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Computational Study of Drug kinetics in the Vitreous Humor

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ABSTRACT
A comprehensive study of drug delivery in vitreous body was analyzed and zero order reaction rate mechanism compared with first order mechanism. A simple Mathematical model was developed and numerical solution obtained by using numerical iterative techniques. The effect of various parameter elimination rate reaction, diffusion coefficient, vitreous humor volume on drug concentration was observed. Initially at a constant reaction rate the drug concentration increases linearly and after some time it decays exponentially. MATLAB and other simulation software have been instrumental in these studies, seeing to tremendous advancements in intravitreal drug kinetics modeling, many parameters are still untouched like mathematically model and simulate intravitreal drug kinetics, focusing on the comparative analysis of zero-order and first-order release mechanisms using MATLAB.

Keywords: *Intravitreal Drug Delivery, Mathematical Model, Zero-Order Release, First-Order kinematics, MATLAB Simulation.*

1. INTRODUCTION

The posterior segment of the eye covers with the vitreous body, retina, choroid and the optic nerve. Vitreous body is a gel like substance which is responsible to maintain the structure of the eye. The most common diseases in the posterior segment of the eye are age related macular degeneration, glaucoma , diabetic retinopathy. A huge number of population across the globe are suffering with these diseases. These vitroretinal diseases are treated by intravitral drug administration or control implant of drugs. Many clinical studies reveals that drug diffusion, convection, metabolic rate may control the drug bioavailability.

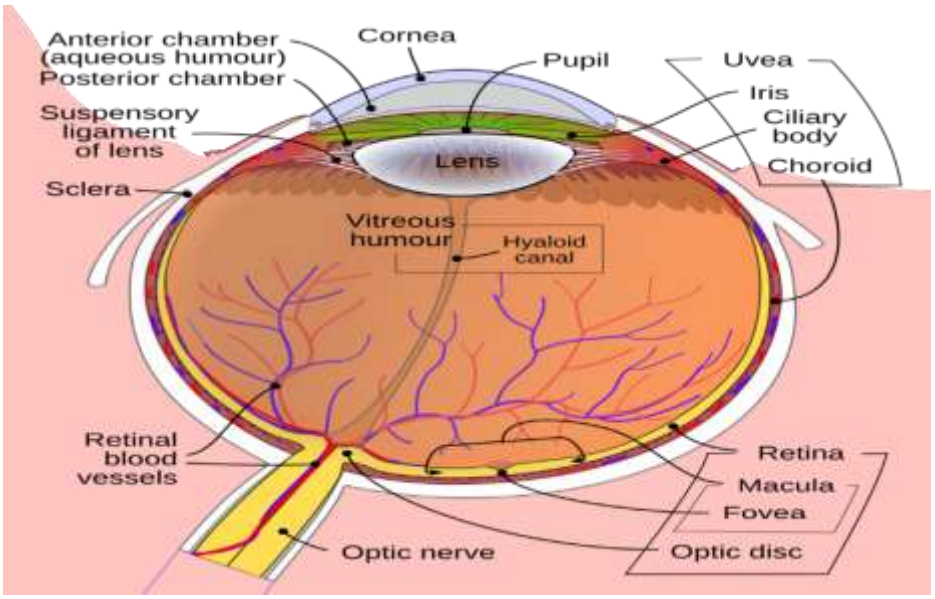


Fig. 1: Schematic diagram of Vitreous humor.

Traditional systematic drug delivery methods often fail to provide the adequate drug levels due to the retinal barrier at the target site. A mechanism of drug transport in the vitreous body may understand by developing the mathematical model of the invitreal drug transport, and theoretical investigation of the various parameters on the intravitreal drug concentration.

Numerous theoretical and experimental studies have analyzed the intravitral drug distribution

And drug elimination from the vitreous. Stay M. S investigated the mathematical model on how drugs behave within the vitreous humor, considering factors like drug molecular weight, solubility, and interaction with ocular tissues [1].

