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(RESEARCH ARTICLE)

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The application of Pennes' bioheat equation to determine the effect of temperature on drug diffusion

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Abstract

In this work, we discuss how temperature (internal heat) affects medication distribution between the stomach and circulatory compartments. The study shows that the behavior of medication distribution is related to high or low temperatures in the compartments under examination (the stomach and bloodstream). Here, we attempted to comprehend the behavior of a medicine supplied to the body over time by solving the models set up to mimic the system. The model (a system of ODEs) was solved both analytically and computationally using Wolfram Mathematica. The results reveal that as the temperature increases, the medication delivered into the system diffuses quicker between the compartments, and as the temperature decreases, the medication diffuses slower, demonstrating the peculiarity of this study effort.

Keywords: Mathematical Models; Pharmacokinetics; Pennes' Bio-heat Equation; Drug Distribution; Ordinary Differential Equations; Temperature; Drug Diffusion

1. Introduction

The curiosity about how drugs diffuse in our bodies and what effect temperature has on this process gave birth to this research. Studies have shown that ambient temperature, in conjunction with an organism's adaptive capacity, can influence a wide range of physiological and pharmacological processes in our bodies. Temperature studies on biochemical reactions are useful in distinguishing between physical and chemical processes, the latter of which is highly sensitive to temperature change, but they are not always easy to interpret. However, using temperature coefficients in calculations is always beneficial (Fuhrman, 1961). Temperature (heat) can easily influence drug pharmacokinetics or pharmacodynamics, and it can be used as a medical therapy to treat pain, cancer, or even to develop temperature-sensitive vaccines. Temperature is not usually distributed evenly throughout the body. The temperature in one region of the body may differ from that in another, according to Singh *et al.* (2017). This raises the issue of temperature distribution in the body, which is an important topic in pharmacokinetics. The bioheat equation model is required to comprehend the concept of temperature (heat) distribution in the body.

For the sake of simplicity in the investigation, we consider using Pennes' bioheat Equation, Valvano (2005), identifying the sources of heat as metabolic heat generated by the cells and heat exchange from the blood to the tissues (known as the perfusion rate). The study of drug transport rates from one compartment to another is important because it helps in the optimization of therapeutic system engineering by yielding data on the efficacy of new drugs and determining the optimal concentration of drug to be administered to a patient.

According to Xu *et al.* (2009), all biological bodies exist in a spatial temperature field (environment), which means that even within a single organism, organs and tissues do not have uniform temperatures. The non-uniformity of the temperature in a field causes energy transfer between organs (and tissues) and perfused blood, as well as at the skin-

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body interface. Now this current study looks into the effect of the body's heat generated by this energy on drug distribution in a patient.

Bunonyo *et al*. (2023): This study looked into the behavior of drug distribution in relation to high or low surrounding temperatures in the organs under investigation (the stomach as well as the bloodstream). In this study, the mathematical models used in previous studies by Khanday *et al*. (2017) and Bunonyo and Amadi (2023) were reformulated by introducing a temperature component in an attempt to understand the behavior of a drug administered into the body in the presence of the temperature component. According to Johansson (2001), the temperature affects drug diffusion rate; he stated that it's time to request the results of a cold test before a new drug can be approved for widespread use, particularly in hypothermic patients.

The distribution of drugs administered orally into the body is investigated in this study using a mathematical model based on Fick's law of diffusion and the law of mass action, which is similar to the models reported by Bunonyo *et al*. (2023). In this study, however, we look at how heat generated by the body affects drug distribution as the drug diffuses across the various organs under consideration. The heat component in the system is represented in the study by a one-dimensional modified version of Pennes' Bioheat Equation. Pennes' bioheat equation, according to Wang *et al.* (2020), is the most widely used thermal model for investigating heat distribution in biological systems exposed to radiofrequency energy. Cremer (1971) investigated the interaction of environmental and body temperature changes in his study of neurochemical changes in relation to body temperature. He emphasized that environmental and temperature factors can influence the distribution and metabolism of drugs used in the central nervous system. However, the goal of this study is to ascertain the effect of heat generated by the system on drug diffusion and to illustrate the effect of temperature on drugs administered to the body using graphs and tables.

