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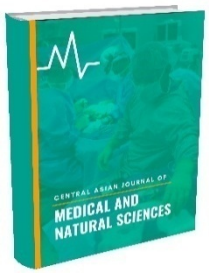

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Modeling Cholesterol and Treatment Effects on Drug Concentration in the Arterial Blood, Tissue, and Venous Blood Compartments

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Abstract: Mathematical modeling is the most rapidly developing branch of pharmacokinetics right now. Along with traditional pharmacokinetic aspects such as drug absorption, distribution, metabolism, and elimination, cholesterol research is also increasingly involving mathematical modeling. Complex pharmacokinetic-dynamic models are becoming a more widely used tool in drug therapy optimization.This study is a companion piece to the earlier studies. The study investigates the effect of cholesterol on drug distribution in the body. It demonstrates the utility of the study's model in assessing the behavior of medication distribution in the body associated with high or low cholesterol levels, for example, by lowering or raising cholesterol levels with a treatment control. In this study, we extend previous work by introducing a constant cholesterol parameter and treatment control into the mathematical models in order to better understand the behavior of drugs administered in the human body over time. The analytical solutions for the drug concentrations in the bloodstream (using the arterial blood compartment as the source of drug administration) and tissues were obtained using the modified models that were solved using Laplace's method. The Wolfram Mathematica software was used to simulate the analytical results, and the simulation was to investigate the effect of cholesterol and treatment effects on drug concentration. The study showed that an increase in cholesterol and treatment affect the drug concentration. This study could be useful for scientists and pharmacists who are interested in caring for patients using drugs.

Key words: Mathematical Models, Pharmacokinetics, Cholesterol, Drug Distribution, Ordinary Differential Equations.

1. Introduction

After a drug enters the systemic circulation, it is distributed to the body's tissues. Diffusion is generally uneven because of differences in blood perfusion, tissue binding (e.g., because of lipid content), regional pH, and permeability of cell membranes. However, in this study, we evaluated the influence of cholesterol (lipid) contained in the circulatory system on the movement (diffusion) of administered medication as the injected medicine travels through various compartments of the body.

In the body, cholesterol is a fat-like substance. It is made by your body and can also be found in food. While cholesterol is necessary for good health, too much of it can be harmful to your system.Cholesterol is a type of lipid. Lipids are any group of organic compounds that include fats, oils, waxes, sterols, and triglycerides and are usually insoluble in water. They account for the majority of the fat in the human body. Cholesterol is a waxy, fat-like substance produced by the liver. It is required for the formation of cell membranes, certain hormones, and vitamin D, among other things. Cholesterol cannot circulate through the bloodstream on its own because it does not dissolve in water. Lipoproteins are produced by the liver to aid in the transfer of cholesterol. Lipoproteins are fat and protein particles.They transport cholesterol and triglycerides (a type of fat) throughout the body. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are classified into two types. LDL cholesterol refers to any cholesterol transported by low-density lipoproteins. If your blood contains an abnormally high level of LDL cholesterol, you may be diagnosed with high cholesterol. Untreated high cholesterol can lead to a variety of health issues, including heart attack and stroke. The HDL cholesterol helps the body remove LDL cholesterol by returning it to the liver. This prevents the formation of cholesterol plaque in the arteries. Healthy levels of HDL cholesterol can help to reduce the risk of blood clots, heart disease, and stroke. Heather (2021), and Bunonyo and Eli (2020).

The convergence of mathematics and medicine has given rise to new areas of mathematics in which ideas from both fields are combined and used to solve a wide range of problems through mathematical modeling. Haines and Crouch (2007) describe mathematical modeling as the process of using mathematics to express real-life situations and their relationships. A mathematical model uses mathematical language, symbols, and concepts to describe the behavior of a real-world system. This study proposes a mathematical model for analyzing drug administration into the human systemic circulation.

This is one of a three-part series of studies we've carried out on the "effect of cholesterol on drug distribution in the human body" (Bunonyo, Ebiwareme & Awomi, 2022) and Eykhoff (1974). We used a mathematical model based on the law of mass action in this study to investigate the distribution of medications injected into the body, similar to the models reported by Khanday *et al.* (2017) and Bunonyo *et al.* (2022). However, unlike in Khanday's work, we evaluated the influence of cholesterol in the circulatory system on the movement of the administered medication as it travels through the various compartments of the body in our model.

The study of the rate of drug transportation from one compartment to another, particularly to a target site, is critical because it aids in the optimization of therapeutic system design, yielding information on the efficacy of new drugs and determining the appropriate drug concentration to be administered to a patient at a given point in time. The dose to be administered may vary depending on the patient's health and the severity of the disease, as well as the method of administration. Because the distribution of medications in the body has both positive and negative consequences, pharmacokinetics researchers have conducted a number of studies to investigate the behavior of pharmaceuticals that are ingested. Some of these studies are discussed briefly below.

In the work of McKenna *et al.* (2019), they decoupled and quantified pharmacokinetic and pharmacodynamic pathways using mathematical modeling. In this work, they demonstrated how

mathematical modeling can be used to precisely compare treatment responses across cell lines. Precision cancer therapy's ultimate goal is to deliver the optimal therapy on the optimal schedule for each individual patient, McKenna et al. (2018). Establishing a strong functional relationship between applied treatment and subsequent response is a necessary step toward this goal. One of the primary goals of their research was to demonstrate the utility of the modeling framework and provide additional evidence that therapy response is predictable.

