World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

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Temperature effect on drug diffusion in the stomach and bloodstream compartments

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World Journal of Biology Pharmacy and Health Sciences, 2023, 13(02), 178–188

Publication history: Received on 02 January 2023; revised on 11February 2023; accepted on 14 February 2023

Article DOI: https://doi.org/10.30574/wjbphs.2023.13.2.0093

Abstract

In this paper, we explain the effect of temperature on the distribution of drugs between the stomach and the bloodstream compartments of the human body. The study demonstrates that the behavior of drug distribution is linked with high or low surrounding temperatures in the compartments (the stomach and bloodstream) under study. In the study, we converted real-world problems into mathematical equations and then solved the resulting remodeled system and the mathematical models found in previous research by introducing a temperature component in an attempt to understand the behavior of a drug administered in the human body over time. The analytical solutions for the drug concentration in the stomach and bloodstream were obtained using separation of variables and variation of parameters techniques of solving ODEs, while the numerical solutions and the graphical results were obtained using Wolfram Mathematica. The results show that as the temperature rises, the drug administered into the system diffuses faster between the compartments and diffuses slower as the temperature falls, which shows the novelty of this research project.

Keywords: Mathematical Models; Pharmacokinetics; Cholesterol; Drug Distribution; Ordinary Differential Equations; Temperature

1. Introduction

The study of drug transportation from one compartment to another, particularly to the target site, is important because it helps optimize therapeutic systems engineering, provides information on the efficacy of new drugs, and can be used to determine the right drug concentration to give a patient. The patient's health, the severity of the disease, and the method of administration—oral or intravenous—may all influence the dosage.

Drugs frequently react to changes in body temperature. The influence that changes in temperature have on intermediary metabolism has been frequently overlooked in recent times. In particular when the medication is administered topically, a growing body of evidence indicates that elevated temperature during normal product wear can significantly disrupt the well-controlled, consistent drug delivery rate. Given the growing use of hypothermia as a therapeutic adjuvant, the possibility that hypothermia can have an effect on drug pharmacokinetics and pharmacodynamics is of significant clinical significance. According to Johansson (2001**),** the conclusion of this paper, which looks at how temperature affects drug diffusion rates, is that it is now time to request the results of a "cold effect test" before a new drug is approved for widespread use, particularly in hypothermic patients. Temperature increases accelerate drug degradation; Because of this, researchers are considering how temperature affects the body's response to drugs. Although many medications cannot be taken orally and must be injected or applied topically to the skin using hypodermic needles, the focus of this study is on medications taken orally; consequently, drug diffusion from the administration site to the target site is an important consideration.

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Khanday *et al*. (2017) conducted an investigation into drug diffusion using a mathematical model. Mathematical modeling for drug diffusion is an effective prediction method for gaining a fundamental understanding of biotransport processes, according to their findings.

In 2001, Johansson discovered a number of connections between colds and drugs. His research showed that drugs can affect a variety of physiological and pharmacological processes and lower body temperature as well as ambient temperature in conjunction with the organism's adaptive capacity. Cremer (1971) investigated the relationship between body temperature and drug effects on neurochemical changes. They thought about how body temperatures and the environment interact.

Hao *et al.* (2016), in their study, "Heat effects on drug delivery across human skin," they found that heat can affect the clinical efficacy and safety of tropical drug production and that elevated temperature can increase transdermal or topical drug delivery. The study demonstrated the significance of developing meaningful in vitro and in vivo methods for studying and evaluating skin-dosing drug products as well as comprehending the effects of heat.

Caldwell *et al*. (2000) looked into the effect that temperature has on vecuronium's pharmacokinetics and pharmacodynamics. They discovered that mild core hypothermia has a duration that is twice as long as normal. The increased duration of vecuronium's action as the core temperature decreases is explained by their findings of decreased clearance and rate of effect.

According to Khanday *et al*. (2017), pharmaceuticals have mathematically simulated the effects of medications on tumor genesis and cholesterol levels in the body in an effort to comprehend how medications behave over time in the human body, as well as Bunonyo *et al*. (2022).

