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Research Article

A Mathematical Analysis of Intravitreal Drug Transport

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Abstract

Purpose: *The aim of our present work is the development of a quasi steady-state model for the distribution of intravitreally injected drugs and investigation of the effects of various model parameters on the drug distribution in normal and diseased eyes.*
Method: *A simple mathematical model for the intravitreal transport of drugs was developed using Fick's law of diffusion, Darcy's law of convective flow, and Michaelis –Menten kinetics of metabolism. A Crank-Nicolson finite difference scheme of the equation describing the drug transport in the vitreous body was written, in which the radial and axial diffusive terms and convective terms of the equation were approximated by central differences, while the temporal terms were approximated by average of forward and backward time differences. A system of linear algebraic equations obtained from the Crank Nicolson finite difference scheme was solved by line Jacobi iterative scheme in which successive improved approximate results are obtained.*
Result: *The model predicts that an increase in the metabolic (consumption) rate and drug release rate constant reduces the concentration of intravitreally injected drug at the centre of retina and along centreline of vitreous body. A significant increase in the drug concentration at the centre of retina and along the centreline of the vitreous body in the eye afflicted with glaucoma and retinal detachment is observed and the decay rate of drug concentration in these pathological states is higher than that in the normal eyes.*
Conclusion: *The vitreous outflow as observed in the glaucomatous and/- or rhegmatogenous eyes may contribute to the transport of intravitreally injected drug in the vitreous body. The drug concentration in the vitreous body and at the centre of retina in such diseased eyes is higher than that in the normal eyes and the decay rate of drug concentration is significantly enhanced.*

Keywords: *Convective-diffusive transport, intravitreal injection, line-Jacobi iterative technique, release rate.*

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INTRODUCTION

Several vitroretinal diseases such as cytomegalovirus retinitis, age- related macular degeneration (AMD), retinitis pigmentosa (R.P), diabetic retinopathy and a combination of similar retinal diseases are currently being treated by using drug intravitreal injection or control release implant of drugs[1]. The diffusion of drug, convection of vitreous outflow, enzymatic reaction (metabolism), drug binding and efficacy of delivery system mainly control the bioavailability of drug after its intravitreal injection and controlled release implant. Many drugs used to treat vitreoretinal diseases have a narrow concentration range in which they are effective and may be toxic at higher concentrations [2, 3]. Therefore, it is critical to know the drug distribution within the vitreous following delivery by intravitreal injection or controlled release implant. The ability to predict drug distribution can maximize the therapeutic benefits and minimize potential adverse effect such as possible tissue damage caused by excessively high concentrations of drug. A mathematical analysis of the drug concentration and theoretical investigation of the effects of physiological parameters on the concentration may elucidate the mechanism of drug transport in the vitreous and may contribute to the improvement of present understanding of the bioavailability of drugs required for the treatment of vitroretinal diseases.

Several studies[4, 5, 6, 7] have analyzed intravitreal drug distribution and the elimination of drug from the vitreous of the eye. Previous studies[6, 8] have assumed that the vitreous humor was stagnant, ignoring convective drug transport within the vitreous body. It is well known that during the pathogenesis of glaucoma, intraocular pressure (IOP) is elevated (40-80 mm Hg) due to the obstruction of the aqueous outflow system which may increase the flow of aqueous humor through the vitreous. Under extreme pathophysiologic conditions, e.g rhegmatogenous retinal detachment, the integrity of the retina is broken, allowing vitreous outflow to pass into the subretinal space. The rate of fluid movement through a retinal tear was estimated to be 1.2 µL/min[9], signifying a ten-fold increase and a maximum condition for elevated flow, when compared to normal vitreous outflow of 0.1 µL/min[10].This increase in the vitreous outflow may be caused by the enhanced hydraulic conductivity of the retina. Thus, the vitreous outflow can play a significant role in drug distribution in glaucomatous or rhegmatogenous retinal detached eyes.

Stay MS. et al [6] developed a mathematical model for prediction of the biodistribution of drug in the vitreous body released from injectable biodegradable polymer microspheres. They considered the diffusive and convective mass transport of drug within the vitreous and neglected the metabolic consumption and degradation of drug in vitreous body. Kakuji [11] has also presented a pharmacokinetic model for ocular drug delivery in the spherical modified cylindrical eye based on Fick's law of diffusion but neglected the convective transport.