Olga *et al.* (2014) investigated cholesterol transport and de novo production in the liver using a two-compartment mathematical model. A pair of simultaneous linear differential equations were employed to define the model. The study demonstrates the model's utility in investigating the mechanisms underlying high blood cholesterol levels, such as lowering cholesterol levels by preventing de novo cholesterol production. It also demonstrates how the model could aid in the diagnosis of high blood cholesterol by determining whether the disturbances in cholesterol homeostasis are caused by impaired transport from the liver to the bloodstream or vice versa, using the analytically derived relationships for the steady state (equilibrium).

Khanday *et al.* (2017) investigated mathematical models for drug diffusion via blood and tissue medium and sought to develop mathematical models to explain the distribution of drugs administered into the human body via oral and intravenous routes. They discovered that mathematical modeling for drug diffusion is an effective prediction technique for gaining a fundamental understanding of bio-transport processes.

In their study, Groh *et al.* (2014) looked at the use of mathematical and computational modeling techniques to help improve understanding of the fundamental mechanisms underlying drug delivery and compared the performance of a simple model to more complex approaches. Three drug transport models were created, all based on the same drug binding model and parametrized by custom in vitro experiments. When compared to a 'tumor cord' geometry, their predictions were qualitatively and quantitatively similar. They investigated the effects of varying the supplied drug's pharmacokinetic profile and binding affinity to tumor cells on the concentration of drug reaching cells and the cumulative exposure of cells to drug at arbitrary distances from a supplying blood vessel.

In their study, Ruwizhi and Aderibigbe (2020) investigated the efficacy of cholesterol-based carriers in drug delivery. They emphasized the presence of cholesterol in cell membranes and its widespread distribution in the body, which has led to its use in the preparation of carriers for the delivery of a variety of therapeutic agents such as anticancer, antimalarial, and antiviral agents. They also discovered that using cholesterol in the design of these systems influenced particle size, stability, drug entrapment efficiency, drug release profile, and cellular uptake. This is a significant advancement in the field of pharmacokinetics. However, useful cholesterol may also pose a risk to the human body. Although many positive outcomes have been drawn from the conjugation of therapeutic agents to cholesterol, there is still much work that needs to be done to ensure that they reach all advanced stages in clinical trials, Ruwizhi and Aderibigbe cautioned.

From many angles, the behavior of pharmaceuticals in the human body, the impact of medications on tumor formation, and the influence of cholesterol in the human body have been mathematically simulated by different researchers. However, the goal of this work is to extend the models developed by Bunonyo *et al.* (2022), in which we integrate a cholesterol parameter and therapy in an attempt to understand the behavior of medications delivered in the human body over time.

2 FORMULATION OF MATHEMATICAL MODEL

A mathematical model is an abstract model that employs mathematical language to explain the behavior of a system. A mathematical model, according to Eykhoff (1974), is a representation of the main elements of an existing system (or a system to be developed) that offers knowledge of that system in useable form. Predicting how far a drug will penetrate into the tumor microenvironment over its pharmacokinetic lifetime would provide useful information about treatment efficacy. Due to the fact that the pharmacokinetic profile is directly related to the route and schedule of drug administration, a mathematical tool that can predict the drug administration schedule that results in optimal drug delivery to tumors would simplify clinical trial design, according to Groh *et al.* (2014). Thus, it is important to develop mathematical models to estimate the concentration of drugs in different compartments within the body.

3 MODEL DEVELOPMENT

Blood flow in the cardiovascular system is one-directional, therefore the drug administration through venous blood takes the pattern shown in Fig. 1 below. It is evident that the drug carried by the venous blood hits the target site through the capillary bed and the residual drug either gets eliminated or taken back by the arterial blood to the systemic circulatory. Assume that the consumption of drugs by arterial blood towards tissue flows at the rate of and from the tissue compartment to the venous blood at the rate of supposing an initial dosage is administered into the arterial blood. Because the level of drug in the venous blood increases with time and ultimately falls back to zero when the kidneys and liver excrete the drug from the body organs; let the clearance rate of drug from the venous blood be constant.

In this study, it is assumed that the drug concentration in the system is associated with some level of cholesterol (lipid) produced by Trans fats and the liver. To determine the distribution of the administered drug in the system, a treatment parameter was introduced to control the level of cholesterol present in the system to help understand the rate of distribution in the system. Like the models found in the studies carried out by Khanday *et al.* (2017) and Bunonyo *et al.* (2022), a compartment model has been introduced in this study to investigate the rates of drug distribution in the body.

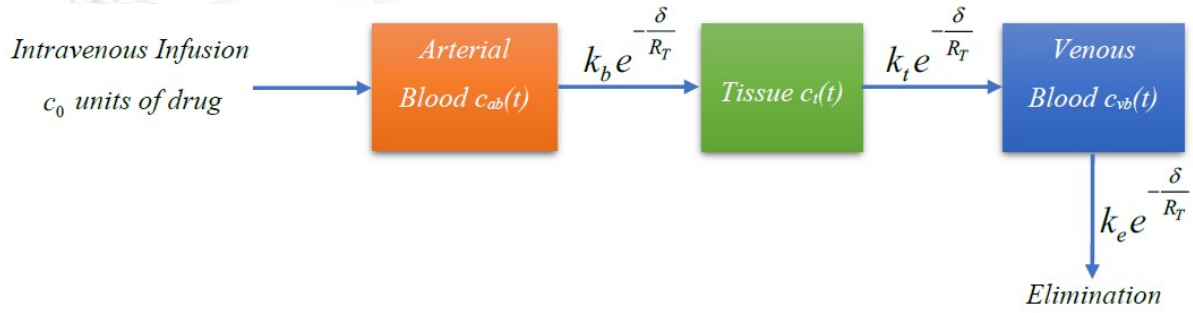

FIG. 1 DRUG DISTRIBUTION PROCESS

The first compartment in the preceeding figure relates to the arterial blood where initial dosage of the drug is administered, the second compartment represents the tissue compartment where the drug carries out its pharmacological effects and the third compartment corresponds to the venous blood, where the residual drug may get eliminated from the body or taken back to the systemic circulatory by the arterial blood.