Bunonyo and co. (2022) examined how cholesterol affects drug concentration and transport in the human body. Additionally, the influence of temperature on drug distribution between the gastrointestinal tract and bloodstream must be taken into account. The focus of the study was on how cholesterol affects the rate of drug diffusion in the human body. However, the current objective of this research, the temperature effect on drug diffusion, was not addressed in their study.

2. Material and methods

2.1. Model Formulation

To formulate a mathematical model that represents the absorption and distribution of drugs administered orally into the body via the gastrointestinal tract (stomach) and then into the bloodstream, we consider how the concentrations of the drug in the stomach and bloodstream are influenced by the compartments' environmental temperatures. Meanwhile, for the sake of simplicity, it is assumed that the temperature in each compartment under investigation is the same. See Figure 1 for a diagram of the system.

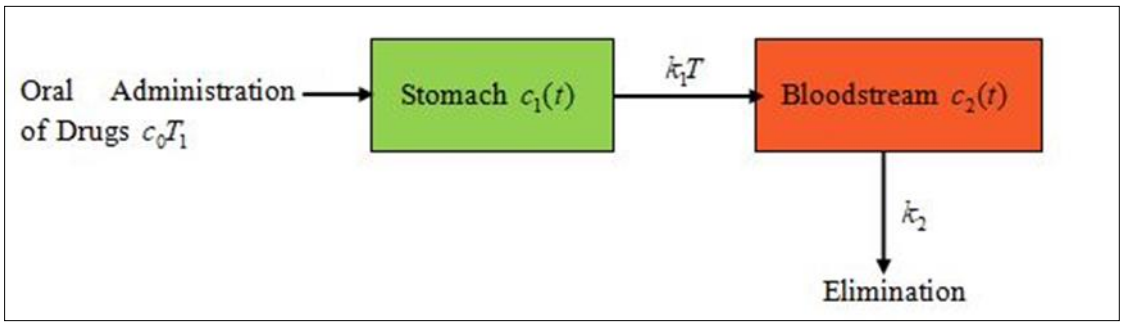

Figure 1 Drug Distribution Process

The first compartment in the preceding figure relates to the stomach or GI tract where initial dosage of the drug with temperature is administered, the second compartment represents the bloodstream compartment where the drug is eliminated from the body with an elimination rate k_2. In the Figure 1, $c_1(t)$ and $c_2(t)$ denote the concentrations of

drug in the stomach and bloodstream compartments respectively, with the c_0 as the initial dosage of drug administered into the stomach. Where $T(t)$ represent the temperature of the compartments.

2.2. Mathematical Models

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

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

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

$$\frac{dT}{dt} = -k_T \left(T - T_s\right) \quad \text{----------} \quad (3)$$

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

$$\left.\begin{aligned} c_1(0) = c_0, c_2(0) = 0 \\ T(0) = T_0 = T_1 \end{aligned}\right\} \quad \text{----------} \quad (4)$$

The third differential equation, which constitutes Newton's law of cooling, has been introduced to determine the effect of temperature on the system. This third equation fits into the model by answering questions such as: "How fast or how slow will an administered drug diffuse between the compartments, given a certain temperature of the compartment where the drug is found and the probably evolving temperature of the drug as it moves between the compartments?"

Newton's law of cooling is a physical law that states that a body's rate of heat loss is directly proportional to the temperature difference between the body and its surroundings. This immediately implies that if the surrounding temperature continues to rise or remains stable at a certain level, the temperature of the drug will also rise or remain stable at that level. The parameters, k_T represents the relative decay constant known as the coefficient of heat transfer, T_0 represents the temperature of the drug when it's introduced into the stomach, T_s represents the temperature of the compartments or the surrounding environments of the drug administered. The variable $T = T(t)$ represents the temperature of the drug in the system at any particular time. In view of the aforementioned system of differential equations in equations (1), (2) and (3) above, we shall solve the system analytically by firstly, solving for the temperature in the third equation in equation (3) as follows:

2.3. Method of Solution

In order to investigate the effect of temperature rise or lose on the drug administered in stomach and bloodstream, we solve equation (3) as follows:

$$\int \frac{dT}{T - T_s} = -k_T \int dt \quad \text{----------} \quad (5)$$

Simplifying equation (5), we have:

$$\log\left(T - T_s\right) = -k_T t + \beta \quad \text{----------} \quad (6)$$

Simplifying equation (6), we have:

$$T - T_s = Ae^{-k_T t} \text{ ---------- (7)}$$

$$T(t) = T_s + Ae^{-k_T t} \text{ ---------- (8)}$$

Solving for the constant coefficient in equation (8) using the initial condition in equation (4), we have the following:

$$T(t) = T_s + \left(T_1 - T_s\right)e^{-k_T t} \text{ ---------- (9)}$$

Substitute equation (9) into equation (1), which is:

$$\frac{dc_1}{dt} = -k_1\left(T_s + \left(T_1 - T_s\right)e^{-k_T t}\right)c_1 \text{ ---------- (10)}$$

Simplifying equation (10), we have:

$$\frac{dc_1}{dt} = \left(-k_1 T_s - k_1\left(T_1 - T_s\right)e^{-k_T t}\right)c_1 \text{ ---------- (11)}$$

Solving equation (11), we have:

$$\frac{dc_1}{c_1} = \left(-k_1 T_s - k_1\left(T_1 - T_s\right)e^{-k_T t}\right)dt \text{ ---------- (12)}$$

$$\log c_1 = \left(-k_1 T_s t + \frac{k_1}{k_T}\left(T_1 - T_s\right)e^{-k_T t}\right) + A \text{ ---------- (13)}$$

$$c_1 = Ae^{\left(-k_1 T_s t + \frac{k_1}{k_T}(T_1 - T_s)e^{-k_T t}\right)} \text{ ---------- (14)}$$

$$A = c_0 e^{-\frac{k_1}{k_T}(T_1 - T_s)} \text{ ---------- (15)}$$

$$c_1\left(t\right) = c_0 e^{-\frac{k_1}{k_T}(T_1 - T_s)} e^{\left(-k_1 T_s t + \frac{k_1}{k_T}(T_1 - T_s)e^{-k_T t}\right)} \text{ ---------- (16)}$$

In order to investigate the effect of temperature on the drug concentration in the bloodstream, we shall substitute equation (16) into equation (2), which is:

$$\frac{dc_2}{dt} + k_2 c_2 = k_1 c_0 e^{-\frac{k_1}{k_T}(T_1 - T_s)} e^{\left(-k_1 T_s t + \frac{k_1}{k_T}(T_1 - T_s)e^{-k_T t}\right)}\left(T_s + \left(T_1 - T_s\right)e^{-k_T t}\right) \text{ ---------- (17)}$$

Simplifying equation (17), we obtained:

$$\frac{dc_2}{dt} + k_2 c_2 = k_1 c_0 e^{-\frac{k_1}{k_T}(T_1 - T_s)} T_s e^{\left(-k_1 T_s t + \frac{k_1}{k_T}(T_1 - T_s)e^{-k_T t}\right)} + k_1 c_0 e^{-\frac{k_1}{k_T}(T_1 - T_s)}\left(T_1 - T_s\right)e^{\left(-(k_1 T_s + k_T)t + \frac{k_1}{k_T}(T_1 - T_s)e^{-k_T t}\right)} \text{ -- (18)}$$

Simplifying equation (18), we obtained:

$$\frac{dc_2}{dt}+k_2c_2=k_1c_0e^{-\frac{k_1}{k_T}(T_1-T_s)}T_se^{\left(-k_1T_st+\frac{k_1}{k_T}(T_1-T_s)e^{-k_Tt}\right)}+k_1c_0e^{-\frac{k_1}{k_T}(T_1-T_s)}\left(T_1-T_s\right)e^{\left(-(k_1T_s+k_T)t+\frac{k_1}{k_T}(T_1-T_s)e^{-k_Tt}\right)} \quad \text{-- (18)}$$