The present work is concerned with the development of a simple mathematical model for the quasi-steady state concentration distribution of drug in the viteous body. The objective of the present work was to investigate the effects of the parameters metabolic rate and intraocular pressure on the drug concentration distribution of the intravitreally injected drugs and on change in drug concentration with time at the centre of retina. Besides the some other physiological parameters on the drug concentration also has been observed.

MATHEMATICAL FORMULATION

$$q_c(r,z,t) = \begin{cases} \dfrac{MK_1}{V\sqrt{t}} & t>0 \\ 0 & t=0 \end{cases} \qquad \ldots.(3)$$

where m, B are the reaction rate and Michaelis Menten rate constants, respectively, for the metabolic process in the vitreous body. In the present study, the metabolic and degradation of drug is approximated by a first order metabolic rate constant in the vitreous body for intravitreal injection. The delivery of drug at the injected site is described by the following form [10]

$$\frac{\partial c}{\partial t} + v_r \frac{\partial c}{\partial r} + v_z \frac{\partial c}{\partial z} = \frac{1}{r}\frac{\partial}{\partial r}(D\, r \frac{\partial c}{\partial r}) + \frac{\partial}{\partial z}(D\frac{\partial c}{\partial z}) - k_1 c + \frac{MK_1}{V\sqrt{t}} \qquad \ldots..(4)$$

where M is the initial loading of the drug (kg), $K_1\ (\sec^{-1})$ the release rate constant of the drug, and V the volume of the drug injected (m^3).The release term is defined only at the injection site and is zero for all other positions within the vitreous body.
Now, Eq. (1) can be written in the form:

The aqueous flow in the porous vitreous body is described by Darcy's Law:

$$v = -\frac{k}{\mu}\nabla p \qquad \ldots.(5)$$

where k is the permeability of the vitreous body, μ , the viscosity of the permeating aqueous humor, and p, the fluid pressure in the vitreous body. A ratio $\frac{k}{\mu}$ is termed as the hydraulic conductivity of vitreous body.

Using continuity equation $\nabla.v = 0$,we get:

$$\nabla^2 p = 0 \qquad \ldots.(6)$$

where, ∇^2 is the Laplacian operator in a cylindrical co-ordinate system.

Boundary Conditions for Pressure: The physiologically relevant and mathematically consistent boundary conditions required for the determination of velocity components of vitreous body are described below:

$$(\frac{\partial p}{\partial r})_{r=0} = 0; \qquad (-\frac{k}{\mu}\frac{\partial p}{\partial z})_{z=H} = k_r((p)_{r=R} - p_v) \qquad \ldots.7(a,b)$$

$$(-\frac{k}{\mu}\frac{\partial p}{\partial z})_{z=0} = k_r((p)_{z=0} - p_v) \qquad \begin{matrix}(\frac{k}{\mu}\frac{\partial p}{\partial z})_{z=H} = 0 \\ = k_p((p)_{z=H} - p_a)\end{matrix} \qquad \ldots.8(a,b)$$

where, k_r the hydraulic conductivity of the retina , k_p the hydraulic conductivity of posterior chamber –vitreous body interface , p the fluid pressure in the vitreous body, p_v, the pressure of the vein downstream flow, and p_a ,the intraocular pressure. **Initial Condition for Concentration:** For the intravitreal injection of drug, the initial condition is described as follows:

$c(r,z,0) = \begin{cases} c_o, & \text{inside the hypothetical cylindrical cavity} \\ 0, & \text{outside the cylindrical cavity} \end{cases}$ ….(9)

Boundary Conditions for Concentration: The boundary conditions for the drug concentration are given as follows:

$$(\frac{\partial c}{\partial r})_{r=0} = 0 \qquad \text{….(10)}$$

$$[(-D\frac{\partial c}{\partial r}) + v_r c]_{r=R} = [\frac{D_r k_r}{l_r}((c) - c_r) + \frac{R_{act}}{l_r} c]_{r=R} \qquad \text{…(11)}$$

$$[(-D\frac{\partial c}{\partial z}) + v_z c]_{z=0} = [\frac{D_r k_r}{l_r}((c) - c_r) + \frac{R_{act} c}{l_p}]_{z=0} \qquad \text{….(12)}$$

$$[(-D\frac{\partial c}{\partial z})]_{z=H} = [\frac{D_l k_l}{l_l}((c) - c_l)]_{z=H} \qquad 0 \le r \le b_o \qquad \text{….13(a)}$$

$$[(-D\frac{\partial c}{\partial z}) + v_z c]_{z=H} = [\frac{D_p k_p}{l_p}((c) - c_a)]_{z=H} \qquad b_0 \le r \le R \qquad \text{….13(b)}$$

Where c is the drug concentration in the vitreous body,b_o the effective radius of lens.The subscripts p,l,r refer to as the posterior chamber membrane, posterior lens surface and the RCS membrane, respectively.