Degradation and drug release presented by Ferreivra et al [2] by Mathematical Model for degradation and drug release from an intravitreal biodegradable in plant, compartmental and COMSOL Multi physics 3D Model of Drug Diffusion to the Vitreaous following the administration of a sustained- Release Drug Delivery System [3]. Mathematical Assessment of drug build-up in the posterior eye following transceltral delivery [4]. Kim et al [5,6] contribution in Intraocular Distribution and Kinetics of Intravitreally injected antibodies and nanoparticles in Rabbit Eyes. In the research of Drug Kinetics [7,8,9] are considered as drug delivery system and vitreous Humor. In 2023, Toffoletto et al [10] made a physiology based mathematical model to the back of the eye.

Several Studies [11, 12,13,14] have analyzed intravitreal drug release and the elimination of drug from the vitreous of the eye. Previous studies [15, 16, 17] have assumed that the ocular transport of drugs released from an intravitreal implant using magnetic resonance imaging.

The aim of this paper is to about the development of the Mathematical model for the invitreal drug concentration in the vitreous body and investigation of various model parameter on the invitreal drug concentration. MATLAB and other simulation software have been instrumental in these studies, seeing to tremendous advancements in intravitreal drug kinetics modeling, many parameters are still untouched like mathematically model and simulate intravitreal drug kinetics, focusing on the comparative analysis of zero-order and first-order release mechanisms using MATLAB. By examining both release profiles under controlled conditions, it aims to offer insights that can guide future formulations and optimize treatment strategies for intravitreal drug delivery [18]. Further it assist in developing a robust computational framework, and will explore the implications of different release profiles on drug concentration over time, peak plasma levels, and elimination half-lives. The findings are expected to provide valuable insights into optimizing drug formulations and delivery strategies, ultimately contributing to improved therapeutic outcomes in ophthalmic treatments [19].

2. MATHEMATICAL MODEL

2.1 Governing Equations for Drug Transport

The intravitreal drug transport process is governed by a combination of diffusion, convection, and elimination mechanisms. The general transport equation in the vitreous humor can be represented as:

$$\frac{\partial C}{\partial t} = D\nabla^2 C - v \cdot \nabla C - k_{elim} \, . C + S \qquad (1)$$

where:

C(x,y,t): Drug concentration (mg/mL) as a function of space and time.

D: Diffusion coefficient of the drug in the vitreous humor (cm^2/day).

v: Convective velocity vector (cm/day), representing bulk fluid motion.

k_{elim}: Elimination rate constant (per day).

S: Drug generation term

2.2 Assumptions and Boundary Conditions

Assumptions:

- The vitreous humor is treated as a homogeneous and isotropic medium.
- The drug is uniformly distributed upon injection.
- The effects of convection are negligible (if the vitreous humor is not liquefied).
- The elimination process is first-order and proportional to the drug concentration.
- Drug binding to ocular tissues and other biochemical interactions are not considered.

Boundary Conditions:

- At the scleral boundary: C=0 (drug is eliminated at the boundary).
- At the injection site (for zero-order release): R(t)=constant

- At the injection site (for first-order release): R(t)=$k_{release}C_{reservoir}$, where C reservoir is the concentration of the drug in the release system.

First-Order Release Model

In a first-order release mechanism, the drug release rate depends on the remaining drug amount in the delivery system.

Drug Release Rate:

$$R(t) = k_{release} \cdot C_{reservoir} \quad (2)$$

where,

- $k_{release}$: First-order release constant.
- $C_{reservoir}$: Initial drug concentration in the reservoir.

Simplified Transport Equation:

With negligible convection:

$$\frac{\partial C}{\partial t} = D\nabla^2 C - k_{elim}.C + k_{release} \cdot C_{reservoir} + S \quad (3)$$

This model typically results in an exponential decay of drug release over time.

3. Simulation Methodology

3.1 Numerical Model Development:

In Real world biological problems, most of the partial differential equation are either non linear or they have the complex boundaries , which makes impossible to find a analytical solution. Thus, by using numerical iterative techniques the solution can be approximated with high accuracy.

The present mathematical model a non steady state partial differential equation is formulated which includes the diffusion process , convection, first order metabolic reaction rate along x and y axis and S is the drug generation term. The implicit Crank Nicolson iterative technique is used to solve transient state partial differential equation which describes the drug transport in the vitreous body.

