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Mathematical Model for the Oral Intake of Artemether Drugs Through Gastrointestinal Tract and Bloodstream as Compartments

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Abstract

Malaria remains one of the leading causes of morbidity and mortality across Africa, particularly in Nigeria, where it continues to constitute a major public health challenge despite sustained control efforts. Consequently, optimizing antimalarial drug therapy remains a critical priority. Artemether is one of the most widely prescribed artemisinin-based antimalarial drugs for the treatment of uncomplicated malaria due to its rapid therapeutic action. Following oral administration, Artemether is absorbed through the gastrointestinal tract, enters the systemic circulation, undergoes metabolism, is distributed to body tissues, and is eventually eliminated from the body. In this study, the pharmacokinetic processes of Artemether, namely absorption, metabolism, distribution, and elimination (ADME), were represented using a simplified two-compartment model consisting of the gastrointestinal tract and bloodstream compartments. A system of linear ordinary differential equations describing the transfer of the drug between these compartments was formulated to characterize the temporal variation in drug concentration. The resulting mathematical model was solved analytically using the Laplace transformation technique to obtain explicit expressions for drug concentration profiles in both compartments. Numerical simulations of the analytical solutions were performed using MATLAB R2018b to investigate the pharmacokinetic behaviour of Artemether over time. Simulation results demonstrate that the concentration of Artemether in both the gastrointestinal tract and bloodstream is directly proportional to the absorption rate constants governing drug transfer between the compartments. Conversely, drug concentration decreases progressively with increasing time, reflecting the combined effects of distribution, metabolism, and elimination. The developed model provides a simple yet effective mathematical framework for describing Artemether pharmacokinetics and offers a useful foundation for pharmacokinetic analysis, dosage optimization, and future studies involving more complex multicompartment drug delivery systems.

Keywords

Laplace Transform;
Eigenvalue method;
Drug concentration;
Malaria;
Artemether;
MATLAB simulation

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1. Introduction

Drugs are substances that providers a therapeutic medication for certain ailment, drugs are sometimes classified as; Depressants drugs slow down the function of the central nervous system in the body, Stimulants drugs increases the speed function of the nervous system, Opioids (sometimes called Narcotics) drugs are pain relievers, Hallucinogens drugs distorts a patient's feeling, some drugs are categorized as inhalants to create an immediate balance, Dissociative drugs inhibit pain by disconnecting the brain's feeling about pain while Image enhancing drugs alter a patient's physical appearance. Drugs are produced chemically or naturally (depending on the ailment). Production of drugs involves series of pharmaceutical processes ranging from research and development of the drug to final or continuous manufacturing of the drug.

Malaria on the other hand, is a disease caused by an infected female anopheles' mosquito. The mosquito carries the parasite to human through bite. The major parasites species of malaria is the plasmodium Falciparum and plasmodium Vivax and Plasmodium falciparum is of greatest risk to non-immune humans (Philip *et al.*, 2017, Duffy & Patrick, 2020 and Miller *et al.*, 2013). Plasmodium falciparum parasites accounts for 80% of cases and 90% of deaths and malaria is one of the major causes of morbidity and mortality, it ranks alongside with acute respiratory infections, measles and diarrhea diseases as a major cause of mortality worldwide (Adams *et al.*, 2013). The symptoms in an infected human include bouts of fever, headache, vomiting flu-like, anemia (destroying red blood cell) and malaria can kill by clogging the capillaries that carry blood to the brain (cerebral malaria) or other vital organs. On the average, the incubation period of Plasmodium falciparum is about 12 days in humans.

Malaria can be prevented and treated. The most effective treatment available for malaria is the Artemisinin-based therapy in Combination Treatment (ACT). There are four therapies for Plasmodium falciparum infections acquired in chloroquine-resistant areas. Artemether-lumefantrine (Coartem), which is the recommended combination if available and atovaquoneproguanil MalaroneTM are fixed dose combination medicines for young children weighing less than 5 kg (Ashley *et al.*, 2014 and Taylor *et al.*, 2015). Quinine sulfate in combination with doxycycline, tetracycline, or clindamycin, is another therapy option. Quinine sulfate plus whether doxycycline or tetracycline is often chosen over quinine sulfate plus clindamycin because there is more data on the effectiveness of quinine sulfate plus doxycycline or tetracycline (Hwang *et al.*, 2011, Rehman *et al.*, 2014 and Taylor *et al.*, 2015).

