnati, OH.
study the pharmacokinetics of drugs. However, it is still difficult to understand the behavior of drugs with varying physicochemical properties inside the ocular chambers as a result of a pathophysiologic condition.

Of all the factors affecting drug distribution and elimination, the main ones are the physicochemical properties of drugs and the pathophysiologic conditions. Physicochemical properties, such as drug diffusivity (D) and permeability (P) of the retina to the drugs, are constant for a particular drug; however, the permeability of the retina could change as a result of a diseased condition, which is unknown. Though many researchers have neglected the effect of convective flow inside the vitreous on drug distribution, there is strong evidence that a fraction of fluid generated from the ciliary processes flows through the vitreous and across the retina in the healthy eye as vitreous outflow. The vitreous outflow increases during abnormalities, such as glaucoma and retinal detachment.

From the drug-delivery perspective, intravitreal injection (IJ) and controlled release implant (IP) are the most common modes of administration, as they can overcome the blood-retinal barrier. Thus, the IJ and IP have the ability to attain the necessary therapeutic range to cure the diseases. Most previous works on the numeric calculation of drug distribution and elimination in the eye have focused on the combined effects of permeability and diffusivity changes and the effects of varying coupled diffusion and convection. Recently, Park et al. have numerically shown only the effect of drug diffusivity and convection in the vitreous on drug distribution in the rabbit eye by using a computational eye model. However, there is no study that has focused on the combined effects of all the three factors (P, D, and F) on drug distribution not only within the vitreous, but also the entire anterior and posterior segments of the eye.

In this study, the retinal permeability (P), diffusivity (D), and vitreous outflow (F) values were varied to simulate the drug distribution and elimination from the ocular chambers when drugs were administered by IJ and IP. The variation of P, D, and F covers a wide range of drugs, which have different physicochemical properties (P and D) and pathophysiologic conditions (P and F). Also, many drugs that are used to treat such diseases have a narrow concentration range, in which they are effective and may be toxic at higher concentrations. Therefore, a prior knowledge of drug distribution not only for a particular physicochemical property, but also the behavior under the influence of pathophysiologic condition is absolutely critical to develop the effective treatment protocol for targeted retinal diseases while simultaneously avoiding the toxic effects of these drugs. As a result, the effect of retinal-permeability variation on drug behavior inside the eye could be delineated and the drug distribution that maximizes the therapeutic effect of drugs can be predicted.

METHODS

Computational model

The three-dimensional (3D) eye model, which is comprised of the cornea, sclera, retinachoroid, vitreous, posterior and anterior chambers, iris, ciliary processes, hyaloid membrane, lens, Schemm’s canal, and a drug source (which gives the drug-delivery location for either an IJ or IP) is shown in Figure 1. 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 the drug source as well as all other eye compartments. The drug source was represented as a sphere of a 0.1-cm radius that was administered by IJ and IP. The drug delivered from the drug source was eliminated from the eye by convection and diffusion through two pathways: the aqueous outflow pathway and the vitreous outflow pathway, as shown in Figure 1. In addition, this model also took into account the varying effects of convection during normal and pathophysiologic conditions. To validate this numeric model, the in vivo data of spatial concentration profile from the lens to the retina at 15 h after IJ were compared with the numeric data. The difference was less than 5% between the numerical and experimental data.

Numerical method, governing equations, and initial and boundary conditions

The Navier–Stokes equations (Eqs. 1 and 2) were used to solve the flow field first for the vitreous outflow; then, the output of the flow was coupled with the species transport equation (Eq. 3) to calculate the drug distribution in the eye for
changing permeability and diffusivity (Fidap; Ansys Inc., ver 8.6):

\[ \rho \nabla \cdot (U) = 0 \]  
\[ \rho U \nabla U = -\nabla P + \mu \nabla^2 U \]  
\[ \frac{\partial C}{\partial t} + U \cdot \nabla C = D \nabla^2 C \]

where, U: Velocity, 2: Density of medium, C: Drug concentration, D: Diffusivity

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The fluid velocity of the generation of aqueous humor was modeled as a fluid source with a constant flow rate of 2.2 \( \mu \text{L/min} \) from the ciliary processes. The fluid velocity of aqueous humor was set to zero in the iris, lens, and cornea. The velocity component normal to the symmetric surfaces of the various compartments of the eye was set to zero. Vitreous outflow was modeled by assigning a velocity normal to the outer surface of the retina-choroid compartment. The two tangential velocity components were set to zero at the outer surface of the retina-choroid compartment. 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; thus, the concentration was set to zero to model complete clearance by the blood. The initial concentration was specified at the spheric location of the injected bolus of the drug within the vitreous. An initial concentration of 15 \( \mu \text{g} \) of drug was specified throughout the hemispheric volume for IJ. In contrast, for the IP, an equivalent amount of the drug was delivered with a constant flux at the outer surface of the drug over a time period of 15 h. Elsewhere, the initial concentration was set to zero for both IJ and IP.