2. Material and methods

2.1. Mathematical Models Formulation

A mathematical model is an abstract model that uses mathematical terminology to explain the behavior of a system. According to Budd *et al.* (2021), mathematical modeling is the process of mathematically expressing a real-world situation in the form of equations and then utilizing these equations to both comprehend the original problem and find new aspects about it. Most of our understanding of the world is based on modeling, which permits engineers to develop future technologies. As a result, building mathematical models to predict medication concentrations in various compartments of the body is crucial.

To formulate a system of mathematical models that capture the absorption and distribution of medications taken orally into the body via the gastrointestinal tract (stomach) and subsequently into the circulation, we analyze how heat influences drug concentrations in the stomach and bloodstream. See Figure 1, depicting the drug distribution process.

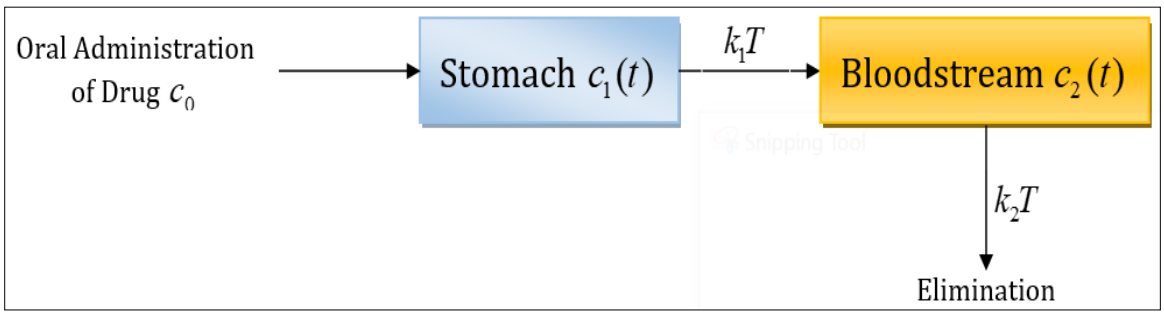

Figure 1 Drug Distribution Process

Following Figure 1, the first compartment denotes the stomach where the first dosage of the medicine is administered, and the second compartment refers to the bloodstream, where the drug is eliminated from the system, and $c_1(t)$ and $c_2(t)$ show the drug concentrations in the stomach and bloodstream compartments, respectively, with c_0 as the initial dosage of medication administered into the stomach, where $T(t)$ denotes the temperature as a result of the heat generated by the body. Based on the aforementioned Figure 1 and Bunonyo and Amadi (2023), we shall formulate a system of ordinary differential equations for drug concentration in respect to these compartments.

2.2. Mathematical Models

The mathematical formulation for the drug concentration with respect to these compartments follows the principle adopted by Khanday *et al*. (2017), Bunonyo *et al.* (2022), and Bunonyo and Amadi (2023):

$$\frac{dc_1(t)}{dt} = -k_1 c_1(t)T \quad \text{----------} \quad (1)$$

$$\frac{dc_2(t)}{dt} = k_1 c_1(t)T - k_2 c_2(t)T \quad \text{----------} \quad (2)$$

According to Valvano (2005), the Pennes' Bio-heat equation is:

$$\rho c_p \frac{\partial T}{\partial t} = k_T \frac{\partial^2 T}{\partial y^2} + \rho_b c_b w_b \left(T_a - T\right) + Q_m \quad \text{----------} \quad (3)$$

Equations (1)-(3) are subject to the following initial conditions:

$$\left.\begin{aligned} c_1(0) &= c_0 \\ c_2(0) &= 0 \\ t &= 0 \end{aligned}\right\} \quad \text{----------} \quad (4)$$

To evaluate the influence of temperature on the system, the third differential equation, a modified version of Pennes' bio-heat equation, has been included. This third equation fits into the model by addressing problems such as "How quickly or slowly would an administered drug disperse between the compartments, given a specific temperature of the compartment in which the drug is discovered and the drug's likely changing temperature as it flows between the compartments?"