By expansion of equation (18), we obtained:

$$e^{\left(-k_1T_st+\frac{k_1}{k_T}(T_1-T_s)e^{-k_Tt}\right)}=e^{\frac{k_1}{k_T}(T_1-T_s)}-T_1k_1e^{\frac{k_1}{k_T}(T_1-T_s)}t+\frac{1}{2}e^{\frac{k_1}{k_T}(T_1-T_s)}\left(k_1^2T_1^2+k_1k_T\left(T_1-T_s\right)\right)t^2+\ldots \quad \text{-------- (19)}$$

Simplifying equation (19), we obtained:

$$e^{\left(-(k_1T_s+k_T)t+\frac{k_1}{k_T}(T_1-T_s)e^{-k_Tt}\right)}=e^{\frac{k_1}{k_T}(T_1-T_s)}-\left(k_T+T_1k_1\right)e^{\frac{k_1}{k_T}(T_1-T_s)}t+\frac{1}{2}e^{\frac{k_1}{k_T}(T_1-T_s)}\left(\left(-k_T-k_1T_1\right)^2+k_1k_T\left(T_1-T_s\right)\right)t^2+\ldots$$

---------- (20)

Substituting equation (20) into equation (18), we obtained:

$$\frac{dc_2}{dt}+k_2c_2=\begin{bmatrix}k_1c_0e^{-\frac{k_1}{k_T}(T_1-T_s)}T_s\left(e^{\frac{k_1}{k_T}(T_1-T_s)}-T_1k_1e^{\frac{k_1}{k_T}(T_1-T_s)}t+\frac{1}{2}e^{\frac{k_1}{k_T}(T_1-T_s)}\left(k_1^2T_1^2+k_1k_T\left(T_1-T_s\right)\right)t^2\right)\\+k_1c_0e^{-\frac{k_1}{k_T}(T_1-T_s)}\left(T_1-T_s\right)\left(e^{\frac{k_1}{k_T}(T_1-T_s)}-\left(k_T+T_1k_1\right)e^{\frac{k_1}{k_T}(T_1-T_s)}t+\frac{1}{2}e^{\frac{k_1}{k_T}(T_1-T_s)}\left(\left(-k_T-k_1T_1\right)^2+k_1k_T\left(T_1-T_s\right)\right)t^2\right)\end{bmatrix}$$

---------- ------- (21)

Further simplification of equation (21) gives:

$$\frac{dc_2}{dt}+k_2c_2=\left[\left(\begin{matrix}\left(k_1c_0\left(T_1-T_s\right)+k_1c_0T_s\right)-\left(\left(k_T+T_1k_1\right)\left(T_1-T_s\right)k_1c_0+k_1c_0T_sT_1k_1\right)t\\+\frac{1}{2}k_1c_0\left[\left(T_1-T_s\right)\left(\left(-k_T-k_1T_1\right)^2+k_1k_T\left(T_1-T_s\right)\right)+T_s\left(k_1^2T_1^2+k_1k_T\left(T_1-T_s\right)\right)\right]t^2\end{matrix}\right)\right]$$

---------- (22)

The particular solution of equation (22) gives:

$$c_{2p}=A_0+A_1t+A_2t^2 \quad \text{---------- (23)}$$

The homogenous solution of equation (22) is:

$$c_{2h}\left(t\right)=B_0e^{-k_2t} \quad \text{---------- (24)}$$

The general solution of equation (21) is the sum of equations (23) and (24), which are:

$$c_2\left(t\right)=B_0e^{-k_2t}+A_0+A_1t+A_2t^2 \quad \text{---------- (25)}$$

where the coefficients in equation (25) are seen at the appendix.