Artemether is an antimalarial medication used to treat uncomplicated acute malaria (Derbie *et al.*, 2020). It is mostly administered together with lumefantrine to increase efficacy of the drugs (Patil *et al.*, 2020). Its molecular formula is C_{16} H_{26} O_5 and molecular weight is 298.37g/mol. It has a melting point of 86 – 90^{0}C. Artemether is soluble in solvents like ethanol, dimethyl formamide (DMF) and insoluble in water (Swapnil *et al.*, 2024). It is white crystalline power in appearance with bitter taste. The injectable dosage is 3.2mg/kg at first followed by 1.6mg/kg daily for 7 days before changing to oral administration and Capsule formulation: 160 mg the first day, then 80 mg per day for the next four days (Swapnil *et al.*, 2024). Artemether When administered orally, Artemether absorbs quickly, reaching its maximum concentration within 2hours and undergoing extensive first pass metabolism (Ezeani, 2020).

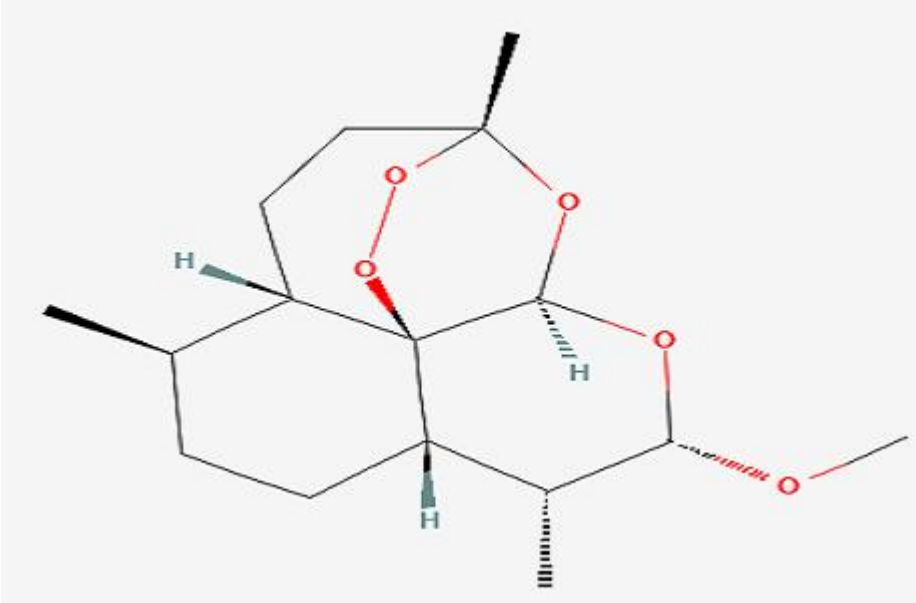

Figure 1: Structure of Artemether by Swapnil *et al.*, (2024).

Drugs administration deals with the method through which a given drugs are received in a patient's body. Administration of drugs is generally classified into three major routes; Enteral Routes: This involve absorptions through gastrointestinal tracts method such as oral swallow of drugs, sublingual method like dissolving the drugs under the tongue absorption is done directly through the capillaries into the blood stream, Buccal method involves placing the drug between the chick and the gum and Rectal method involves inserting the drug into the rectum. Parenteral Routes:

These routes are more effective due to the fact that it bypasses the digestive system and the dosage administered is more précised. The methods under this route are; Intravenous method – use of injection in the vein, Intramuscular – injection in the muscles, subcutaneous – injection in the fatty skin layer, Intrathecal – drugs are injected around the spinal cord. Local Application/Inhalation Routes: these are drugs that are administered by applying it locally to the affected area or inhalation by mucus membrane. This routes ranges from; topical – application is done on the skin, Nasal – dropping of drugs in the nostrils, Ocular – use of eye drops and Vagina – inserting drugs in the vagina.