2.3. Analytical Solutions

In order to explore the influence of temperature rise or fall on the diffusion of the drug administered in stomach into the bloodstream and eventually out the system, we have the following:

Since all the media are considered to have constant parameters with respect time and space and the initial time where $t = 0$, equation (3) reduces to the following:

$$\rho_b c_b w_b \left(T_a - T\right) + Q_m = 0 \quad \text{----------} \quad (5)$$

Solving for the temperature effect in equation (5), we obtained:

$$T = T_a + \frac{Q_m}{\rho_b c_b w_b} \quad \text{----------} \quad (6)$$

In order to investigate the effect of heat on drug distribution in the stomach and in the bloodstream, we substitute equation (6) into equation (1), which yields:

$$\frac{dc_1}{dt} = -k_1\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)c_1 \quad \text{----------} \quad (7)$$

Solving equation (7), we have:

$$\frac{dc_1}{c_1} = -k_1\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)dt \quad \text{----------} \quad (8)$$

Integrating equation (8), we get:

$$\int \frac{1}{c_1} dc_1 = -k_1\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)\int dt \quad \text{----------} \quad (9)$$

Solving equation (9), we have:

$$c_1(t) = Ae^{-k_1\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)t} \text{ ---------- (10)}$$

Solving for the constant coefficient in equating **Error! Reference source not found.** using equation (4), we have:

$$c_1 = c_0 e^{-k_1\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)t} \text{ ---------- (11)}$$

To investigate the effect of temperature and the concentration drug in stomach on the concentration of drug in the bloodstream, we substitute equation **Error! Reference source not found.** into equation (2), which is:

$$\frac{dc_2}{dt} + k_2\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)c_2 = k_1 c_0\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)e^{-k_1\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)t} \text{ ---------- (12)}$$

The homogenous part of equation **Error! Reference source not found.** is:

$$\frac{dc_{2h}}{dt} + k_2\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)c_{2h} = 0 \text{ ---------- (13)}$$

The particular solution of equation (12) can be stated as:

$$c_{2p} = Ae^{-k_1\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)t} \text{ ---------- (14)}$$

We can solve equation (13), using the method of separation of variable, which is:

$$\frac{dc_{2h}}{c_{2h}} = -k_2\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)dt \text{ ---------- (15)}$$

Integrating both sides of equation (15), we have:

$$\int \frac{dc_{2h}}{c_{2h}} = -k_2\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)\int dt \text{ ---------- (16)}$$

Solving equation (16), we have:

$$c_{2h} = B_0 e^{-k_2\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)t} \text{ ---------- (17)}$$

The solution of the particular equation (14) is:

$$c_{2p} = Ae^{-k_1\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)t} \text{ ---------- (18)}$$

where $A = \dfrac{k_1 c_0\left(T_a + \dfrac{Q_m}{\rho_b c_b w_b}\right)}{\left(k_2 - k_1\right)\left(T_a + \dfrac{Q_m}{\rho_b c_b w_b}\right)}$ and $B_0 = \left(\dfrac{k_1 c_0\left(T_a + \dfrac{Q_m}{\rho_b c_b w_b}\right)}{\left(k_1 - k_2\right)\left(T_a + \dfrac{Q_m}{\rho_b c_b w_b}\right)}\right)$

The general solution of equation (12) is the sum of equations (17) and (18), which is:

$$c_2(t) = B_0 e^{-k_2\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)t} + \left(\frac{k_1 c_0\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)}{\left(k_2 - k_1\right)\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)}\right)e^{-k_1\left(T_a + \frac{Q_m}{\rho_b c_b w_b}\right)t} \text{ ---------- (19)}$$