Solution to the model. The analytical solution to Eq. 6 subject to the boundary conditions 8(a,b)-10(a,b) is given by :

$$p(r,z) = [C\,J_0(k_2 r)][Ge^{k_2 z} + H\,e^{k_2 z}] \qquad 0 \le r \le b_0 \qquad \text{…..(14)}$$

$$p(r,z) = [C\,J_0(k_3 r)][G_1 e^{k_3 z} + H_1\,e^{k_3 z}] \qquad b_0 \le r \le R \qquad \text{.....(15)}$$

And, the radial and axial velocity components of vitreous outflow are obtained as given below:

$$v_r = -\frac{kk_2}{\mu}[C\,J_0'(k_2 r)][Ge^{k_2 z} + H\,e^{-k_2 z}], v_z = -\frac{kk_2}{\mu}[C\,J_0(k_2 r)][Ge^{k_2 z} - H\,e^{-k_2 z}] \qquad 0 \le r \le b_o$$

$$v_r = -\frac{kk_3}{\mu}[C\,J_0'(k_3 r)][G_1 e^{k_3 z} + H_1\,e^{-k_3 z}], v_z = -\frac{kk_3}{\mu}[C\,J_0(k_3 r)][G_1 e^{k_3 z} - H_1\,e^{-k_3 z}] \qquad b_0 \le r \le R$$

Where, $G = \frac{-p_v}{A(1-e^{2k_2 H}) - (1+e^{2k_2 H})}$, $H = \frac{-p_v e^{2k_2 H}}{A(1-e^{2k_2 H}) - (1+e^{2k_2 H})}$

$$G_1 = \frac{p_a(A-1) - p_v(B-1)e^{k_3 H}}{-2AB\sinh(k_3 H) + 2(A-B)\cosh(k_3 H) + 2\sinh(k_3 H)},$$

$$H_1 = \frac{p_v[(A-B)(2e^{k_2 H} + e^{-k_2 H}) + (1-AB)(2e^{k_2 H} - e^{-k_2 H}) + p_a(A^2-1)]}{[-2AB\sinh(k_3 H) + 2(A-B)\cosh(k_3 H) + 2\sinh(k_3 H)]}$$

$$A = -\frac{kk_2}{\mu k_r};\ B = -\frac{kk_2}{\mu k_p}; \qquad C = -\frac{p_v}{AJ_0'(k_2 R) - J_0(k_2 R)}, k_2 = \frac{z_n}{b_0};\ k_3 = \frac{z_n}{R};$$

where z_n are the possible zeros of the Bessel function.

The approximate steady-state distributions of radial and axial velocities were computed and use in numerical solution of the mathematical model.

Numerical Solution to the Model: A numerical solution of the partial differential equation governing the quasi-steady state distribution of drug in the vitreous body is obtained by using d in numerical solution of the mathematical model. the implicit Crank-Nicolson scheme[16]. The finite difference analogue of Eq.4, obtained by using the implicit Crank-Nicolson's scheme[16], is given by:

$$c_{i-1,j,k+1}\{\frac{-D}{(\Delta r)^2}-\frac{v_{r_{i,j}}}{(2\Delta r)}+\frac{D}{r_i(2\Delta r)}\}+c_{i,j-1,k+1}\{\frac{-D}{(\Delta z)^2}-\frac{v_{z_{i,j}}}{(2\Delta z)}\}+c_{i,j,k+1}\{\frac{2}{\Delta t}+k_1+\frac{2D}{(\Delta r)^2}+\frac{2D}{(\Delta z)^2}\} \quad ...(16)$$