In Fig. 1 above, $c_{ab}(t)$, $c_t(t)$ and $c_{vb}(t)$ denote the concentrations of drug in the arterial blood, tissue and venous blood compartments respectively, with the c_0 as the initial drug dosage and δ and $-R_T$ representing the amount of cholesterol found in the system and treatment to control the growth of the

cholesterol level respectively. The mathematical formulation for the drug concentration with respect to these compartments is given by the following system of ordinary differential equations following Fig. 1, and the works of Khanday *et al*. (2017) and Bunonyo *et al*. (2022):

$$\left.\begin{aligned} \frac{dc_{ab}(t)}{dt} &= -k_b e^{-\frac{\delta}{R_T}} c_{ab}(t) && at\ c_{ab}(0) = c_0 \\ \frac{dc_t(t)}{dt} &= k_b e^{-\frac{\delta}{R_T}} c_{ab}(t) - k_t e^{-\frac{\delta}{R_T}} c_t(t) && at\ c_t(0) = 0 \\ \frac{dc_{vb}(t)}{dt} &= k_t e^{-\frac{\delta}{R_T}} c_t(t) - k_e e^{-\frac{\delta}{R_T}} c_{vb}(t) && at\ c_{vb}(0) = 0 \end{aligned}\right\} \quad (1)$$

To solve the model in equation (1) analytically, let $\dot{c}_{ab}(t)$ represent $\frac{dc_{ab}(t)}{dt}$, $\dot{c}_t(t)$ represent $\frac{dc_t(t)}{dt}$ and $\dot{c}_{vb}(t)$ represent $\frac{dc_{vb}(t)}{dt}$, then equation(1) rewritten as follows:

$$\left.\begin{aligned} \dot{c}_{ab}(t) &= -k_b e^{-\frac{\delta}{R_T}} c_{ab}(t) && at\ c_{ab}(0) = c_0 \\ \dot{c}_t(t) &= k_b e^{-\frac{\delta}{R_T}} c_{ab}(t) - k_t e^{-\frac{\delta}{R_T}} c_t(t) && at\ c_t(0) = 0 \\ \dot{c}_{vb}(t) &= k_t e^{-\frac{\delta}{R_T}} c_t(t) - k_e e^{-\frac{\delta}{R_T}} c_{vb}(t) && at\ c_{vb}(0) = 0 \end{aligned}\right\} \quad (2)$$

Now, by applying Laplace transform on equation (2), we get the following:

$$L\{\dot{c}_{ab}(t)\} = -k_b e^{-\frac{\delta}{R_T}} L\{c_{ab}(t)\} \quad (3)$$

$$L\{\dot{c}_t(t)\} = k_b e^{-\frac{\delta}{R_T}} L\{c_{ab}(t)\} - k_t e^{-\frac{\delta}{R_T}} L\{c_t(t)\} \quad (4)$$

$$L\{\dot{c}_{vb}(t)\} = k_t e^{-\frac{\delta}{R_T}} L\{c_t(t)\} - k_e e^{-\frac{\delta}{R_T}} L\{c_{vb}(t)\} \quad (5)$$

Setting $c_{ab}(s) = L\{c_{ab}(t)\}$, $c_t(s) = L\{c_t(t)\}$ and $c_{vb}(s) = L\{c_{vb}(t)\}$ then using the result that $L\{f'\}(s) = sL\{f\}(s) - f(0)$, equations (3), (4) and (5) are reduced to the following:

$$sc_{ab}(s) - c_0 = -k_b e^{-\frac{\delta}{R_T}} c_{ab}(s) \quad (6)$$

$$sc_t(s) = k_b e^{-\frac{\delta}{R_T}} c_{ab}(s) - k_t e^{-\frac{\delta}{R_T}} c_t(s) \quad (7)$$

$$sc_{vb}(s) = k_t e^{-\frac{\delta}{R_T}} c_t(s) - k_e e^{-\frac{\delta}{R_T}} c_{vb}(s) \quad (8)$$

Rewriting equations(6),we get the following:

$$(s + k_b e^{-\frac{\delta}{R_T}}) c_{ab}(s) = c_0 \quad (9)$$

$$c_{ab}(s) = \frac{c_0}{(s + k_b e^{-\frac{\delta}{R_T}})} \quad (10)$$

Rewriting equation (7), we obtain the following equation:

$$sc_t(s) = k_b e^{-\frac{\delta}{R_T}} \left(\frac{c_0}{s + k_b e^{-\frac{\delta}{R_T}}} \right) - k_t e^{-\frac{\delta}{R_T}} c_t(s) \tag{11}$$

$$\left(s + k_t e^{-\frac{\delta}{R_T}} \right) c_t(s) = k_b e^{-\frac{\delta}{R_T}} \left(\frac{c_0}{s + k_b e^{-\frac{\delta}{R_T}}} \right) \tag{12}$$

$$c_t(s) = \frac{k_b e^{-\frac{\delta}{R_T}} c_0}{\left(s + k_t e^{-\frac{\delta}{R_T}} \right)\left(s + k_b e^{-\frac{\delta}{R_T}} \right)} \tag{13}$$