Solving for the constant coefficient in equation (25) using the initial condition in equation (4), the general solution is:

$$c_2\left(t\right)=A_0\left(1-e^{-k_2t}\right)+A_1t+A_2t^2 \quad \text{---------- (26)}$$

3. Results

Simulation was performed using Wolfram Mathematica, to demonstrate the influence of the pertinent parameters. The values of the parameters are given as follows: $c_0 = 50$, $T_1 = 10$ ℃, $k_1 = 0.05$, $k_2 = 0.72$, $k_T = 0.693$, $t_0 = 0$ and $t_f = 10$ for different levels of the surrounding temperatures $T_s = 20$ ℃, $T_s = 30$ ℃, $T_s = 40$ ℃ and $T_s = 60$ ℃, $c_0 = 50$, $T_1 = 10$ ℃, $T_s = 20$ ℃, $k_1 = 0.052$, for different rates of drug elimination from the bloodstream given by $k_2 = 0.05$, $k_2 = 0.1$, $k_2 = 0.15$ and $k_2 = 0.2$.

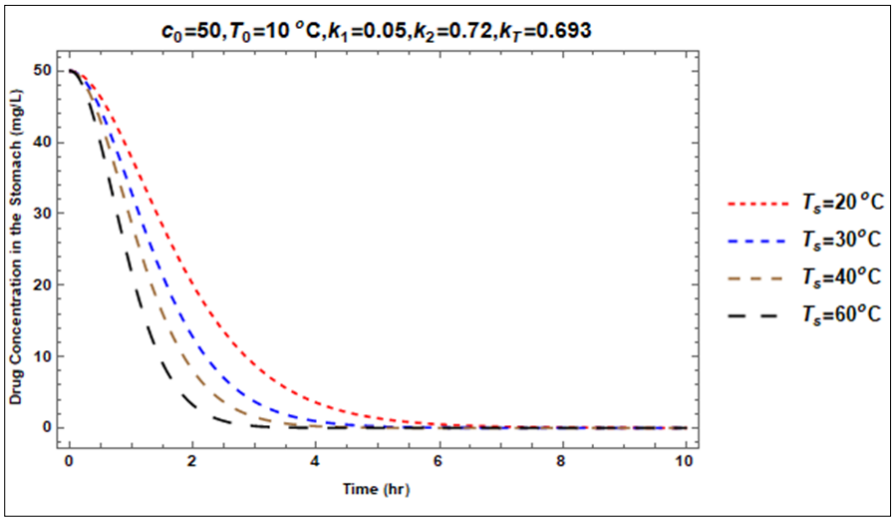

Figure 2 Drug Concentration in Stomach Compartment with parameters $c_0 = 50$, $T_1 = 10$ ℃, $k_1 = 0.05$, $k_2 = 0.72$, $k_T = 0.693$

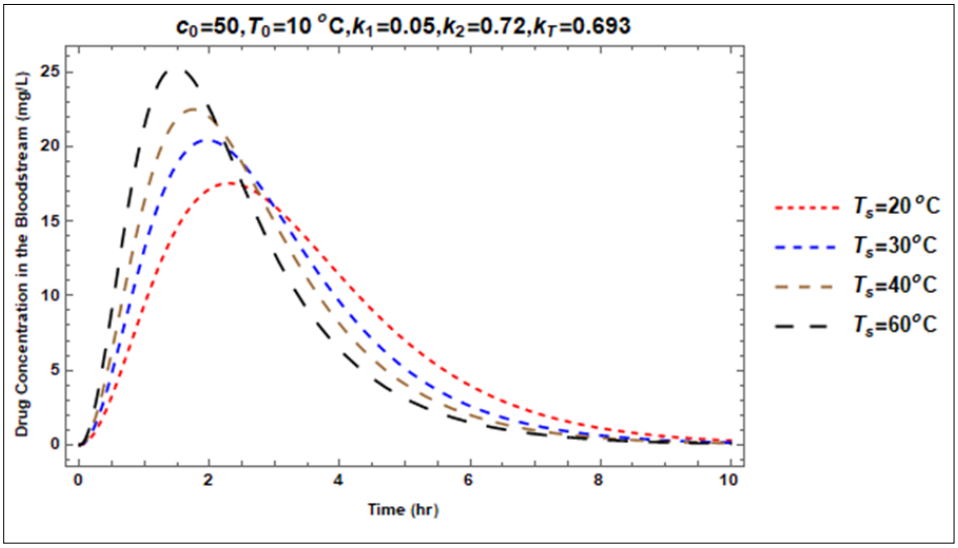

Figure 3 Drug Concentration in Blood Compartment with parameters $c_0 = 50$, $T_1 = 10$ ℃, $k_1 = 0.05$, $k_2 = 0.72$, $k_T = 0.693$