$$+c_{i,j+1,k+1}\{\frac{-D}{(\Delta z)^2}+\frac{v_{z_{i,j}}}{(2\Delta z)}\}+c_{i+1,j,k+1}\{\frac{-D}{(\Delta r)^2}-\frac{D}{r_i(2\Delta r)}+\frac{v_{r_{i,j}}}{(2\Delta r)}\}-\frac{MK_1}{V\sqrt{k\Delta t}}\equiv f(c_{i,j,k})$$

where $f(c_{i,j,k})$ denotes the term corresponding to the equation for location (i,j) in the grid and is given by:

$$f(c_{i,j,k})=c_{i-1,j,k}\{\frac{D}{(\Delta r)^2}+\frac{v_{r_{i,j}}}{(2\Delta r)}-\frac{D}{r_i(2\Delta r)}\}+c_{i,j-1,k}\{\frac{D}{(\Delta z)^2}+\frac{v_{z_{i,j}}}{(2\Delta z)}\}+c_{i,j,k}\{\frac{2}{\Delta t}-k_1-\frac{2D}{(\Delta r)^2}-\frac{2D}{(\Delta z)^2}\}$$

$$+c_{i,j+1,k}\{\frac{D}{(\Delta z)^2}-\frac{v_{z_{i,j}}}{(2\Delta z)}\}+c_{i+1,j,k}\{\frac{D}{(\Delta r)^2}+\frac{D}{r_i(2\Delta r)}-\frac{v_{r_{i,j}}}{(2\Delta r)}\}$$

Finite difference analogues of the initial condition (9) and boundary conditions (10-13(b)) are given below

$$c_{i,j,1}=c_o \qquad i=1,\ j=4,7$$

$$c_{i,j,1}=0 \qquad i\neq 1,\ j\neq 4,7$$

$$D[\frac{c_{i+1,j,k+1}-c_{i-1,j,k+1}}{2\Delta r}]=0\Rightarrow c_{i+1,j,k+1}=c_{i-1,j,k+1} \qquad i=1,\ j=1,2....13 \quad ...(17)$$

$$-D[\frac{c_{i+1,j,k+1}-c_{i-1,j,k+1}}{2\Delta r}]+v_{r_{i,j}}\,c_{i,j,k+1}=\frac{D_r k_r}{l_r}[c_{i,j,k+1}-c_r]+\frac{R_{act}}{l_r}c_{i,j,k+1} \qquad i=9,\ j=1,2....13$$

$$-D[\frac{c_{i,j+1,k+1}-c_{i,j-1,k+1}}{2\Delta z}]=\frac{D_l k_l}{l_l}[c_{i,j,k+1}-c_a] \qquad j=13,\ i=1.....5$$

$$-D[\frac{c_{i,j+1,k+1}-c_{i,j-1,k+1}}{2\Delta z}]+v_{z_{i,,j}}[c_{i,j,k+1}]=\frac{D_p k_p}{l_p}[c_{i,j,k+1}-c_r]+\frac{R_{act}}{l_p}c_{i,j,k+1} \qquad j=13,\ i=5....9$$

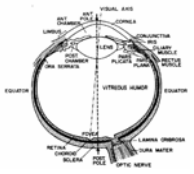

Figure 1: Schematic diagram showing the interrelationship of the various compartments of the eye.[10] Diffusive drug is released at the center of the cavity (vitreous chamber) and the injected fluid has a homogenous distribution within a cylindrical region. The drug elimination in the vitreous body is assumed to occur across three different diffusion-convection routes of the eye: the posterior chamber, posterior lens capsule, and retina/choroids membrane.

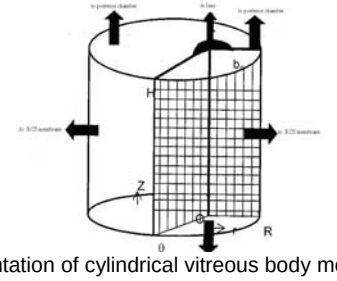

Figure 2: Schematic representation of cylindrical vitreous body model [12]. R: radius of vitreous body, H: height of vitreous body, r: radial distance, z: axial distance, b_0 :effective radius of lens respectively.