We can solve for the constant coefficient in equation (19) using the initial conditions in equation (4), which gives

$$c_2(t)=\left(\frac{k_1c_0\left(T_a+\frac{Q_m}{\rho_b c_b w_b}\right)}{(k_1-k_2)\left(T_a+\frac{Q_m}{\rho_b c_b w_b}\right)}\right)e^{-k_2\left(T_a+\frac{Q_m}{\rho_b c_b w_b}\right)t}+\left(\frac{k_1c_0\left(T_a+\frac{Q_m}{\rho_b c_b w_b}\right)}{(k_2-k_1)\left(T_a+\frac{Q_m}{\rho_b c_b w_b}\right)}\right)e^{-k_1\left(T_a+\frac{Q_m}{\rho_b c_b w_b}\right)t} \quad \text{----------} \quad (20)$$

The answers in equations (11) and (20) relate to the exponential decay of a medication administered into the stomach as it is taken up by the body and then removed from the circulatory compartment.

3. Results

To show the effect of the parameters, computational simulation was done using Wolfram Mathematica. The graphical results are presented in Figures 2-6 and Tables 1-6 respectively. The parameters' values are as follows: $c_0=50$, $k_1=0.05$, $k_2=0.032$, $Q_m=344$, $\rho_b=1050$, $w_b=15.5$, $c_b=3770$ for varied levels of the arterial temperature given by $T_a=10$ ℃, $T_a=37$ ℃, $T_a=60$ ℃ and $T_a=80$ ℃ and $c_0=50$, $T_a=37$ ℃, $Q_m=344$, $\rho_b=1050$, $w_b=15.5$, $c_b=3770$ for varying rates of medication removal from the circulation provided by $k_1=0.05$ and $k_2=0.032$, $k_1=0.1$ and $k_2=0.12$ and finally $k_1=0.2$ and $k_2=0.22$.

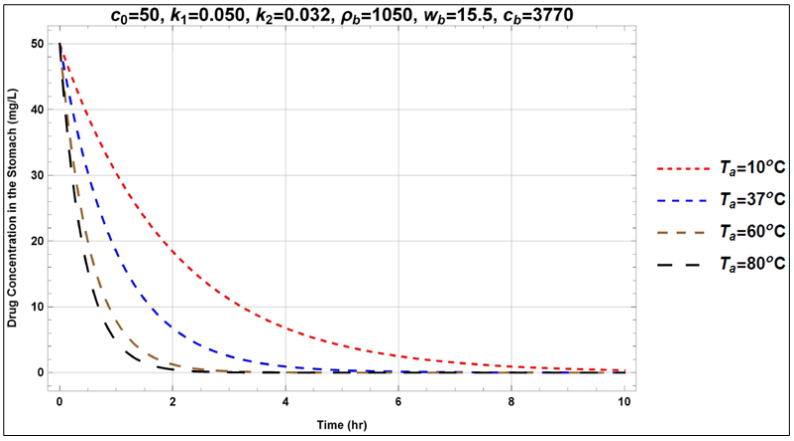

Figure 2 Drug Concentration in Stomach Compartment with parameters $c_0=50$, $k_1=0.05$, $k_2=0.032$, $Q_m=344$, $\rho_b=150$, $w_b=15.5$, $c_b=3770$