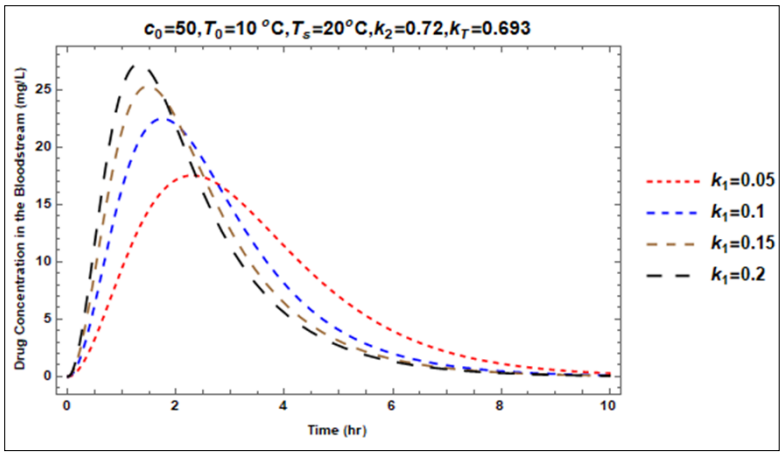

Figure 4 Drug Concentration in Blood Compartment with parameters $c_0 = 50$, $T_1 = 10$ ℃, $T_s = 20$ ℃, $k_2 = 0.72$, $k_T = 0.693$

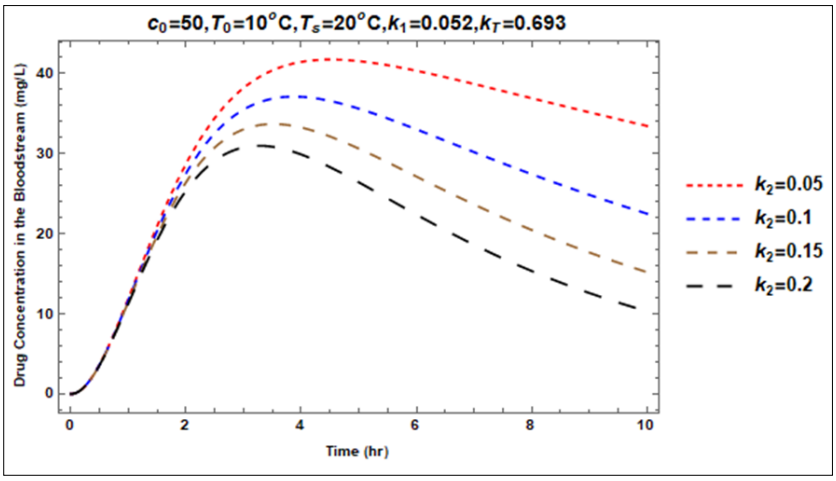

Figure 5 Drug Concentration in Blood Compartment with parameters $c_0 = 50$, $T_1 = 10$ ℃, $T_s = 20$ ℃, $k_1 = 0.052$, $k_T = 0.693$

Table 1 Drug Concentration in Stomach Compartment with parameters $c_0 = 50$, $T_1 = 10$ ℃, $k_1 = 0.05$, $k_2 = 0.72$, $k_T = 0.693$