The concentration of a drug in the vitreous body is described by the partial differential equation which incorporated convective drug transport term in the equation proposed by [10]:

$$[1+B(r,z,t]\frac{\partial c}{\partial t}+v_r\frac{\partial c}{\partial r}+v_z\frac{\partial c}{\partial z}=\frac{1}{r}\frac{\partial}{\partial r}(rD\frac{\partial c}{\partial r})+\frac{\partial}{\partial z}(D\frac{\partial c}{\partial z})-R(r,z,t)+q_c(r,z,t) \qquad \ldots(1)$$

where c is the concentration of drug in the vitreous body, D the diffusion coefficient of drug, R(r,z,t) the metabolism and degradation rate, B(r,z,t) drug binding term and $q_c(r,z,t)$ release rate of injected drug. Effect of drug binding in the drug concentration is negligible compared to that of convection, diffusion and metabolism of drug. The metabolism and degradation of drug in the vitreous body is assumed to follow Michaelis Menten kinetics described by[11,13.]

$$R(r,z,t)=\frac{mc}{B+c} \qquad \ldots(2)$$

where m, B are the reaction rate and Michaelis Menten rate constants, respectively, for the metabolic process in the vitreous body. In the present study, the metabolic and degradation of drug is approximated by a first order metabolic rate constant in the vitreous body for intravitreal injection. The delivery of drug at the injected site is described by the following form Kakuji[11]

$$q_c(r,z,t)=\begin{cases}\dfrac{MK_1}{V\sqrt{t}} & t>0\\ 0 & t=0\end{cases} \qquad \ldots.(3)$$

The almost spherical vitreous body Fig.(1) is represented as a porous fluid filled cylinder in contacts with the retina/choroids membrane, the lens posterior capsule (chamber), and the posterior aqueous humor Fig.(2). A hypothetical cylindrical cavity is assumed placed on the axis of symmetry behind the lens in the vitreous body. We assume that the diffusion of drug and moving liquid will originate in this cavity.

The *impli*cit iterative scheme given by Eq.16 is simplified in the light of finite difference analogues of the initial and boundary conditions 10-13(b) and the resulting system of algebraic equations written in the pentadiagonal matrix form $Ac_{i,j,k+1} = f(c_{i,j,k})$ was solved by the line-Jacobi iterative technique. Computations were conducted and post processed on a COMPAQ-PC, Intel Pentium IV 2.40 GHz processor, with 1.0 GB of RAM, and 80 GB hard disk. The results were plotted in Excel.

RESULTS

The computational results of the present model have been obtained by solving the system of algebraic equations obtained from Eq.16 along with Eq.17 and using estimated values of the physiological parameters listed in Table.1. The concentration plot of the drug at the centre of retinal surface with respect to time and effects of various model parameters on the concentration change with time have been displayed in Fig.3(a)-(e). It is observed from curves that the drug concentration increases with time in initial hours after intravitreal injection. The concentration of high diffusivity drugs is lower than that of low diffusivity drugs in initial hours. After 100 hours the concentration of high diffusivity drugs becomes higher than that of low diffusivity drugs. As is evident from the graphs in Fig.3(b) an increase in the metabolic reaction rate decreases the drug concentration at the centre of retina. This is true because when the value of metabolic reaction rate is increased, more amount of drug will be consumed and degraded leading to a decrease in the drug concentration at the centre of retina. The drug concentration change with time is influenced by the rate of drug delivery.

DISCUSSION

The concentration distribution of intravitreally injected drug and the change in drug concentration with time at the centre of retina are relevant for treatment of some vitro-retinal diseases such as, age-related macular degeneration (AMD), retinitis pigmentosa, glaucoma, rhegmatogenous retinal detachment etc. The present analysis has been primarily concerned with the theoretical investigations of independent effects of the intraocular pressure and metabolic consumption of drug on the concentration distribution in the vitreous body and time-variation in the concentration of low and high diffusivity drugs at the centre of retina. As has been observed a rise in the intraocular pressure and a retarded metabolic consumption causes an increase in the drug concentration and concentration change at the retinal surface. Some future experimental studies must be directed towards the investigations of such effects and focus on the similar analysis.

The present analysis has been concerned with the investigation of independent effects of various model parameters on the drug concentration. But in practical situations these parameters will interact and there should be a consideration for the interactive effects. For the purpose, future studies in this field should try to propose and establish relationships among/ between model parameters. However the interactive effects of the parameters can be observed by using different sets of values of model parameters of interest.

The mathematical model proposed in this study will be a useful approach for predicting the drug availability and its elimination in normal and pathological states. The model results may be useful in the design of therapeutic procedures required for the safe and effective therapeutic use of a drug.