Rewriting equation (8), we obtain the following equation:

$$\left(s + k_e e^{-\frac{\delta}{R_T}} \right) c_{vb}(s) = k_t e^{-\frac{\delta}{R_T}} c_t(s) \tag{14}$$

$$c_{vb}(s) = \frac{k_t e^{-\frac{\delta}{R_T}} c_t(s)}{\left(s + k_e e^{-\frac{\delta}{R_T}} \right)} \tag{15}$$

$$c_{vb}(s) = \frac{c_0 k_b k_t \left(e^{-\frac{\delta}{R_T}} \right)^2}{\left(s + k_t e^{-\frac{\delta}{R_T}} \right)\left(s + k_e e^{-\frac{\delta}{R_T}} \right)\left(s + k_b e^{-\frac{\delta}{R_T}} \right)} \tag{16}$$

By applying inverse Laplace transform on equations (10), (13) and (16), we have the following:

$$L_s^{-1}\{c_{ab}(s)\}(t) = L_s^{-1}\left\{ \frac{c_0}{(s + k_b e^{-\frac{\delta}{R_T}})} \right\}(t) \tag{17}$$

$$c_{ab}(t) = c_0 e^{-k_b e^{-\frac{\delta}{R_T}} t} \tag{18}$$

$$L_s^{-1}\{c_t(s)\}(t) = L_s^{-1}\left\{ \frac{c_0 k_b e^{-\frac{\delta}{R_T}}}{(s + k_t e^{-\frac{\delta}{R_T}})(s + k_b e^{-\frac{\delta}{R_T}})} \right\}(t) \tag{19}$$

$$c_t(t) = c_0 k_b e^{-\frac{\delta}{R_T}} \left(\frac{e^{-k_t e^{-\frac{\delta}{R_T}} t + \frac{\delta}{R_T}}}{k_b - k_t} - \frac{e^{-k_b e^{-\frac{\delta}{R_T}} t + \frac{\delta}{R_T}}}{k_b - k_t} \right) \tag{20}$$

$$L_s^{-1}\{c_{vb}(s)\}(t) = L_s^{-1}\left\{ \frac{c_0 k_b k_t \left(e^{-\frac{\delta}{R_T}} \right)^2}{(s + k_e e^{-\frac{\delta}{R_T}})(s + k_t e^{-\frac{\delta}{R_T}})(s + k_b e^{-\frac{\delta}{R_T}})} \right\}(t) \tag{21}$$

$$c_{vb}(t) = e^{-\frac{2\delta}{R_T}} c_0 k_b k_t \left(\frac{e^{-k_b e^{-\frac{\delta}{R_T}} t + \frac{2\delta}{R_T}}}{(k_b - k_e)(k_b - k_t)} - \frac{e^{-k_e e^{-\frac{\delta}{R_T}} t + \frac{2\delta}{R_T}}}{(k_b - k_e)(k_e - k_t)} - \frac{e^{-k_t e^{-\frac{\delta}{R_T}} t + \frac{2\delta}{R_T}}}{(k_b - k_t)(-k_e + k_t)} \right) \quad (22)$$

The solutions in equations (18), (20) and (22)correspond to the exponential decay of a drug delivered into the arteries as it is absorbed by the body into the tissue compartment and then back into the veins.

4 RESULTS

The mathematical model was solved analytically using Laplace's transformation technique, and the results in equations(18), (20) and (22) were simulated using Wolfram Mathematica to demonstrate the influence of the supplied parameters. For the numerical computations, the values of the parameters were given by the following $c_0 = 500, k_b = 0.50/hr, k_e = 0.05/hr, k_t = 0.25/hr, R_T = 5, t_0 = 0, t_f = 20$ for different levels of cholesterol present in the system, $\delta_1 = 5, \delta_2 = 4, \delta_3 = 3$ and $\delta_4 = 2$. These values constitute the plots in Fig. 2 and the numerical results are found in TABLE 2. The values of the parameters that constitute the plots in Fig. 3 and the results or numerical values found in TABLE 3 below are given by $c_0 = 500, k_b = 0.9776/hr, k_e = 0.2213/hr, k_t = 0.7448/hr, R_T = 5, t_0 = 0, t_f = 20$ for different levels of cholesterol present in the system, $\delta_1 = 5, \delta_2 = 4, \delta_3 = 3$ and $\delta_4 = 2$. Furthermore, the plots in Fig. 4 and the numerical results in TABLE 4 (all shown below) are constituted by the following parameters $c_0 = 500, k_b = 0.50/hr, k_e = 0.05/hr, k_t = 0.25/hr, \delta = 5, t_0 = 0, t_f = 20$ for different levels of cholesterol treatment, $R_{T1} = 5, R_{T2} = 4, R_{T3} = 3$ and $R_{T4} = 2$.