The pharmacokinetics of Artemether drugs entails the interaction of the drugs with the body; it starts with its administration which is either oral intake (tablets or syrups that is absorbed by the body through gastrointestinal tract - enteral) or deep intramuscular (this involves the use of injection - parenteral). For gastrointestinal tract, the drugs dissolves in the stomach and major absorption is done in the small intestine through intestinal walls. This process is followed by metabolism and distribution. For intramuscular injection, the only solution is administered at the anterior thigh (buttock) and then released into the systemic circulation. It is then metabolized into its primary active metabolite, dihydroartemisinin (DHA).

The interaction of malaria drugs with the body (where the therapeutic effect is been carried out) has been of great concern in pharmacokinetics, in terms of require volume, its concentration in the blood, absorption rate and clearance from the body. One of the major biological compartments is the Gastrointestinal Tract (GI) and the blood stream. Khanday and Rafiq (2015) describes drugs diffusion as the process where a drug is consumed orally, it dissolves and released into the gastrointestinal tract, then to the blood and the blood will transport it the therapeutic site, finally, the medication is eliminated from the blood through the liver and the kidney. Many researches have been carried out to understand the dynamics of drug, starting from oral administration, absorption and clearance and a mathematical model is one of the approaches adopted.

Mathematical model is a tool that plays a vital role in the field of pharmacokinetics, pharmacodynamics of drugs due to its predictive, estimation and descriptive nature. Many researchers have developed mathematical models to gain more knowledge on the dynamics of drugs administration. Although the mathematical modeling is theoretical in nature; however, the results established lead to realistic outcome once compared and verified empirically. In the absence of experiments, a good number of mathematical models and numerical simulations were carried out with efficiency up to large extent.

Hrydziuszko *et al.,* (2014) investigated a mathematical two-compartment model of human Cholesterol diagnosis and Treatment. In their work, the developed a simultaneous linear differential equation and the solution yields the change over time in the liver and bloodstream. El-Kareh and Secomb (2000) focused a Mathematical Model for Comparison of Bolus Injection, Continuous infusion, and Liposomal Delivery of Donoxorubicin to Tumor Cell. Their result show that continuous infusion for optimal duration is superior to the other protocol and thermo-sensitive liposomes indicates a potential advantage at some doses.

Again, Abd-el-Malek *et al.,* (2002) focused on group theoretic approach for solving the problem of diffusion of a drug through a thin membrane. They developed a partial differential equation with boundary and initial condition and transform it to ordinary differential equation and it was solved numerically using shooting method. Khanday and Najar (2015) established the mathematical models on oxygen transport in biological tissues through capillary bed using both analytical and numerical methods.

Furthermore, Khanday *et al.,* (2016) focused on Mathematical Model for drug diffusion through the compartments of blood and tissue. Three models containing different linear ordinary differential equation each was form and solved using Laplace Transformation and eigenvalue method and it has been observed from the simulation result that the drug concentration decreases in the first compartment and gradually increases in other compartments.

However, Bunonyo *et al.,* (2023) investigated on Mathematical Modeling of Alcohol-Drug Concentration in the Bloodstream and in their research work, they form two compartments to represent the human body and blood stream, they solve the system of linear ordinary differential equation using Laplace transform method and the numerical result reveals that the various rate constants, dosage

increase and the volumetric increase have impact and showed a corresponding effect on the drug concentration in the bloodstream.

In this study, we shall extend the research work done by Bunonyo *et al.*, (2023) and focus on the mechanism of Artemether drugs through the gastrointestinal tract and blood stream as compartments, and we shall also consider the fraction of Artemether drugs that fail to be absorbed in the GI tract due to some factors like; poor dissolving of the drug particle that cannot pass the intestine walls, presence of low-fats and bile salts, low dissolution of some tablets and presence of P-glycoprotein.