Model parameters: Retinal permeability, diffusivity, and convective flow

In this study, the retinal-permeability value has been varied between 1 \( \times 10^{-5} \) cm/sec: P(-5) and 1 \( \times 10^{-7} \) cm/sec: P(-7).26,27 P(-5) represents good permeation through the retina and, hence, lipophilicity, whereas P(-7) represents poor permeation through the retina and hydrophilicity. This retinal-permeability range includes both the effect of passive and active transport processes. An equivalent amount of bulk diffusivity (retinal permeability \( \times \) thickness of retina) was applied over the retinal volume to signify retinal permeability instead of retinal-surface permeability. Two extreme values of vitreous drug diffusivity, 1 \( \times 10^{-5} \) cm\(^2\)/sec: D(-5) and 1 \( \times 10^{-7} \) cm\(^2\)/sec: D(-7), signifying high- and low molecular weights, respectively, were used in this study.11 In order to see the effect of convective species transfer on drug distribution in the eye, two vitreous flow rates
were assumed: 0.1 μL/min (F1) and 1 μL/min (F10). These flow rates signify the normal (F1) and the abnormal conditions (F10) caused as a result of glaucoma or retinal detachment conditions.

**RESULTS**

In this section, we delineate the effects of retinal-permeability change along with the change in diffusivity on drug distribution in the vitreous and aqueous chambers. Also, the combined effects of normal and pathophysiologic flow conditions, retinal permeability, and drug diffusivity on the pharmacokinetics of the drugs are discussed.

**Effect of retinal permeability on spatial distribution**

Figure 2 shows the spatial distribution of drugs injected intravitreally ([IJ]) in the vitreous along the center line joining the axis from the lens (x = 0 cm) to the retina (x = 0.78 cm) following a drug injection. Figure 2A and 2B shows the spatial distribution at different times for normal flow conditions (F1), when the retinal permeability varies from P(-5) to P(-7) for D(-5) (Fig. 2A) and D(-7) (Fig. 2B) diffusivities. The spatial distribution for abnormal flow (F10) is provided in Fig. 2C and 2D. Flow has a significant impact on drug distribution when there is low diffusivity in the vitreous (Fig. 2B and 2D). For IP, the distribution is shown in Figure 3 A–D for normal flow: F1 (Fig. 3A and 3B) and abnormal flow: F10 (Fig. 3C and 3D). The trend of drug distribution for the IP was similar to that of IJ, but the magnitude was lower than that of IJ for the same release rate.

**Effect of retinal permeability and drug diffusivity on macular temporal distribution**

Figure 4 shows the temporal variation of the concentration at the center of the retina for dif-
different retinal permeability values when the drug was administered through IJ and IP. The plots are shown until 500 h after the administration of the drugs by IJ and IP.

Figure 4A and 4B describes the temporal variation of concentration at the center of the retina for varying P and D for drugs that were administered through IJ for F1 and F10, respectively. For F1 flow and D(-5) diffusivity, the decrease in retinal permeability from P(-5) to P(-7) caused an increase in the peak concentration value by 1.4-fold (Fig. 4A, arrow #1), whereas it caused a sixtyfold increase for F1 flow and D(-7) (Fig. 4A, arrow 2). Thus, for F1 flow, the combined effect of P and D increased the peak concentration at the center of the retina for D(-7), as compared to D(-5). Higher diffusivity, for example, D(-5) encountered lower resistance in the vitreous for drug transport as compared to D(-7) case.