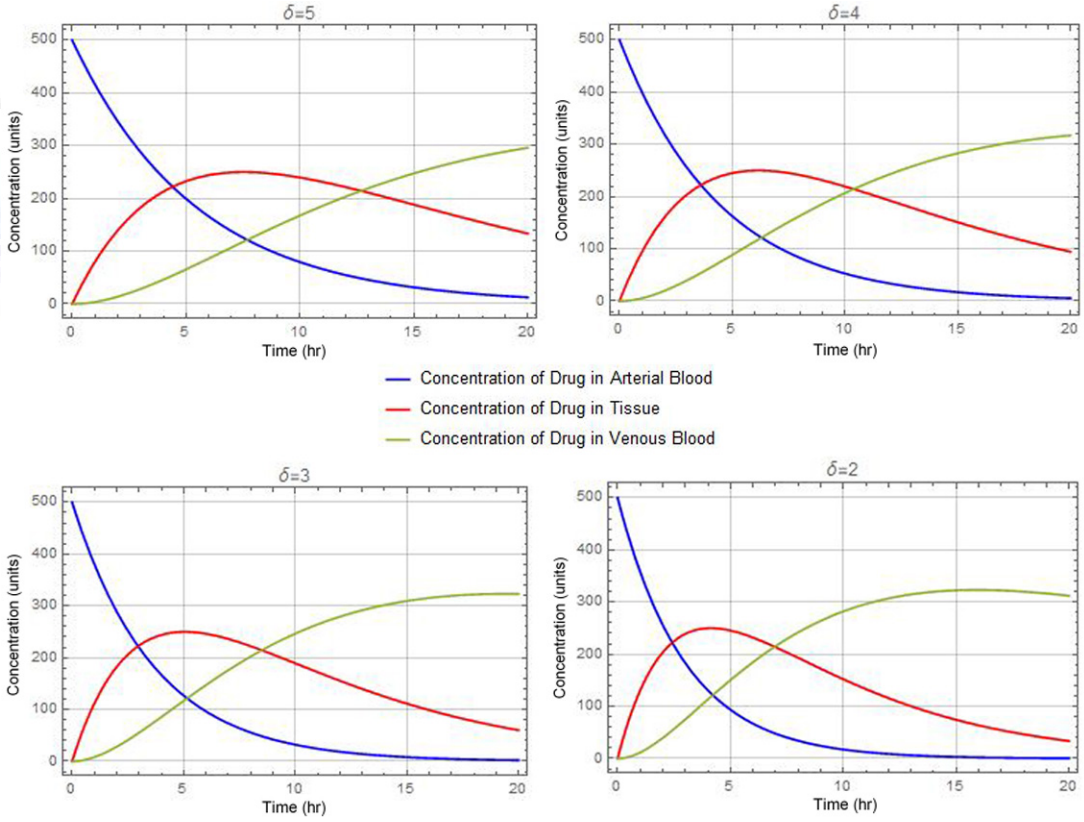

FIG. 2 *EFFECT OF CHOLESTEROL ON DRUG CONCENTRATION IN BLOOD AND TISSUE COMPARTMENTS WITH* $k_b = 0.50, k_e = 0.05$ *AND* $k_t = 0.25$

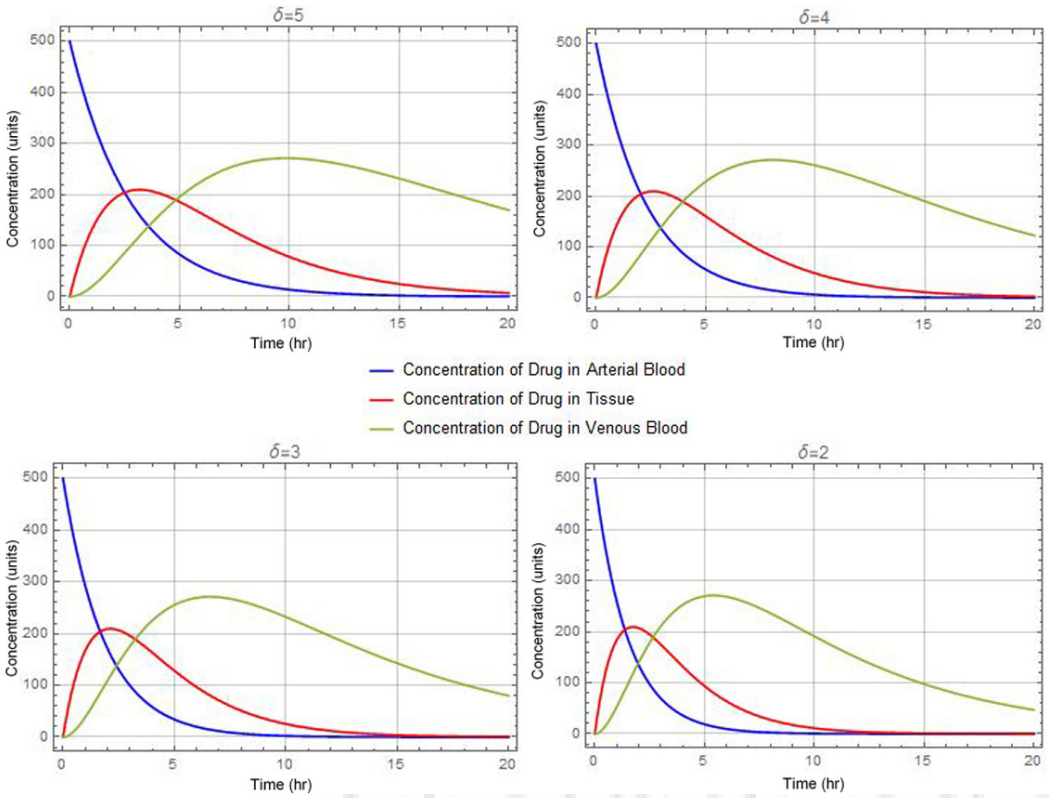

FIG. 3 *EFFECT OF CHOLESTEROL ON DRUG CONCENTRATION IN BLOOD AND TISSUE COMPARTMENTS WITH* $k_b = 0.9776,\ k_e = 0.2213$ *AND* $k_t = 0.7448$