2. Material and methods

We begin by compartmentalizing the entire human part that involves the drug before it gets to its therapeutic site. Let $C_1(t)$ be the concentration of drugs in the gastrointestinal tract after orally administered at time t and $C_2(t)$ denotes the concentration of drug in the blood stream at time t. Based on the law of conservation of mass (also known as the Balance Law), the change in the concentration is given by;

$$\frac{dC}{dt} = \text{Drug input rate} - \text{Drug output rate}$$

In formulating the model for the dynamics of artemether in the gastrointestinal tract and bloodstream, we assume that artemether diffuse from the gastrointestinal tract to the bloodstream compartment, that there could be an influence of the inter-compartmental distribution rate constants on the diffusion in the bloodstream compartment, that excretion of a fraction artemether drug in the body is possible only in the gastrointestinal tract, and the change in volumetric and dosage could influence the artemether concentration in the bloodstream. The schematic diagram for the mechanism of artemether drug through gastrointestinal tract and blood stream is given in figure 2 below;

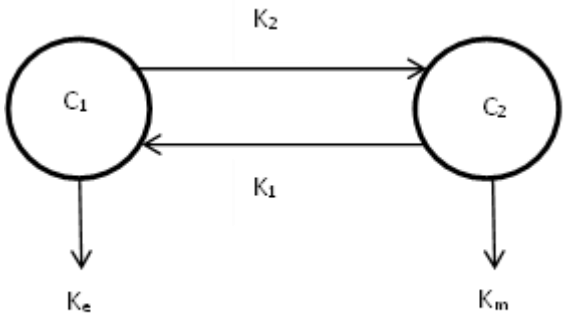

Figure 2: Diagram Showing the Concentration of Artemether Drugs in the Gastrointestinal Tract and Blood Stream

The differential equation that governs the dynamics of drug concentration in the body through gastrointestinal tract is given by

$$\frac{dC_1}{dt} = k_1 C_2 - (k_2 + k_e) C_1 \tag{1}$$

$$\frac{dC_2}{dt} = k_2 C_1 - (k_1 + k_m) C_2 \tag{2}$$

$k_1, k_2 > k_e$, $k_1, k_2 > k_m$, $k_m > k_e$ and $k_1 > k_2$

The term $k_1 C_2$, is the concentration of Artemether drug in the bloodstream that returns to the GI tract, and the term $k_2 C_1$ is the concentration of Artemether drug that is absorbed in the bloodstream, $k_e C_1$ is the concentration of Artemether drug that is excreted out of the body through the feces and finally, the term $k_m C_2$ is the concentration of Artemether drug that is eliminated from the bloodstream (venous blood) due to the impact of the liver and kidney. where k_1 and k_2 are compartmental distribution rates, k_e is the rate at which some fraction of Artemether drug fail to be absorbed in the (may be as a result of poor aqueous solubility of the drug, instability in the GI tract or low dissolving rate of the drug before absorption) gastrointestinal tract and k_m is the clearance rate of the drugs from the blood stream. Equation (1) – (2) is subjected to the initial condition;

$$\left.\begin{aligned} C_1(0) &= \frac{V}{D} \\ C_2(0) &= 0 \end{aligned}\right\} \tag{3}$$

Where V is the volume of Artemether in both compartments and D is the dosage of the drug in both compartments

2.1 Analysis

In this section, we carried out analysis using the Laplace transformation Method. We define Laplace transformation as;

$$L\{C_1(t)\} = C_1(s) = \int_0^\infty e^{-st} C_1(t) dt \tag{4}$$

$$L\{C_2(t)\} = C_2(s) = \int_0^\infty e^{-st} C_2(t)dt \tag{5}$$

Taking the Laplace of Equation (1) and (2), that is

$$L\left\{\frac{dC_1}{dt}\right\} = k_1 L\{C_2\} - (k_2 + k_e)L\{C_1\} \tag{6}$$

$$L\left\{\frac{dC_2}{dt}\right\} = k_2 L\{C_1\} - (k_1 + k_m)L\{C_2\} \tag{7}$$

From equation (6), we get,

$$sC_1(s) - C_1(0) = k_1 C_2(s) - k_2 C_1(s) - k_e C_1(s) \tag{8}$$

Equation (8) can be simplified as;

$$C_1(s) = \frac{k_1 C_2(s)}{(s + k_2 + k_e)} + \frac{D}{V(s + k_2 + k_e)} \tag{9}$$