For F10 flow and D(-5) diffusivity, when the retinal permeability changes from P(-5) to P(-7), there was a threefold increase in peak concentration values at the center of the retina (Fig. 4B, arrow 1). However, for F10 flow and D(-7) diffusivity, the change in retinal permeability from P(-5) to P(-7) caused the concentration at the center of the retina to double in magnitude (Fig. 4B, arrow 2). Thus, compared to F1, for F10 flow, the combined effect of P and D tended to result in an overall decreased peak concentration at the center of the retina. It is also evident from Figure 4A and 4B that the change in magnitude of peak-flow value for extreme cases, that is, from P(-5) D(-5) case to P(-7) D(-7) case, was a 54% increase for normal flow: F1 [27.1 µg/mL for P(-5) D(-5) to 41.8 µg/mL for P(-7) D(-7)] and a 18.75% decrease for abnormal flow: F10 [16.2 µg/mL for P(-5) D(-5) to 13.1 µg/mL for P(-7) D(-7)]. Thus, when the diffusivity was fixed, flow had a significant effect on peak concentration, particularly when the retinal permeability was low. This effect was more pronounced when the drug had the lowest diffusivity value.
Figure 4C and 4D shows the temporal variation in the concentration at the center of the retina for IP. The trend was similar to that of IJ, except that IP reduced the overall peak concentration and delayed the time to achieve these levels. Thus, in order to show the effect of change in physicochemical factors on elimination and mean distribution, only the results pertaining to IJ were discussed from this point forward and the variation for IP for the following cases could be obtained in a similar fashion.

Effect of retinal permeability change and vitreous outflow on clearance

Figure 5 illustrates the percentage cumulative amount of drugs that reach the retina and the Schemm’s canal for F1 (Fig. 5A) and F10 (Fig. 5B). Since it was desired to study the effect of change in retinal permeability and flow on drug clearance, only the trend pertaining to high diffusivity of drugs are shown in this illustration. The plots are shown until the first 200 h. It can be observed from the Figure 5A and 5B that P(-5) eliminates the fastest under F1 as well as F10 conditions, predominantly getting eliminated through the retina (70%). As a result of a flow change to F10, the cumulative concentration reached at the retina increases for all the retinal permeability values. The increase is significant particularly for the case of F10 flow and P(-6) permeability. It is also evident that more amount of drug clears through the retina for F10 flow and P(-6) case (38%, as shown in Fig. 5B) than F1 flow and P(-6) case (22%, as shown in Fig. 5A). There is also a simultaneous decrease in the clearance through the Schemm’s canal. Figure 5B also shows that the trend for P(-5) and P(-6) reaches a constant value after a certain time point. Thus, flow has a significant effect on clearance in the first 200 h for fixed drug diffusivity in the vitreous, especially when the retinal permeability is low. As men-
tioned earlier, the effect of flow is more pronounced when both the drug diffusivity in the vitreous and retinal permeability values are low.

Combined effects of physicochemical and pathophysiologic properties on distribution and elimination

Vitreous and aqueous humor drug distribution. Figure 6 discusses the trend of volume of averaged mean concentration of drugs inside the vitreous administered through IJ. The trend during the first 300 h after IJ is displayed by Figure 6A and 6B for normal flow: F1 and abnormal flow: F10, respectively. For a particular flow rate and drug diffusivity, as the retinal permeability decreases from P(-5) to P(-7), the slope of the mean concentration versus time curve decreases. The elimination rates can be calculated from the slope of the mean concentration of drugs inside the vitreous, assuming the elimination occurs through the first-order process. It can be observed that during F1 flow, the effect of low drug diffusivity, D(-7), decreases the slope for P(-5) and P(-6) by

FIG. 5. Cumulative amount of drugs reaching the retina and Schemm’s canal for varying permeability of the retina. (A) Cumulative amount of drugs reaching the retina when the retinal permeability changes from P-5 to P-7. (B) Cumulative amount of drugs reaching the Schemm’s canal when the retinal permeability changes from P-5 to P-7.
fourteen- and 1.7-fold (arrows 1 and 2, respectively, shown in Fig. 6A), as compared to high drug diffusivity, D(-5). However, for F1 flow, the slope of P(-7) D(-7) is increased by 3.4-fold, as compared to P(-7) D(-5) (arrow 3, Fig. 6A). For F10 flow, the effect of D(-7) diffusivity decreases the slope for P(-5) D(-7) by 3.5-fold, as shown by arrow 1 in Figure 6B, and increases the slope for P(-6) D(-7) and P(-7) D(-7) by 1.3- and 1.7-fold, respectively (shown by arrows 2 and 3, respectively, in Fig. 6B), as compared to the slopes for D(-5) drugs. Thus, the abnormal (F10) flow has a significant effect when there is low retinal permeability.