Time(hr)	$T_s = 20$ ℃	$T_s = 30$ ℃	$T_s = 40$ ℃	$T_s = 60$ ℃
0	50.	50.	50.	50.
1	26.383	22.9523	19.9677	15.1123
2	11.6243	7.34609	4.64244	1.85407
3	4.67999	1.96319	0.823528	0.144914
4	1.80111	0.479402	0.127602	0.00904018
5	0.677707	0.111905	0.0184781	0.000503815
6	0.252142	0.0255391	0.00258682	0.0000265398
7	0.0932829	0.0057632	0.000356062	1.3575 × 10-6
8	0.0344138	0.00129322	0.0000485969	6.78783 × 10-8
9	0.012678	0.00028937	6.60474 × 10-6	2.23424 × 10-9
10	0.00466727	0.0000646585	8.96064 × 10-7	2.79213 × 10-11

Table 2 Drug Concentration in Blood Compartment with parameters $c_0 = 50$, $T_1 = 10$ ℃, $k_1 = 0.05$, $k_2 = 0.72$, $k_T = 0.693$

Time(hr)	$T_s = 20$ ℃	$T_s = 30$ ℃	$T_s = 40$ ℃	$T_s = 60$ ℃
0	0.	0.	0.	0.
1	16.5856	19.1265	21.293	24.701
2	18.183	19.8442	20.5446	20.5505
3	13.5586	13.2282	12.4767	11.0663
4	8.54213	7.41468	6.51953	5.46989
5	4.91412	3.84985	3.24304	2.66768
6	2.6781	1.93039	1.58867	1.29879
7	1.41033	0.952539	0.774709	0.632203
8	0.726028	0.466569	0.377287	0.307727
9	0.367996	0.227759	0.183672	0.149787
10	0.184504	0.111009	0.0894063	0.0729092

Table 3 Drug Concentration in Blood Compartment with parameters $c_0 = 50$, $T_1 = 10$ ℃, $T_s = 20$ ℃, $k_2 = 0.72$, $k_T = 0.693$

Time(hr)	$k_1 = 0.05$	$k_1 = 0.10$	$k_1 = 0.15$	$k_1 = 0.20$
0	0.	0.	0.	0.
1	16.5856	24.4119	27.8558	29.1544
2	18.183	19.2136	17.7639	16.4407
3	13.5586	10.8101	9.00775	8.08672
4	8.54213	5.50039	4.40812	3.93843
5	4.91412	2.71281	2.14701	1.91709
6	2.6781	1.3255	1.04513	0.933148
7	1.41033	0.645888	0.508724	0.454212
8	0.726028	0.314483	0.247623	0.221088
9	0.367996	0.153088	0.120531	0.107615
10	0.184504	0.0745179	0.0586687	0.052382

Table 4 Drug Concentration in Blood Compartment with parameters $c_0 = 50$, $T_1 = 10$ ℃, $T_s = 20$ ℃, $k_1 = 0.052$, $k_T = 0.693$

Time(hr)	$k_2 = 0.05$	$k_2 = 0.10$	$k_2 = 0.15$	$k_2 = 0.20$
0	0.	0.	0.	0.
1	23.6596	23.0568	22.474	21.9103
2	36.8532	34.82	32.924	31.1551
3	41.5758	37.8444	34.5003	31.5005
4	42.1519	36.7734	32.1541	28.1813

5	41.0737	34.2237	28.5983	23.9701
6	39.4265	31.3128	24.9509	19.9517
7	37.6314	28.4571	21.596	16.4523
8	35.8416	25.7932	18.6308	13.5117
9	34.1097	23.3543	16.0509	11.0773
10	32.4519	21.1374	13.8205	9.07454

4. Discussion

Figures 2 and 3, and then the results in Tables 1 and 2, reveal rapid absorption of the drug from the stomach compartment to the bloodstream compartment with increasing values for the temperature parameters. The results also reveal that as the surrounding temperature increases, so does the rate at which the drug is eliminated from the bloodstream. On the other hand, the distribution of the drug between the compartments decreases with lowered or reduced values for the surrounding temperature.