Computational Mesh

For the computational study , we draw a two dimensional rectangular grid which consist of 100 equispaced points along the x axis from 1 (at x=0) and 100 equispaced point along the y axis.

$$x_i = (i-1)\Delta x \qquad i = 1...M$$
$$y_j = (j-1)\Delta y \qquad j = 1...N$$
$$t_k = (k-1)\Delta t \qquad k = 1, 2, 3$$

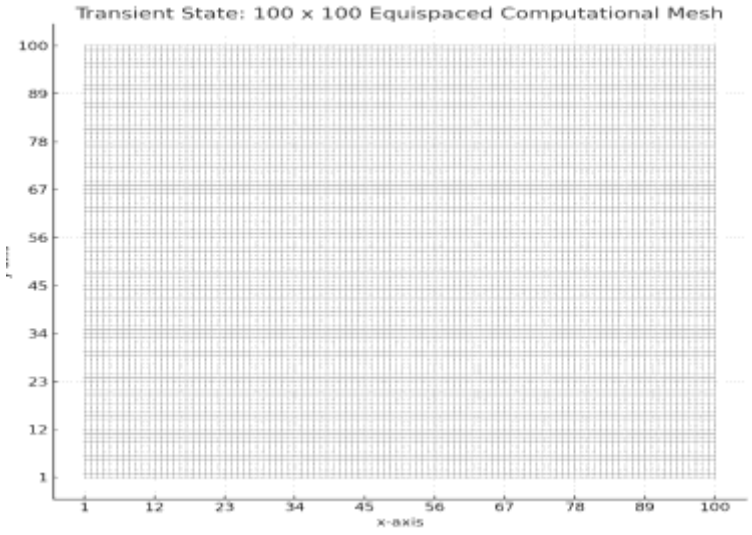


Fig.2: **Computational mesh diagram**

Discretisation of the Model :

This equation can be written in the finite difference form as follows:

$$\frac{c_{i,j,k+1}-c_{i,j,k}}{\Delta t}=\frac{1}{2}\left[D\frac{c_{i+1,j}-2c_{i,j}+c_{i-1,j}}{(\Delta x)^2}\right]_{k+1}+\frac{1}{2}\left[D\frac{c_{i+1,j}-2c_{i,j}+c_{i-1,j}}{(\Delta x)^2}\right]_{k}$$
$$-v_x.\left[\frac{c_{i+1,j,k}-c_{i-1,j,k}}{2\Delta x}\right]-v_y.\left[\frac{c_{i+1,j,k}-c_{i-1,j,k}}{2\Delta y}\right]-k_1c_{i,j,k}+S_{i,j}$$

Discretization of Boundary Condition:

Matrix Generation:

$$\begin{bmatrix} * & * & 0 & 0 & * & 0 & - & 0 & - & 0 & 0 & 0 & 0 & 0 & - \\ * & * & * & 0 & 0 & * & - & 0 & - & 0 & 0 & 0 & 0 & 0 & - \\ 0 & * & * & * & 0 & 0 & - & * & - & 0 & 0 & 0 & 0 & 0 & - \\ - & - & - & - & - & - & - & - & - & - & - & - & - & - & - \\ - & - & - & - & - & - & - & - & - & - & - & - & - & - & - \\ 0 & 0 & a & 0 & 0 & b & - & c & - & 0 & d & 0 & e & 0 & - \\ - & - & - & - & - & - & - & - & - & - & - & - & - & - & - \\ - & - & - & - & - & - & - & - & - & - & - & - & - & - & - \end{bmatrix}^{k+1}\begin{bmatrix} c_{2,2} \\ - \\ c_{2,12} \\ - \\ c_{i-1,j-1} \\ c_{i-1,j} \\ c_{i+1,j} \\ - \\ c_{i-1,12} \\ c_{i,2} \\ - \\ c_{i,j-1} \\ c_{i,j} \\ c_{i,j+1} \\ - \\ c_{i,12} \\ c_{i+1,2} \\ - \\ c_{i+1,j-1} \\ c_{i+1,j} \\ c_{i+1,j+1} \\ - \\ - - - \end{bmatrix} = f_{ij}(c_k)$$