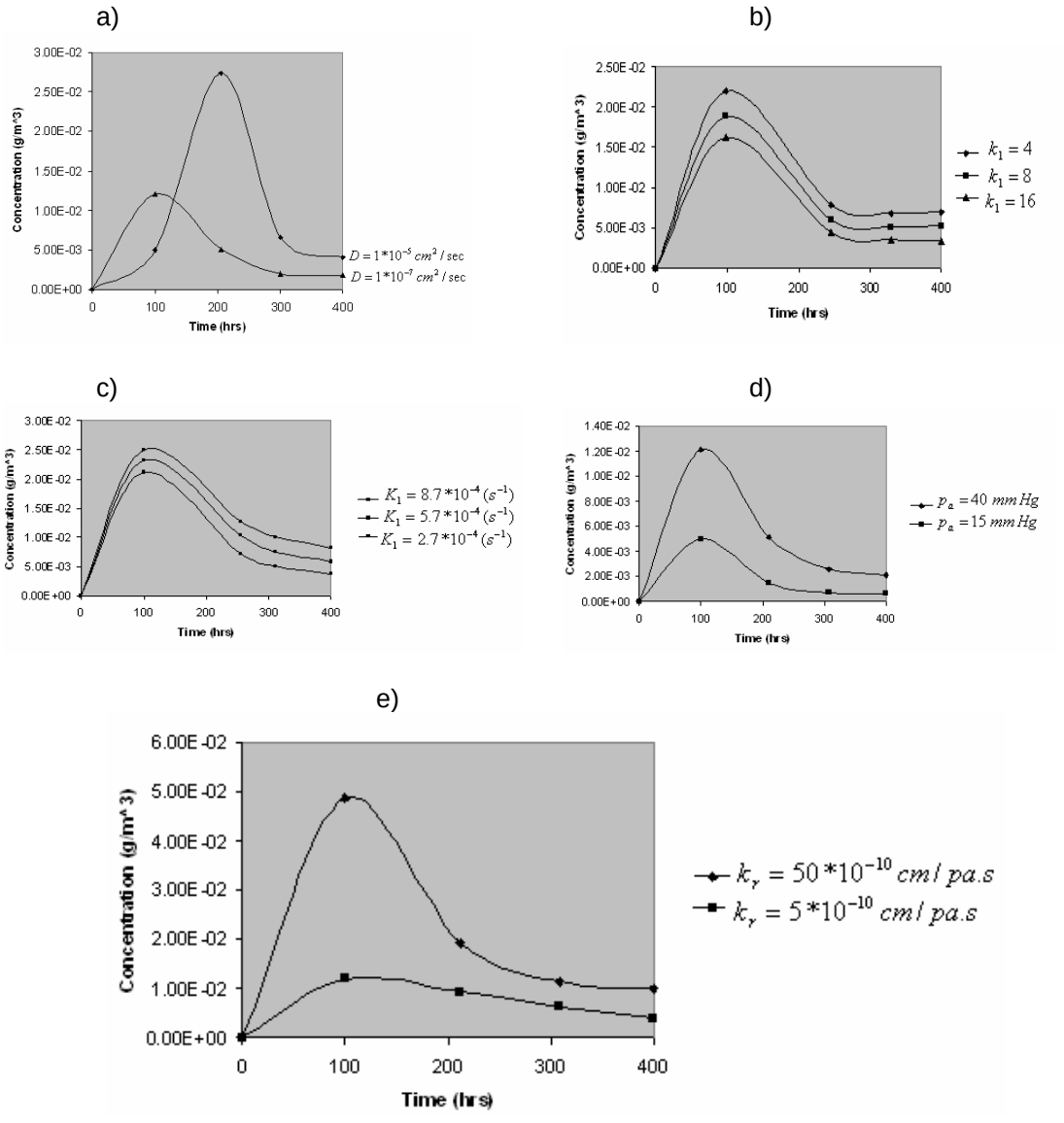

Figure 3: Effect of various parameters (a) diffusivity effect (b) metabolic rate effect (c) release rate effect (d) intraocular pressure effect (e) hydraulic conductivity effect on the drug concentration variation with time at the centre of retina. A decrease in the release rate of drug decreases the drug concentration as evident from the curves in Fig.3(c).The curves in Fig.3(d) depict the variation in the drug concentration rate due to the change in the intraocular pressure. An elevated intraocular pressure as observed in the glaucomatous eyes, increases the drug concentration rate as observed from the graphs in Fig.3(d). Initially, the drug concentration rate increases and assumes its peak value at t=100 hrs. After that it begins to decay. The decay rate of retinal drug concentration is higher in the glaucomatous eyes. The change in the drug concentration at the centre of retina with time is affected by the hydraulic conductivity of the retina. A ten fold increase in the hydraulic conductivity, as observed in a pathological state of retinal detachment increases the concentration time variation. The drug decay rate is higher in the case of retinal detachment as more amount is swept away from the retinal surface due to increased effects of the convection and the drug may be eliminated with a faster rate.