Figure 7A and 7B shows the ratio of aqueous to vitreous humor concentrations (C_{aq}/C_{vit}) for high- and low-diffusivity drugs injected into the vitreous chamber for F1 and F10 flow conditions. For D(-5), for both F1 and F10, the C_{aq}/C_{vit} values have a similar profile by attaining the peak value and, thereafter, attaining a constant value after a sharp decrease. However, the profiles for
D(-7) differ from that of D(-5) by having a gradual increase, followed by a decrease. Overall, during normal (F1) flow and high-diffusivity drugs, D(-5), P(-5) results in vitreous elimination, whereas P(-6) and P(-7) result in effective elimination through the Schemm’s canal. For normal flow and low-diffusivity drugs, D(-7), all the retinal permeability values showed similar trends, with P(-6) achieving the highest peak among the three retinal permeability values (0.91), and thereafter, the concentration ratio decreased with time. Also, it can be seen from Figure 7A and 7B that for both normal and abnormal flows, the drug eliminated rapidly through the vitreous in the case of P(-5), whereas in the case of P(-6), the partition of the drug between the aqueous and the vitreous took place in such a way that there was more of an amount of the drug reaching the aqueous humor during the initial IJ phase (peak at t = 3 h for P(-6) D(-5) in Fig. 7A).
Elimination characteristics from the vitreous humor. Half-life of drugs ($t_{1/2}$) in the vitreous for the varying retinal permeability and diffusivity, for different vitreous outflows, are discussed in Figure 8. The elimination from the vitreous is assumed to occur through a first-order process, whose $t_{1/2}$ is given by the formula, $t_{1/2} = \frac{0.693}{k_{el}}$, where $k_{el}$ (elimination constant) is the slope of the mean concentration curve with time (Fig. 6). The calculated $t_{1/2}$ values are listed in Table 1. Overall, as retinal permeability decreases from $P(-5)$ to $P(-7)$, $t_{1/2}$ increases for a particular flow and diffusivity of the drug, with the increase being linear for normal (F1) and nonlinear for abnormal (F10) flow cases.

When the diffusivity was fixed at D(-5), at high retinal permeability, P(-5), increase in flow resulted in an increase in the value of $t_{1/2}$ (~47%; arrow 1). However, a low permeability, P(-7), resulted in a 30% decrease (arrow 2) in $t_{1/2}$ when there was an elevation in the vitreous outflow from F1 to F10. When the diffusivity was fixed at D(-7), at P(-5) the increase in flow resulted in the decrease in $t_{1/2}$ by 60% (arrow 3), whereas at P(-7) it led to a 40% increase; thus, the effects of convection and the influence of change in retinal permeability on drug distribution were significant. The $t_{1/2}$ for P(-6) increased as flow changed from normal (F1) to abnormal (F10) for both high and low diffusivities, with the increase for high diffusivity (3.3-fold) being much higher than during the low-diffusivity case (1.5-fold; arrow 4).

**DISCUSSION**

A computational model has been developed to predict the drug distribution and elimination characteristics of varying physicochemical properties of drugs, namely the retinal permeability and diffusivity during normal and pathophysiologic conditions. The results obtained from this study have importance in determining the drug-delivery protocol for targeted diseases by using specific or combinations of drugs with particular physicochemical properties.

**TABLE 1. HALF LIFE VALUES FOR DIFFERENT RETINAL PERMEABILITIES, DRUG DIFFUSIVITIES AND VITREOUS CUTFLOWS**

<table>
<thead>
<tr>
<th></th>
<th>Normal flow (F1)</th>
<th>Abnormal flow (F10)</th>
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<tbody>
<tr>
<td></td>
<td>D-5</td>
<td>D-7</td>
</tr>
<tr>
<td>P-5</td>
<td>5.41</td>
<td>76.15</td>
</tr>
<tr>
<td>P-6</td>
<td>58.24</td>
<td>99</td>
</tr>
<tr>
<td>P-7</td>
<td>770</td>
<td>223.55</td>
</tr>
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*Note: All values are expressed in hours.*
First, this study provides significant information about the effect of change in retinal permeability on spatial and temporal concentrations inside the vitreous, particularly at the center of the retina, which otherwise is difficult to measure experimentally. The macula is the region of high-acuity vision and the target point of most of the drugs for treating retinal diseases, such as AMD, which is one of the leading causes of blindness in the United States. The temporal variation from Figure 4 shows that drugs with low retinal permeability result in very high local drug concentrations near the macula. Also, the combined effect of retinal permeability and drug diffusivity was more pronounced in the case of low drug diffusivity. For lower retinal permeability and F1 flow, the drug concentration for the low-drug-diffusivity case was significantly higher than the high-drug-diffusivity case. This trend reversed for the F10 flow.