3.2 Parameter Selection and Justification

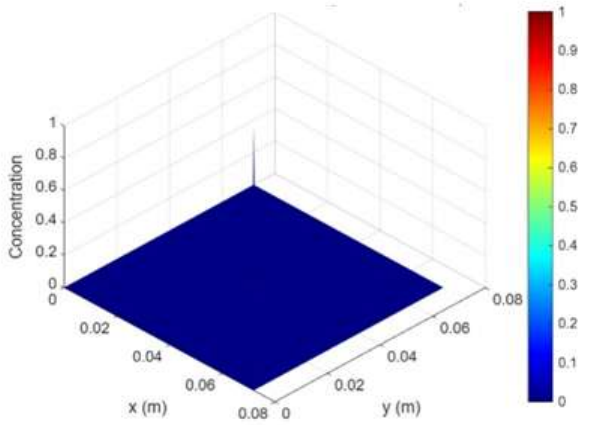
Key parameters were selected based on physiological relevance and available literature: (Hou et al., 2015) [7].

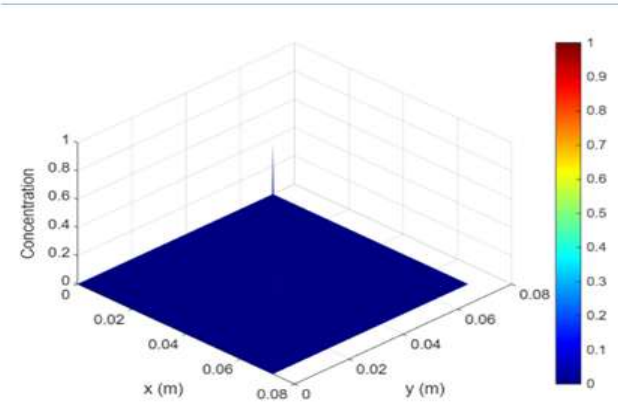
Parameter	Value	Justification
Vitreous humor volume (V)	4.5 mL	Average vitreous humor volume in humans.

Diffusion coefficient (D)	2×10−4 cm²/day	Typical drug diffusivity in vitreous humor for small molecules.
Elimination rate constant (kelim)	0.1 per day	Literature values for elimination of intravitreal drugs.
Zero-order release rate (R0)	1 mg/day	Based on sustained-release implant data.
First-order release constant (krelease)	0.05 per day	Common value for biodegradable drug reservoirs.
Simulation time (tsim)	30 days	Covers the clinically relevant timeframe for intravitreal drug efficacy.
Initial drug concentration (C reservoir)	2 mg/mL	Typical initial loading dose for intravitreal drug delivery.

3. RESULTS AND DISCUSSION

The effect of various model parameters on the concentration plot with respect to time have been displayed in the following graphs**.** The graphs (a,b) depicts that initially when the drug is injected in the vitreous body then the drug concentration reaches its maximum value , after that when the drug diffuses along the radial and axial direction the peak concentration decreases, due to the drug has starting to spread, then as the diffusion increases, the peak concentration attains its minimum value , since the more drug distribute around the vitreous body.