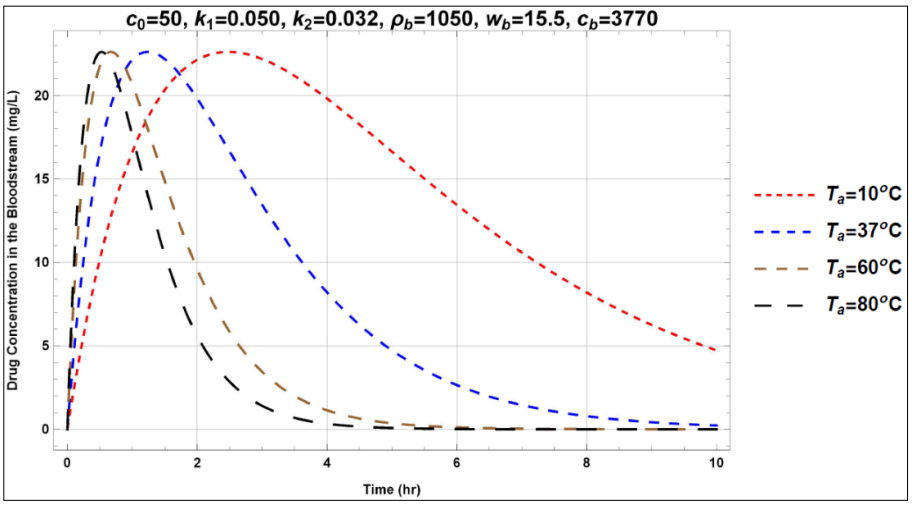

Figure 3 Drug Concentration in Blood Compartment with parameters $c_0=50$, $k_1=0.05$, $k_2=0.032$, $Q_m=344$, $\rho_b=1050$, $w_b=15.5$, $c_b=3770$

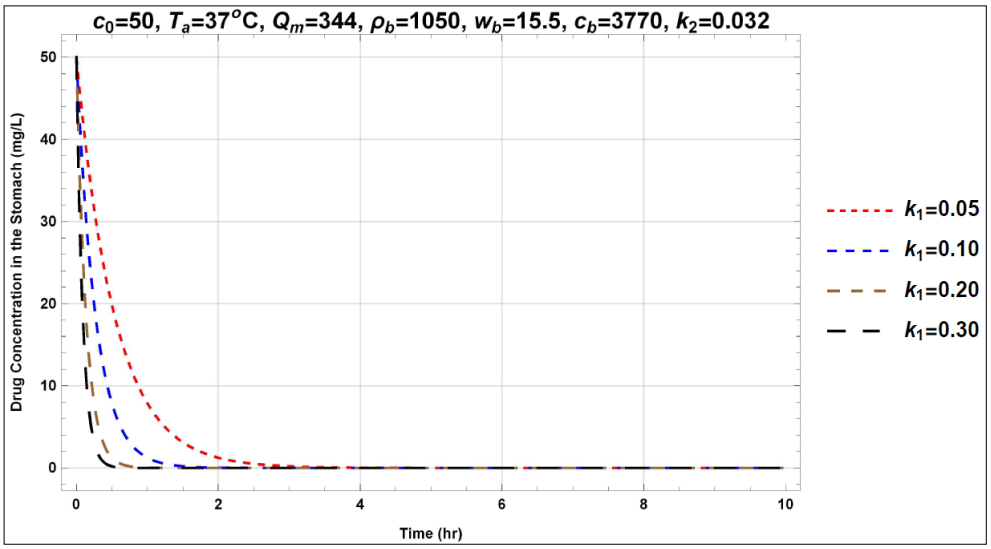

Figure 4 Drug Concentration in Blood Compartment with parameters
$c_0 = 50, T_a = 37^oC, Q_m = 344, \rho_b = 1050, w_b = 15.5, c_b = 3770, k_2 = 0.032$