Similarly, from equation (7), we get;

$$sC_2(s) - C_2(0) = k_2 C_1(s) - k_1 C_2(s) - k_m C_2(s) \tag{10}$$

We also simplify equation (10) as

$$C_2(s) = \frac{k_2 C_1(s)}{(s + k_1 + k_m)} \tag{11}$$

Substituting equation (11) in equation (9) and solving for $C_1(s)$ we get;

$$C_1(s) = \frac{D(s + k_1 + k_m)}{V[(s + k_\alpha)(s + k_1 + k_m) - k_1 k_2]} = \frac{D(s + k_1 + k_m)}{s^2 + (k_\alpha + k_1 + k_m)s + k_\beta} \tag{12}$$

Where $k_\alpha = k_2 + k_e$ and where $k_\beta = k_\alpha(k_1 + k_m) - k_1 k_2$

Also, if we substitute equation (12) in equation (11) we get;

$$C_2(s)=\frac{Dk_2}{V\left[(s+k_\alpha)(s+k_1+k_m)-k_1k_2\right]}=\frac{Dk_2}{V[s^2+(k_\alpha+k_1+k_m)s+k_\beta]} \quad (13)$$

Where $k_\beta=k_\alpha(k_1+k_m)-k_1k_2$

Suppose that $C_1(s)=\frac{D(s+k_1+k_m)}{V\left[(s+k_\alpha)(s+k_1+k_m)-k_1k_2\right]}=\frac{D(s+k_1+k_m)}{V[s^2+(k_\alpha+k_1+k_m)s+k_\beta]}\equiv\frac{A}{(s+\lambda_1)}+\frac{B}{(s+\lambda_2)}$ where λ_1 and λ_2 are the roots of the $s^2+(k_\alpha+k_1+k_m)s+k_\beta$ then solving the partial fraction we get

$$C_1(s)=\frac{D}{V}\left[\frac{(k_1+k_m)-\lambda_1}{\lambda_2-\lambda_1}\right]\left(\frac{1}{s+\lambda_1}\right)+\frac{D}{V}\left[\frac{\lambda_2-(k_1+k_m)}{\lambda_2-\lambda_1}\right]\left(\frac{1}{s+\lambda_2}\right) \quad (14)$$

Taking the inverse Laplace Transformation of equation (14), which states that $C_1(t)=L^{-1}\{C_1(s)\}$, we get;

$$C_1(t)=\frac{D}{V}\left[\frac{(k_1+k_m)-\lambda_1}{\lambda_2-\lambda_1}\right]e^{-\lambda_1 t}+\frac{D}{V}\left[\frac{\lambda_2-(k_1+k_m)}{\lambda_2-\lambda_1}\right]e^{-\lambda_2 t} \quad (15)$$

Where
$$\left.\begin{aligned}\lambda_1&=\frac{-(k_\alpha+k_1+k_m)+\sqrt{(k_\alpha+k_1+k_m)^2-4k_\beta}}{2}\\ \lambda_2&=\frac{-(k_\alpha+k_1+k_m)-\sqrt{(k_\alpha+k_1+k_m)^2-4k_\beta}}{2}\end{aligned}\right\} \quad (16)$$

Where λ_1,λ_2 are the eigenvalues

Again, suppose that $C_2(s)=\frac{Dk_2}{V[s^2+(k_\alpha+k_1+k_m)s+k_\beta]}\equiv\frac{A}{(s+r_1)}+\frac{B}{(s+r_2)}$ where r_1 and r_2 are also the roots of the $s^2+(k_\alpha+k_1+k_m)s+k_\beta$ then solving the partial fraction we get;

$$C_2(s)=\left[\frac{Dk_2}{V(r_2-r_1)}\right]\left(\frac{1}{s+r_1}\right)+\left[\frac{Dk_2}{V(r_1-r_2)}\right]\left(\frac{1}{s+r_2}\right) \quad (17)$$