Similarly, the plots in Figure 4 and Figure 5 with the results in Table 3 and Table 4 show a rapid distribution and elimination pattern of administered drugs associated with increases in the diffusion and elimination rates of the drugs. This implies that increasing the rates of distribution and elimination will likely increase the pace at which drugs move between the compartments and then fizzle out of the body.

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 or intravenous route).
- k_1 = The rate at which drug is taken from the stomach compartment to the blood compartment.
- k_T = The relative temperature decay constant known as the coefficient of heat transfer.
- k_2 = The rate of drug elimination (clearance) from the body.
- T_1 = The initial temperature when the drug is administered into the stomach.
- T_s = The temperature of the compartments or the surrounding environments of the drug administered.
- $T = T(t)$ The temperature of the drug in the system at any particular time.
- 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

where

$$A_0 = \frac{\left(k_1 c_0 \left(T_1 - T_s\right) + k_1 c_0 T_s\right)}{k_2} + \left(\begin{array}{l} \frac{\left(\left(k_T + T_1 k_1\right)\left(T_1 - T_s\right) k_1 c_0 + k_1 c_0 T_s T_1 k_1\right)}{k_2^2} + \\ \frac{k_1 c_0}{k_2^3}\left[\left(T_1 - T_s\right)\left(\left(-k_T - k_1 T_1\right)^2 + k_1 k_T \left(T_1 - T_s\right)\right) + T_s\left(k_1^2 T_1^2 + k_1 k_T \left(T_1 - T_s\right)\right)\right] \end{array} \right)$$

$$A_1 = -\left(\begin{array}{l} \frac{\left(\left(k_T + T_1 k_1\right)\left(T_1 - T_s\right) k_1 c_0 + k_1 c_0 T_s T_1 k_1\right)}{k_2} + \\ \frac{k_1 c_0}{k_2^2}\left[\left(T_1 - T_s\right)\left(\left(-k_T - k_1 T_1\right)^2 + k_1 k_T \left(T_1 - T_s\right)\right) + T_s\left(k_1^2 T_1^2 + k_1 k_T \left(T_1 - T_s\right)\right)\right] \end{array} \right)$$

$$A_2 = \frac{1}{2}\frac{k_1 c_0}{k_2}\left[\left(T_1 - T_s\right)\left(\left(-k_T - k_1 T_1\right)^2 + k_1 k_T \left(T_1 - T_s\right)\right) + T_s\left(k_1^2 T_1^2 + k_1 k_T \left(T_1 - T_s\right)\right)\right]$$

$$B_0 = \frac{k_1 c_0}{k_2^2}\left[\left(T_s k_T - T_1 k_T - k_1 T_1^2\right) - \frac{1}{k_2}\left(\left(k_1^2 T_1^2 T_s + k_1 T_s k_T\left(T_1 - T_s\right) + \left(T_1 - T_s\right)\left(\left(-k_T - k_1 T_1\right)^2 + k_1 k_T\left(T_1 - T_s\right)\right)\right) - k_2 T_1\right]$$

5. Conclusion

Based on the formulation and simulation findings, we conclude that

- Low temperatures (environmental or surrounding temperatures) in the compartments reduce the rate of drug diffusion between the compartments.
- Several factors can influence drug distribution, including the concentration of drug transporters in blood, pH, perfusion, body water composition, body fat composition, and most certainly disease conditions (e.g., volume depletion, burns, third spacing). Meanwhile, the surrounding temperature at which a drug is found in the body can also affect how fast or slowly such a drug diffuses from that environment. This effect can be easily altered by some of the aforementioned factors to either increase or reduce the rate of distribution.
- With lower temperature levels, it's observed that the drug concentration takes longer to reach the peak in the blood compartment before being eliminated from the system.
- Also, increasing the rates of distribution and elimination increased the diffusion kinetics of the drug between the compartments.

Compliance with ethical standards

Acknowledgments

The authors would like to acknowledge the motivation and encouragement from Dr. Mrs. U. C. Amadi and Mr. Odiabara Barnabas in ensuring that this research becomes a reality. We are grateful!

Disclosure of conflict of interest

There is no conflict of interest in this manuscript.

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