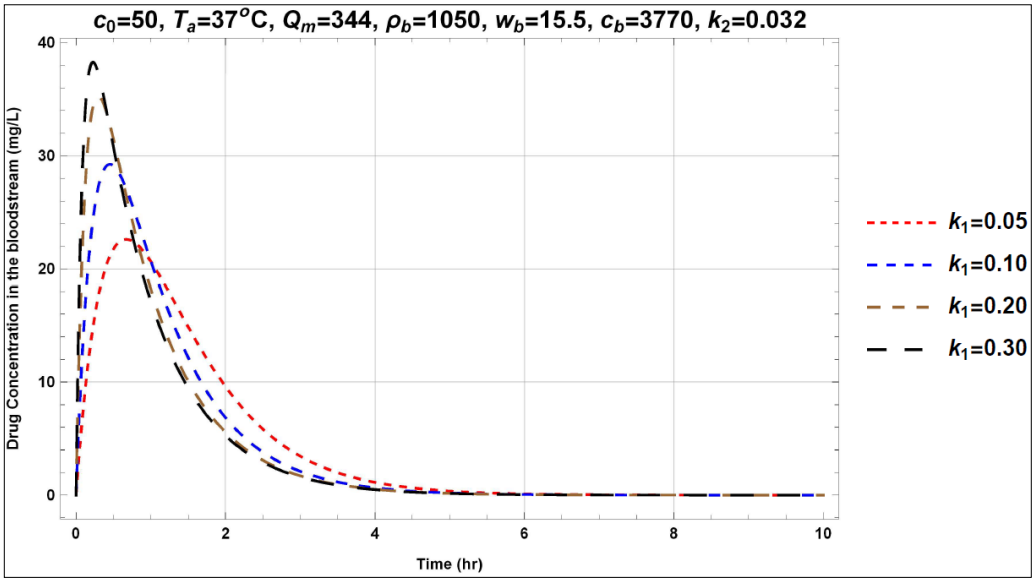

Figure 5 Drug Concentration in Bloodstream Compartment with parameters
$c_0 = 50, T_a = 37^oC, Q_m = 344, \rho_b = 1050, w_b = 15.5, c_b = 3770, k_2 = 0.032$

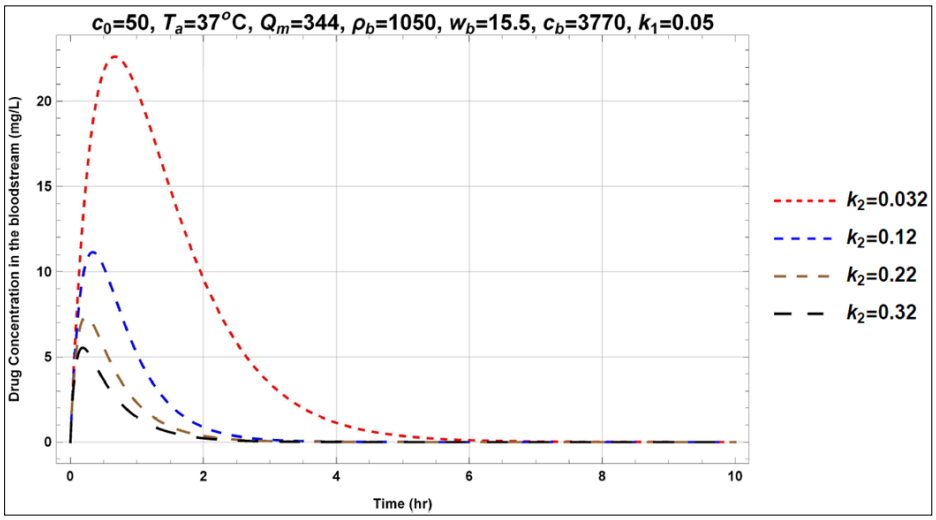

Figure 6 Drug Concentration in Bloodstream Compartment with parameters
$c_0 = 50$, $T_a = 37^oC$, $Q_m = 344$, $\rho_b = 1050$, $w_b = 15.5$, $c_b = 3770$, $k_1 = 0.05$

Table 1 Drug Concentration in Stomach Compartment with parameters
$c_0 = 50$, $k_1 = 0.05$, $k_2 = 0.032$, $\rho_b = 150$, $w_b = 15.5$, $c_b = 3770$

Time(hr)	$T_a = 10$ ℃	$T_a = 37$ ℃	$T_a = 60$ ℃	$T_a = 80$ ℃
0	50.	50.	50.	50.
1	30.3265	18.394	7.86186	4.76845
2	18.394	6.76676	1.23618	0.454763
3	11.1565	2.48935	0.194373	0.0433703
4	6.76675	0.915781	0.0305626	0.00413618
5	4.10424	0.336896	0.00480558	0.000394464
6	2.48935	0.123937	0.000755614	0.0000376192
7	1.50986	0.045594	0.000118809	3.58776 × 10-6
8	0.91578	0.016773	0.0000186813	3.4213 × 10-7
9	0.555448	0.00617046	2.9374 × 10-6	3.26425 × 10-8
10	0.336896	0.00226999	4.61882 × 10-7	3.12162 × 10-9