Similarly, if we take the inverse Laplace Transformation of equation (17) (that is, $C_2(t) = L^{-1}\{C_2(s)\}$), we get;

$$C_2(t) = \left[\frac{Dk_2}{V(r_2 - r_1)}\right]e^{-r_1 t} + \left[\frac{Dk_2}{V(r_1 - r_2)}\right]e^{-r_2 t} \tag{18}$$

Where
$$\left.\begin{aligned} r_1 &= \frac{-(k_\alpha + k_1 + k_m) + \sqrt{(k_\alpha + k_1 + k_m)^2 - 4k_\beta}}{2} \\ r_2 &= \frac{-(k_\alpha + k_1 + k_m) - \sqrt{(k_\alpha + k_1 + k_m)^2 - 4k_\beta}}{2} \end{aligned}\right\} \tag{19}$$

Where r_1, r_2 are the eigenvalues

3. Results

Here, we present the numerical simulation of the model equation, we use MATLAB version 2018b and a dimensional theoretical data was adopted. Below are the graphs of the result.

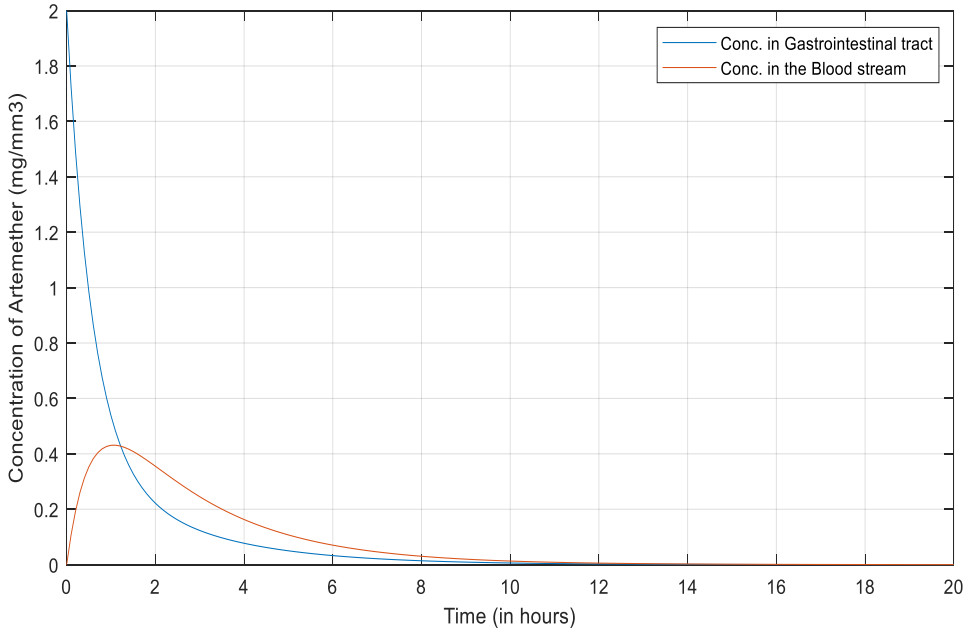

Figure 3: Graph showing the dynamics of Artemether drug on Gastrointestinal Tract and Bloodstream