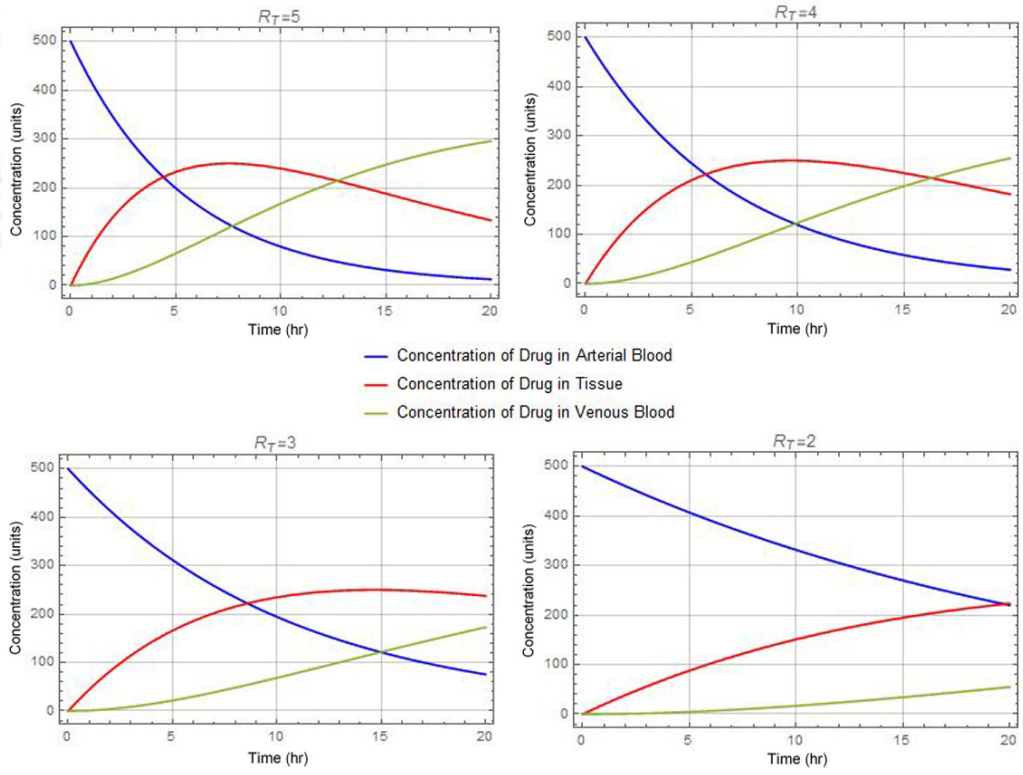

FIG. 4 *EFFECT OF TREATMENT ON DRUG CONCENTRATION IN BLOOD AND TISSUE COMPARTMENTS WITH* $k_b = 0.50,\ k_e = 0.05$ *AND* $k_t = 0.25$

TABLE 2 DRUG CONCENTRATION IN BLOOD AND TISSUE COMPARTMENTS WITH CHOLESTEROL AT $k_b = 0.50, k_e = 0.05$ *AND* $k_t = 0.25$

Time (hr)	$\delta = 5$			$\delta = 4$			$\delta = 3$			$\delta = 2$		
	c_{ab}	c_t	c_{vb}	c_{ab}	c_t	c_{vb}	c_{ab}	c_t	c_{vb}	c_{ab}	c_t	c_{vb}
0	500.	0.	0.	500.	0.	0.	500.	0.	0.	500.	0.	0.
1	415.993	80.1467	3.83623	399.392	94.9631	5.6016	380.012	111.77	8.14124	357.612	130.485	11.7654
2	346.1	139.785	13.9349	319.028	160.728	19.9271	288.818	182.388	28.2388	255.772	203.679	39.5824
3	287.951	182.98	28.505	254.835	204.242	39.9424	219.508	223.567	55.2353	182.934	239.002	75.1867
4	239.571	213.059	46.1235	203.558	230.941	63.3648	166.832	243.973	85.5785	130.839	249.867	113.261
5	199.32	232.74	65.6682	162.599	245.063	88.4969	126.796	249.987	116.823	93.5792	245.46	150.502
6	165.831	244.239	86.261	129.881	249.907	114.095	96.3678	246.281	147.329	66.93	232.009	184.971
7	137.969	249.36	107.223	103.747	248.021	139.267	73.2418	236.248	176.046	47.8699	213.679	215.636
8	114.788	249.565	128.034	82.8715	241.373	163.389	55.6655	222.332	202.341	34.2377	193.203	242.062
9	95.5022	246.036	148.306	66.1965	231.466	186.043	42.3071	206.271	225.879	24.4876	172.328	264.191
10	79.4566	239.726	167.754	52.8767	219.444	206.966	32.1544	189.283	246.531	17.5141	152.13	282.195
11	66.1067	231.398	186.175	42.2371	206.17	226.012	24.4381	172.203	264.312	12.5265	133.228	296.379
12	54.9998	221.662	203.433	33.7383	192.286	243.122	18.5735	155.589	279.326	8.95925	115.942	307.11
13	45.7591	211.002	219.443	26.9496	178.263	258.297	14.1163	139.793	291.738	6.40787	100.391	314.783
14	38.071	199.796	234.163	21.5269	164.44	271.587	10.7287	125.026	301.745	4.58306	86.5738	319.784
15	31.6745	188.343	247.58	17.1954	151.057	283.068	8.15409	111.395	309.558	3.27791	74.4123	322.481
16	26.3527	176.871	259.706	13.7354	138.272	292.84	6.19731	98.9365	315.395	2.34444	63.7866	323.215
17	21.9251	165.554	270.572	10.9716	126.189	301.013	4.7101	87.6375	319.467	1.6768	54.5567	322.291
18	18.2414	154.522	280.22	8.76395	114.865	307.705	3.57978	77.4547	321.976	1.19929	46.5767	319.982
19	15.1766	143.868	288.704	7.00051	104.325	313.033	2.72072	68.3247	323.111	0.857758	39.7033	316.527
20	12.6267	133.66	296.083	5.5919	94.5697	317.116	2.06781	60.1732	323.048	0.613489	33.8013	312.136