The curves in Fig.4(a)-(e) depict the drug concentration distribution along the centreline of vitreous body at t=100 hrs. after intravitreal injection and effects of various model parameters on the drug concentration.

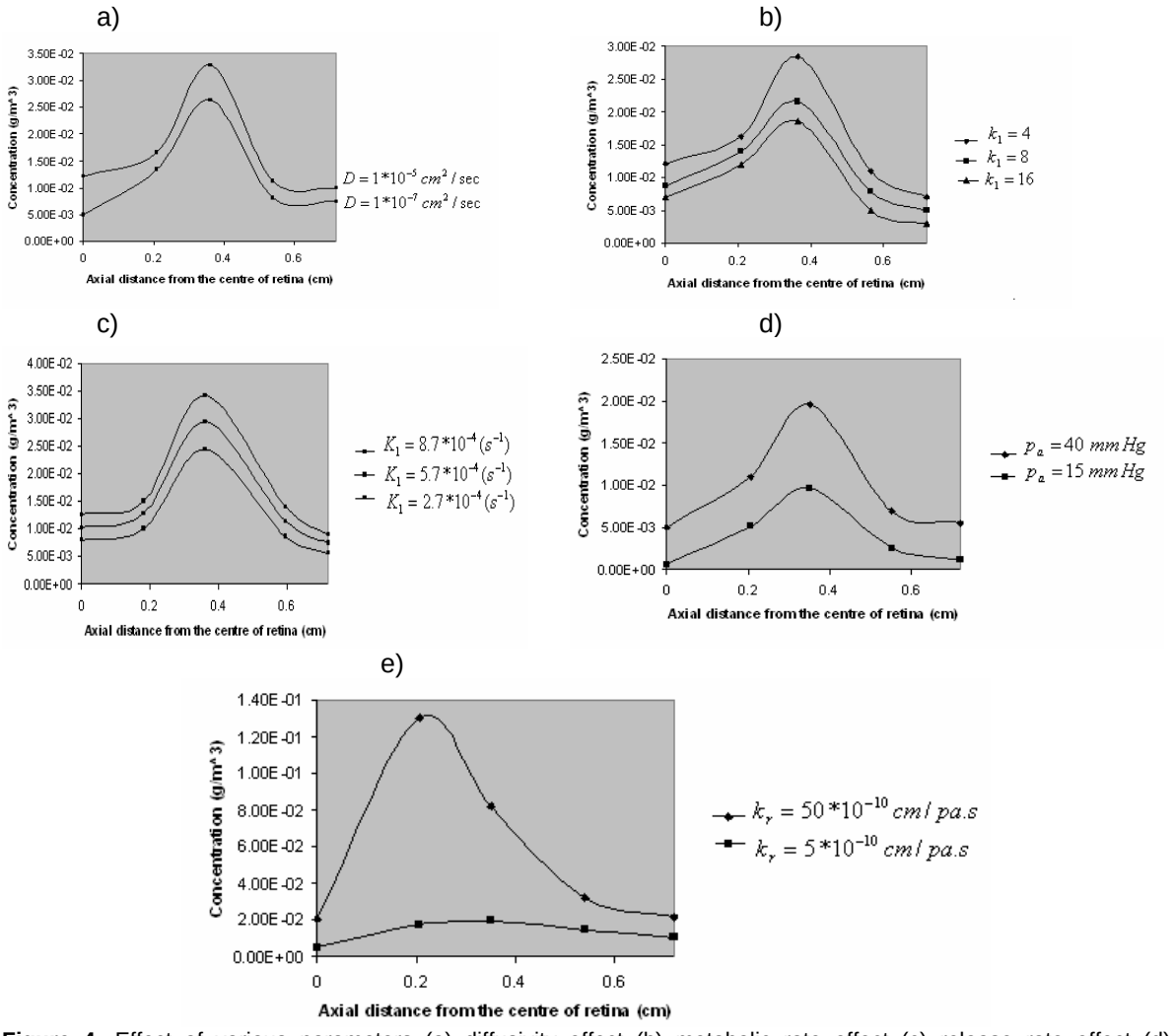

Figure 4: Effect of various parameters (a) diffusivity effect (b) metabolic rate effect (c) release rate effect (d) intraocular pressure effect (e) hydraulic conductivity effect on the drug concentration distribution along the centre line of vitreous body at time t=100 hrs