Table 2 Drug Concentration in Blood Compartment with parameters
$c_0 = 50$, $k_1 = 0.05$, $k_2 = 0.032$, $\rho_b = 1050$, $w_b = 15.5$, $c_b = 3770$

Time(hr)	$T_a = 10$ ℃	$T_a = 37$ ℃	$T_a = 60$ ℃	$T_a = 80$ ℃
0	0.	0.	0.	0.
1	16.6137	22.1407	20.6687	17.6209
2	22.1407	19.8197	9.5756	5.59654
3	22.1893	13.4472	3.44164	1.40404
4	19.8197	8.19293	1.13367	0.327317

5	16.6405	4.72559	0.359595	0.0742004
6	13.4472	2.64095	0.112041	0.0166292
7	10.5918	1.44743	0.0346027	0.00370893
8	8.19292	0.78341	0.0106394	0.000825533
9	6.25357	0.420513	0.00326393	0.000183585
10	4.72558	0.224466	0.00100015	0.0000408124

Table 3 Drug Concentration in Stomach Compartment with parameters $c_0 = 50,\ T_a = 37^oC,\ Q_m = 344,\ \rho_b = 1050,\ w_b = 15.5,\ c_b = 3770,\ k_2 = 0.032$

Time (hr)	$k_1 = 0.050$	$k_1 = 0.10$	$k_1 = 0.20$	$k_1 = 0.30$
0	50.	50.	50.	50.
1	7.86186	1.23617	0.0305626	0.000755611
2	1.23618	0.0305625	0.0000186815	1.11719 × 10-8
3	0.194373	0.000755608	1.13147 × 10-8	- 6.36327 × 10-9
4	0.0305626	0.0000186812	- 1.21996 × 10-10	6.87676 × 10-11
5	0.00480558	4.61624 × 10-7	4.87619 × 10-10	- 4.12259 × 10-10
6	0.000755614	1.14696 × 10-8	7.92946 × 10-10	- 1.21664 × 10-10
7	0.000118809	2.80454 × 10-10	- 8.8306 × 10-12	6.5121 × 10-9
8	0.0000186813	5.76716 × 10-12	4.33319 × 10-11	- 1.12054 × 10-12
9	2.9374 × 10-6	5.03968 × 10-12	- 5.49304 × 10-11	1.45113 × 10-9
10	4.61882 × 10-7	2.50838 × 10-12	- 4.60168 × 10-12	1.60914 × 10-10

Table 4 Drug Concentration in Blood Compartment with parameters
$c_0 = 50,\ T_a = 37^oC,\ Q_m = 344,\ \rho_b = 1050,\ w_b = 15.5,\ c_b = 3770,\ k_2 = 0.032$

Time (hr)	$k_1 = 0.050$	$k_1 = 0.10$	$k_1 = 0.20$	$k_1 = 0.30$
0	0.	0.	0.	0.
1	20.6687	20.6859	18.181	17.1289
2	9.5756	6.8424	5.57544	5.2426
3	3.44164	2.10677	1.70638	1.60451
4	1.13367	0.645095	0.522242	0.491063
5	0.359595	0.19744	0.159833	0.150291
6	0.112041	0.0604272	0.0489173	0.0459968
7	0.0346027	0.0184938	0.0149712	0.0140774
8	0.0106394	0.00566006	0.00458196	0.00430841
9	0.00326393	0.00173227	0.00140232	0.0013186
10	0.00100015	0.000530166	0.00042918	0.00040357

Table 5 Drug Concentration in Stomach Compartment with parameters
$c_0 = 50,\ T_a = 37^oC,\ Q_m = 344,\ \rho_b = 1050,\ w_b = 15.5,\ c_b = 3770,\ k_1 = 0.05$