TABLE 3 DRUG CONCENTRATION IN BLOOD AND TISSUE COMPARTMENTS WITH CHOLESTEROL AT $k_b = 0.9776, k_e = 0.2213$ *AND* $k_t = 0.7448$

Time (hr)	$\delta = 5$			$\delta = 4$			$\delta = 3$			$\delta = 2$		
	c_{ab}	c_t	c_{vb}	c_{ab}	c_t	c_{vb}	c_{ab}	c_t	c_{vb}	c_{ab}	c_t	c_{vb}
0	500.	0.	0.	500.	0.	0.	500.	0.	0.	500.	0.	0.
1	348.964	131.032	19.4437	322.255	149.224	27.5386	292.39	167.335	38.5668	259.642	184.139	53.2794
2	243.552	191.079	61.5972	207.697	202.959	82.9691	170.984	209.045	109.36	134.828	207.389	140.446
3	169.982	209.11	110.151	133.863	207.22	141.351	99.9882	196.129	175.817	70.0139	175.536	210.736
4	118.635	203.54	156.19	86.276	188.234	191.291	58.4712	163.786	225.133	36.357	132.332	252.866
5	82.7988	185.848	195.354	55.6058	160.445	228.758	34.1928	128.401	255.43	18.8796	93.7126	269.917
6	57.7876	163.006	225.997	35.8385	131.407	253.486	19.9953	96.7625	269.256	9.80388	63.8349	268.736
7	40.3316	139.083	248.023	23.0983	104.728	266.945	11.6929	70.9883	270.45	5.09099	42.3572	255.905
8	28.1485	116.319	262.153	14.8871	81.8353	271.225	6.83777	51.0834	262.758	2.64367	27.585	236.544
9	19.6457	95.818	269.474	9.5949	63.0028	268.467	3.9986	36.2321	249.308	1.37281	17.7172	214.229
10	13.7113	78.0022	271.182	6.18402	47.9472	260.595	2.3383	25.4136	232.504	0.712881	11.2596	191.272
11	9.56949	62.901	268.433	3.98566	36.1557	249.214	1.36739	17.6693	214.09	0.370187	7.09695	169.066
12	6.67881	50.3336	262.269	2.5688	27.0619	235.607	0.799626	12.1985	195.27	0.192232	4.44406	148.374
13	4.66133	40.0207	253.587	1.65562	20.1316	220.754	0.467605	8.37322	176.838	0.0998229	2.76826	129.552
14	3.25327	31.6507	243.135	1.06707	14.8999	205.385	0.273447	5.72031	159.284	0.0518364	1.71705	112.707
15	2.27055	24.9177	231.524	0.687735	10.9806	190.027	0.159906	3.89253	142.888	0.0269179	1.06131	97.7978
16	1.58468	19.5408	219.235	0.443252	8.06274	175.043	0.0935102	2.64001	127.784	0.013978	0.654111	84.7032
17	1.106	15.2728	206.645	0.285681	5.90183	160.676	0.054683	1.78552	114.008	0.00725855	0.402182	73.2646
18	0.771905	11.9023	194.04	0.184124	4.3085	147.076	0.0319776	1.20474	101.535	0.00376925	0.246791	63.3109
19	0.538734	9.25202	181.633	0.11867	3.13803	134.329	0.0186999	0.811224	90.3043	0.00195731	0.151186	54.6726
20	0.375998	7.17582	169.578	0.0764841	2.28093	122.468	0.0109353	0.545298	80.2332	0.0010164	0.0924883	47.1903

TABLE 4 DRUG CONCENTRATION IN BLOOD AND TISSUE COMPARTMENTS WITH TREATMENT AT $k_b = 0.50, k_e = 0.05$ *AND* $k_t = 0.25$

Time (hr)	$R_T = 5$			$R_T = 4$			$R_T = 3$			$R_T = 2$		
	c_{ab}	c_t	c_{vb}	c_{ab}	c_t	c_{vb}	c_{ab}	c_t	c_{vb}	c_{ab}	c_t	c_{vb}
0	500.	0.	0.	500.	0.	0.	500.	0.	0.	500.	0.	0.
1	415.993	80.1467	3.83623	433.268	64.3435	2.3773	454.942	43.9942	1.06021	479.894	19.8995	0.206008
2	346.1	139.785	13.9349	375.442	115.652	8.81892	413.945	81.9948	4.03437	460.597	38.5947	0.806256
3	287.951	182.98	28.505	325.334	155.972	18.4149	376.642	114.635	8.63797	442.075	56.1421	1.77505
4	239.571	213.059	46.1235	281.913	187.057	30.403	342.7	142.489	14.6175	424.299	72.5959	3.08795
5	199.32	232.74	65.6682	244.288	210.406	44.1474	311.818	166.07	21.7473	407.237	88.008	4.72166
6	165.831	244.239	86.261	211.684	227.299	59.1196	283.718	185.847	29.8272	390.861	102.428	6.65406
7	137.969	249.36	107.223	183.431	238.829	74.8829	258.151	202.24	38.6793	375.144	115.903	8.8641
8	114.788	249.565	128.034	158.95	245.926	91.0791	234.887	215.627	48.1465	360.059	128.48	11.3318
9	95.5022	246.036	148.306	137.736	249.382	107.416	213.72	226.349	58.0898	345.58	140.2	14.038
10	79.4566	239.726	167.754	119.353	249.87	123.656	194.461	234.714	68.387	331.684	151.106	16.9648
11	66.1067	231.398	186.175	103.423	247.957	139.611	176.937	241.	78.9304	318.347	161.237	20.0949
12	54.9998	221.662	203.433	89.62	244.128	155.133	160.992	245.452	89.6263	305.545	170.632	23.4122
13	45.7591	211.002	219.443	77.6589	238.786	170.105	146.484	248.297	100.392	293.259	179.327	26.9009
14	38.071	199.796	234.163	67.2942	232.275	184.441	133.283	249.735	111.157	281.466	187.356	30.5466
15	31.6745	188.343	247.58	58.3128	224.879	198.077	121.273	249.944	121.858	270.148	194.752	34.3352
16	26.3527	176.871	259.706	50.5301	216.84	210.969	110.344	249.087	132.443	259.285	201.548	38.2536
17	21.9251	165.554	270.572	43.7861	208.354	223.089	100.4	247.307	142.866	248.859	207.773	42.2892
18	18.2414	154.522	280.22	37.9422	199.587	234.421	91.3527	244.735	153.088	238.852	213.457	46.4302
19	15.1766	143.868	288.704	32.8783	190.674	244.964	83.1204	241.486	163.076	229.247	218.628	50.6653
20	12.6267	133.66	296.083	28.4902	181.725	254.721	75.6299	237.662	172.805	220.029	223.311	54.9838