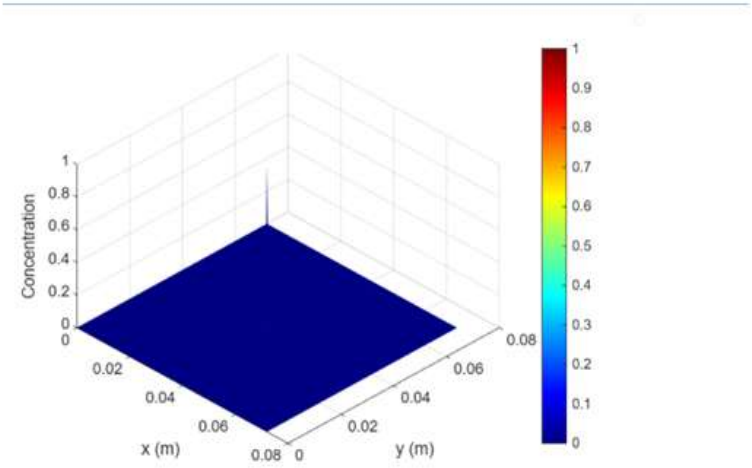
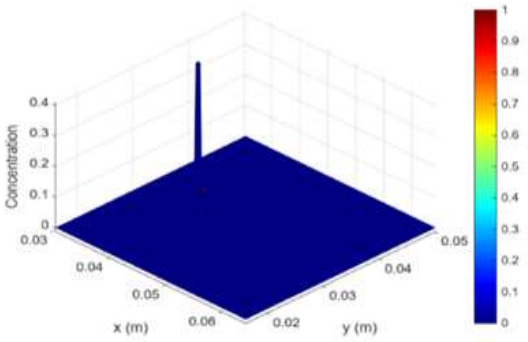
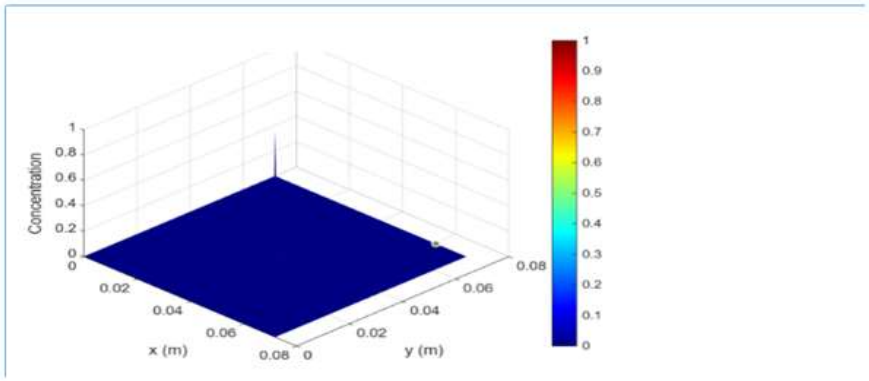


Fig.3: Effect of diffusion coefficient on the Retinal concentration at a hyperoxic condition.

As evident from the curves in Fig.3(a,b,c) shows that the decrease in the drug release rate decreases the peak drug concentration. These result is consistent with results from Nomoto et al. [20] and demo and Urtti [21], who explained the concentration of macromolecules in the vitreous body.





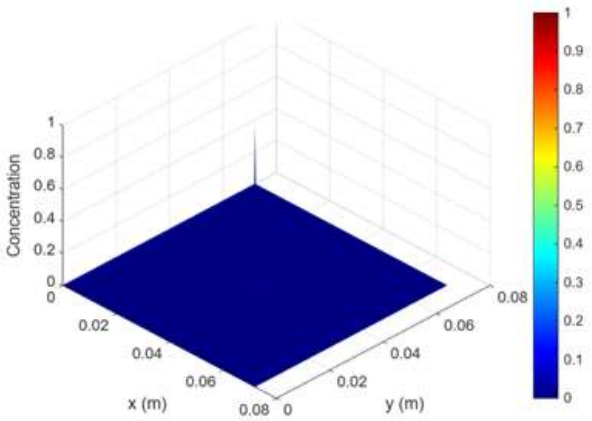


Fig.4: Effect of metabolic rate on the Retinal concentration at a hyperoxic condition

These analyses provided insights into parameter optimization for achieving desired drug profiles.

4. CONCLUSION

The current research demonstrates that intravitreal drug delivery exhibits a characteristic peak in drug concentration immediately after injection, followed by a decline as the drug diffuses radially and axially through the vitreous. The initial high drug concentration decreases as the substance disperses, eventually reaching a more uniform distribution. A slower drug release rate reduces the peak concentration and suggesting that the controlled-release formulations can modulate drug distribution kinetics. The results produces need to optimize drug delivery parameters to maintain therapeutic levels while minimizing sharp concentration fluctuations, thereby enhancing treatment efficacy and safety.

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