It is observed from the curves in Fig.4(a) that the concentration of drug is maximum at the center of vitreous body and decreases towards the outer surface of the vitreous body. The concentration decays as the drug is transported across the vitreous body. The concentration of high diffusivity drugs is higher than that of low diffusivity drugs. An increase in the metabolic reaction rate constant enhances the consumption of drug which causes a decrease in the drug concentration, distributed along the centreline of vitreous body as is observed from the curves in Fig.4(b). The curves in Fig.4(c) shows that an decrease in the release rate of drug decreases the drug concentration along the centreline of vitreous body. The curves in Fig.4(d)-(e) show the spatial variation of drug concentration at time t=100 hrs along the centreline of vitreous body for some patho- physiological states: glaucoma and retinal detachment. It is seen from the curves in Fig.4(d)-(e) that the concentration of drug along the centreline of vitreous body is higher for glaucomatous and retinal detachment eyes as compared to that in normal eye.

This indicates that with the increased convection to the vitreous the drug transport after intravitreal injection is enhanced and there is a sharp decrease in concentration reaching to the retinal surface.

Table 1: Definitions and explanations of terms /symbols

Symbol	Explanation	Numerical value	Reference
D	Diffusion coefficient in the vitreous body	$1*10^{-5}\ cm^2/\sec(small\ molecule)$ $1*10^{-7}\ cm^2/\sec$(large molecule)	1
D_r	Diffusion coefficient in the retina /choroid /sclera	$5.51*10^{-7}\ cm^2/\sec$	12
D_1	Diffusion coefficient in the lens	$1.83*10^{-6}\ cm^2/\sec$	12
D_p	Diffusion coefficient in the aqueous humor	$1.0*10^{-5}\ cm^2/\sec$	12
l_r	Thickness of retina	0.324 cm	12
l_p	Thickness of posterior chamber boundary layer	0.0040 cm	12
l_1	Effective thickness of the lens	0.38±0.044 cm	12
R	Radius of the vitreous body	0.72 cm	12
H	Height of the vitreous body	0.72 cm	12
b_0	Radius of the lens	0.36 cm	12
R_{act}	Active transport term	$5.7*10^{-6}\ cm\ /\sec$	6
k_p	Hydraulic conductivity of the posterior chamber vitreous body interface	$0.74\ cm^2/pa.s$	6
k_r	Hydraulic conductivity of the RCS /vitreous	$5*10^{-10}cm^2/pa.s$	6
k_l	Hydraulic conductivity of the lens/vitreous body interface	$0.324\,cm^2/pa.s$	6
k	Permeability of the vitreous body	$8.4\pm4.5*10^{-7}\ cm^2/pa.s$	16
μ	Viscosity of the vitreous humor	$3.4\pm1.4*10^{4}\ pa.s$	16
p_v	Pressure of the vein down stream flow	9 mm Hg	16
p_a	Pressure in the aqueous humor	15 mm Hg	6
M	Initial loading of the drug	500μg	6
K	Rate constant for the drug release	0.057 days	6
V	Volume of the drug injection	500 μm	6
$k_1 = \frac{M}{B}$	Metabolic rate constant	4,8,16	17
K_1	Release rate constant	$5.7*10^{-4}\ s^{-1}$	6
c_0	Initial concentration in the vitreous body	$5*10^{-3}\ g/cm^{-3}$	1
z	Axial distance	0.8 cm	1

CONCLUSION

The concentration of intravitreally injected drug at the centre of retina an along centreline of vitreous body is reduced as the metabolic reaction(consumption) rate and drug release rate constant increase in normal and diseased eyes. It is seen from the various curves in graphs that drug concentration decay rate in the diseased eye is higher than that in the normal eye.

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