5 DISCUSSION

The plots and figures in FIG. 2 and TABLE 2 respectively, show an increase in drug concentration in the tissue compartment from 0 units at time $(t = 0)$ to 249.565 units at time $(t = 8)$ and then gradually decreased after that, as the drug present in the system moved into the venous blood compartment, causing it (the drug present) to rise from 0 units at time $(t = 0)$ to 323.221 units at time $(t = 29)$ where it reached its peak and fell back down to 0 units as time progressed.The findings also show that as the administered medication moved from the arterial blood compartment to the tissue compartment, the drug concentration in the arterial blood compartment steadily decreased and eventually left the compartment entirely. These findings were associated with a higher level of cholesterol in the system, $\delta = 5$.Similar patterns (i.e., drug movements) were seen in lower levels of cholesterol in the system. However, it is clear that the rate of medication movement from one compartment to the other increases with lower cholesterol levels and decreases with the presence of higher cholesterol for each $\delta_i, i = 5, 4, 3 \text{ and } 2$.

Like those in FIG. 2 and TABLE 2, the plots and results in FIG. 3 and TABLE 3 respectively, show an increase in drug concentration in the tissue compartment from 0 to 209.11 units within the time span $(t = 0 \text{ to } 3)$ hours for the cholesterol level $\delta = 5$. This indicates that as the level of cholesterol in the system decreases, so does the rate at which the drug gets into the tissue compartment. The data in TABLE 2 also show that with a high level of cholesterol present in the system, the rate of drug movement in the system becomes slower and faster when the concentration of cholesterol is low. This

implies that as the amount of cholesterol in the system increases, the rate at which the medicine injected into the circulation goes into the tissue compartment for therapeutic effectand back into the venous blood becomes slower.

The plots and results in FIG. 4 and TABLE 4 reveal an increase in the concentration of drug in the tissue compartment from 0 to 249.565 units in the first eight hours after the medication was delivered into the bloodstream for the cholesterol treatment $R_T = 5$.The results in TABLE 3 further reveal that when the amount of cholesterol in the system is lowered by the treatment parameter, the pace at which the drug performs its therapeutic function in the tissue compartment and subsequently returns to the venous blood compartment for elimination accelerates. TABLE 3 illustrates that diffusion rate of drug concentration increases with increasing treatment values in the arterial blood compartment, but decreases in the tissue and venous blood compartments. Also, as shown by the red oval shapes in TABLE 3, the drug concentration peaks at a certain time before diminishing in concentration in the various compartments. This peak is reached faster, however, when the cholesterol level is reduced by increasing the degree of treatment. Furthermore, once the concentration maxima were reached, the various concentration levels began to fall to their lowest levels as the concentration in the circulatory compartments continued to fall while the drug diffused from one compartment to the other.

6 CONCLUSION

Based on the results of the model's solutions and simulations, we conclude that: (1) excess cholesterol consumption into the circulation hinders drug diffusion from one compartment to another, thereby impeding the free movement of drugs to their target sites to carry out their therapeutic effects. (2) When there is little or no treatment to control the presence of cholesterol, the drug concentration administered into the system takes longer period to reach its peak in the tissue and venous blood compartments before being eliminated from the body. (3) Drug diffusion in the body can be improved by lowering cholesterol concentrations in the system through cholesterol treatment or control. However, in this case, other factors that can impede drug movement or diffusion are overlooked. (4) The rate of drug diffusion increases as rate constants such as the elimination rate, the rate at which drug moves from the arterial blood compartment to the tissue compartment and then from the tissue compartment to the venous blood compartment, increase. While the brain requires some cholesterol to function properly, too much of it can be harmful. Excess cholesterol can reduce or obstruct proper drug movement from one site to another for therapeutic effect and elimination.

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8 DEFINITION OF VARIABLES AND PARAMETERS

c_{ab} Concentration of drug in the arterial blood.

c_t Concentration of drug in the tissue.

c_{vb} Concentration of drug in the venous blood.

c_0 Initial drug concentration administered into the system (through the arterial blood).

k_b The rate at which drug is taken from the arterial blood compartment to the tissue compartment.

k_t The rate at which drug is taken from the tissue compartment to the venous blood compartment for elimination.

k_e The rate of drug elimination (clearance) from the system.

δ The level of cholesterol found in the system.

$-R_T$ Treatment parameter (control) to inhibit or proliferate the level of cholesterol found in the system.

t_0 Initial time. The moment the drug is administered into the system.

t_f Final time under consideration in the observation.