Second, the knowledge of the cumulative concentration at the retina and mode of clearance (the retina or the Schemm’s canal) for varying retinal permeability is essential to estimate the therapeutic range for administering the drugs. The mode of clearance would provide information about how much drug would reach the target site (retina) and how much would clear through the Schemm’s canal. Thus, from the drug-dosage perspective, it would be helpful if an appropriate combination of physicochemical properties is known for specific drugs. Drugs with a high-retinal-permeability value eliminate faster through the vitreous and aqueous chambers and are moderately influenced by flow rates. As a result of a flow change from F1 to F10, the cumulative concentration reached at the retina increases for all the permeability values, with more of an amount clearing through the retina for the F10P(-6) case (Fig. 5B) than the F1P(-6) case and a simultaneous decrease in the clearance through the Schemm’s canal. Finally, this study obtained the drug-concentration values in both the aqueous and vitreous chambers (Fig. 7), which is important from the perspective of drug partitioning that takes place between the vitreous and aqueous chambers. A very high value of aqueous to vitreous concentrations at the beginning of the elimination phase implies that the drugs preferentially eliminate through the aqueous chamber. It has been shown that in the case of F1, for high retinal permeability, vitreous elimination is independent of diffusivity, whereas for low retinal permeability, it is dependent on diffusivity. On the contrary, for F10 flow, for both high and low retinal permeabilities, vitreous elimination is dependent on drug diffusivity.

Pharmacokinetics explain a lot about the drug-elimination rates and the path that each category of drugs takes to clear itself from the ocular chambers (Figs. 6 and 8). For F1, the effect of low drug diffusivity tends to decrease the slope for P(-5) and P(-6) and increase the slope for P(-7). On the contrary, for F10, it tends to decrease the slope for P(-5) and increase the slope for P(-6) and P(-7). Thus, it has been shown that the combined effect of retinal permeability, drug diffusivity, and pathophysiologic condition (flow) significantly affects the $t_{1/2}$ of drugs inside the vitreous.

Clinically, there are several drugs and beta-blocker molecules with varying physicochemical properties that are used therapeutically in the treatment of retinal degeneration and glaucoma. The retinal pigment epithelium (RPE)-choroid permeability values for the beta blockers have been estimated in vitro by Pitkanen et al. Thus, the lipophilic blockers, such as betaxalol and timolol, would eliminate predominantly through the vitreous retina pathway. Also, they have low molecular weights of around 250–320 Da. This would correspond to very high diffusivities in the vitreous. However, there is a lack of knowledge of the complete permeability of the retina and RPE. Though we cannot completely attribute the characteristics seen by P(-5) and D(-5) to these molecules, we could reasonably estimate the drug distribution inside the vitreous.

**CONCLUSIONS**

The main limitations of this study were that the effect of local drug metabolism, the drug binding to intraocular proteins, and the influence of the location of the site of IJ and IP have not been evaluated. Also, the phrase “diseased condition” could imply the change in retinal permeability, abnormal vitreous outflow, or both. Disruption of retina owing to a large number of retinal diseases simultaneously alters the pattern of drug movement and its distribution inside the ocular chambers. Although retinal-permeability changes are both owing to the physicochemical properties of drugs and the pathophysiologic conditions, this study assumed the retinal per-
meability only as a function of the physicochemical property of the drug. The diseased condition was taken care of by the elevated vitreous outflow condition (F10). The retinal permeability variation with various vitreo-retinal diseases, as well as the adoption of a porous model approach for the retinal membrane, could be included in the future. Further study is required to delineate these effects. With the induction of release-rate variations for different implants, the effect of retinal-permeability change on drug distribution could be studied in the future. This study had a lot of application in areas to estimate the drug distribution for a wide range of physicochemical properties of drugs, such as lipophilicity or hydrophilicity, and diffusivity of drugs that are subjected to normal and pathophysiologic flows during the diseased condition of the eye. These results could yield essential information about the treatment protocol for targeted retinal diseases.

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Reprint Requests: Rupak K. Banerjee
Department of Mechanical, Industrial and Nuclear Engineering
University of Cincinnati
598 Rhodes Hall
P.O. Box 210072
Cincinnati, OH 45221-0072

E-mail: Rupak.Banerjee@uc.edu

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