Time (hr)	$k_2 = 0.032$	$k_2 = 0.034$	$k_2 = 0.036$	$k_2 = 0.038$
0	50.	50.	50.	50.
1	7.86186	7.86186	7.86186	7.86186
2	1.23618	1.23618	1.23618	1.23618
3	0.194373	0.194373	0.194373	0.194373
4	0.0305626	0.0305626	0.0305626	0.0305626
5	0.00480558	0.00480557	0.00480558	0.00480558
6	0.000755614	0.00075561	0.000755613	0.000755614
7	0.000118809	0.00011881	0.000118812	0.000118804
8	0.0000186813	0.0000186801	0.0000186816	0.0000186933
9	2.9374 × 10-6	2.93538 × 10-6	2.9365 × 10-6	2.93205 × 10-6
10	4.61882 × 10-7	4.62894 × 10-7	4.61947 × 10-7	4.57738 × 10-7

Table 6 Drug Concentration in Blood Compartment with parameters
$c_0 = 50,\ T_a = 37^oC,\ Q_m = 344,\ \rho_b = 1050,\ w_b = 15.5,\ c_b = 3770,\ k_1 = 0.05$

Time (hr)	$k_2 = 0.032$	$k_2 = 0.034$	$k_2 = 0.036$	$k_2 = 0.038$
0	0.	0.	0.	0.
1	20.6687	5.19433	2.30802	1.45583
2	9.5756	0.878013	0.36358	0.228921
3	3.44164	0.138779	0.0571684	0.0359949
4	1.13367	0.0218297	0.008989	0.00565974
5	0.359595	0.00343254	0.0014134	0.000889922
6	0.112041	0.000539721	0.000222239	0.000139938
7	0.0346027	0.0000848642	0.0000349447	0.0000220008
8	0.0106394	0.0000133429	5.49869 × 10-6	3.46172 × 10-6
9	0.00326393	2.0967 × 10-6	8.63607 × 10-7	.42973 × 10-7
10	0.00100015	3.30642 × 10-7	1.35726 × 10-7	8.47663 × 10-8

4. Discussion

The plots in Figures 2 and 3, as well as the data in Tables 1 and 2, show that rising temperature parameters result in faster medication absorption from the gastrointestinal compartment to the circulation compartment. The findings also show that when the temperature rises, so does the pace at which the medication is removed from the bloodstream. The distribution rate of the medication across the compartments, on the other hand, reduces with lower values for the temperature parameter. Similarly, the plots in Figures 4 and 5 with the data in Tables 3 and 4 demonstrate a fast distribution and clearance pattern of given medications, which is related to increases in drug diffusion and elimination rates. This means that raising the rates of distribution and elimination will presumably speed up the rate at which medications travel across compartments and eventually leave the body.

5. Conclusion

Based on the computations and simulation results carried out, we conclude that

- As the temperature of the compartments drops, the rate of drug diffusion across the compartments decreases.
- Raising the rate constants for distribution and elimination enhances the rates of drug diffusion between the compartments.
- Lower temperatures cause the drug concentration to take longer to reach a peak in the bloodstream compartment before being removed from the system.
- Drug transporter concentrations in blood, pH, perfusion, body water composition, body fat composition, and, of course, disease conditions can all have an influence on medication distribution. Likewise, the heat generated by the body in which a medicine is administered may affect how fast or slowly that medication diffuses in the body. Some of the aforementioned factors, however, may easily adjust this influence to either increase or decrease the pace of diffusion.

5.1. Definition of Variables and Parameters

- c_1 = Concentration of drug in the stomach.
- c_2 = Concentration of drug in the blood.
- c_0 = Initial drug concentration administered into the body (through oral route).
- k_1 = The rate at which drug is taken from the stomach compartment to the blood compartment.
- k_2 = The rate of drug elimination (clearance) from the body.
- T_a = The temperature of the arterial blood.
- $T = T(t)$ The temperature of the tissue surrounding the drug.
- Q_m = Metabolic heat generated by the cells.
- ρ = Tissue density.
- c_b = Specific heat capacity of the blood.
- ρ_b = Blood density.
- w_b =Heat exchange from the blood to the tissues (known as the blood perfusion rate).
- t_0 = Initial time. The moment the drug is administered into the body.
- t_f = Final time under consideration in the observation.
- MMDARG= Mathematical Modeling and Data Analytic Research Group.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest in this manuscript.

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