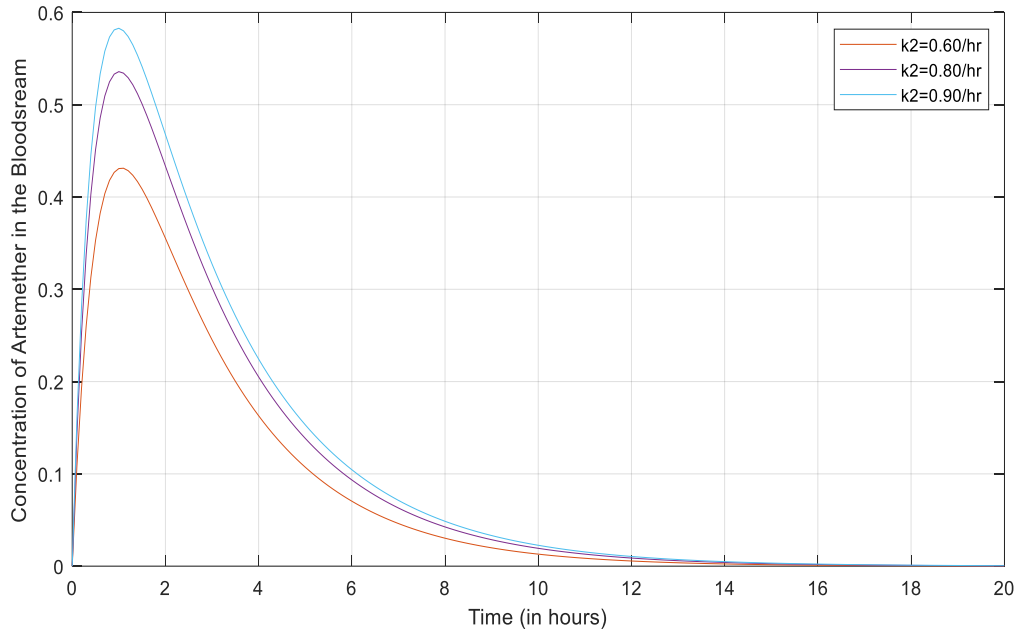

Figure 4: Graph showing the variation of Artemether drug in the Bloodstream with varying rate of k_2

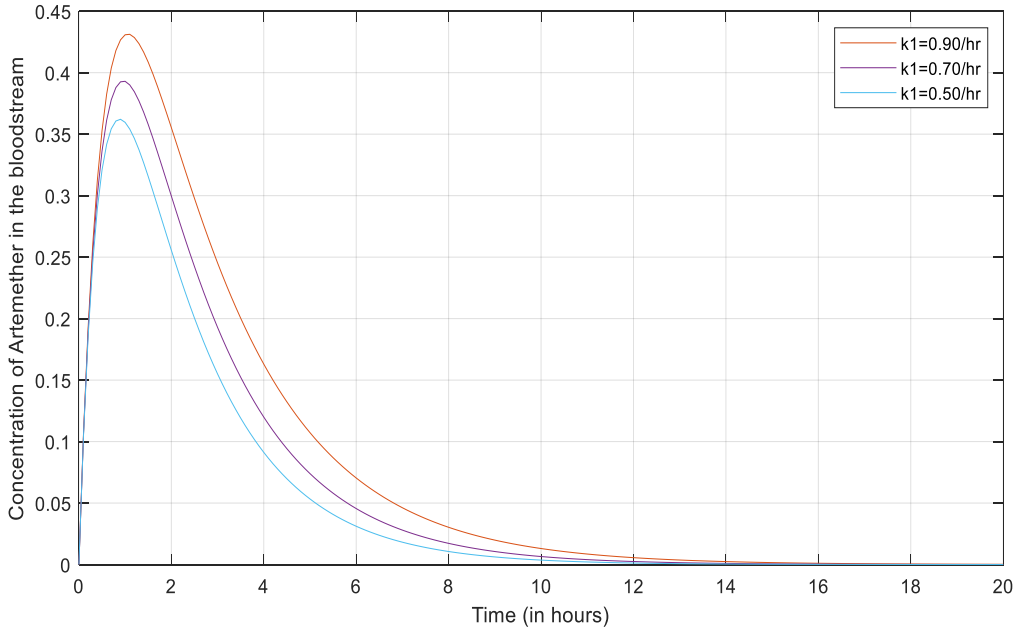

Figure 5: Graph showing the variation of Artemether drug in the Bloodstream with varying rate of k_1

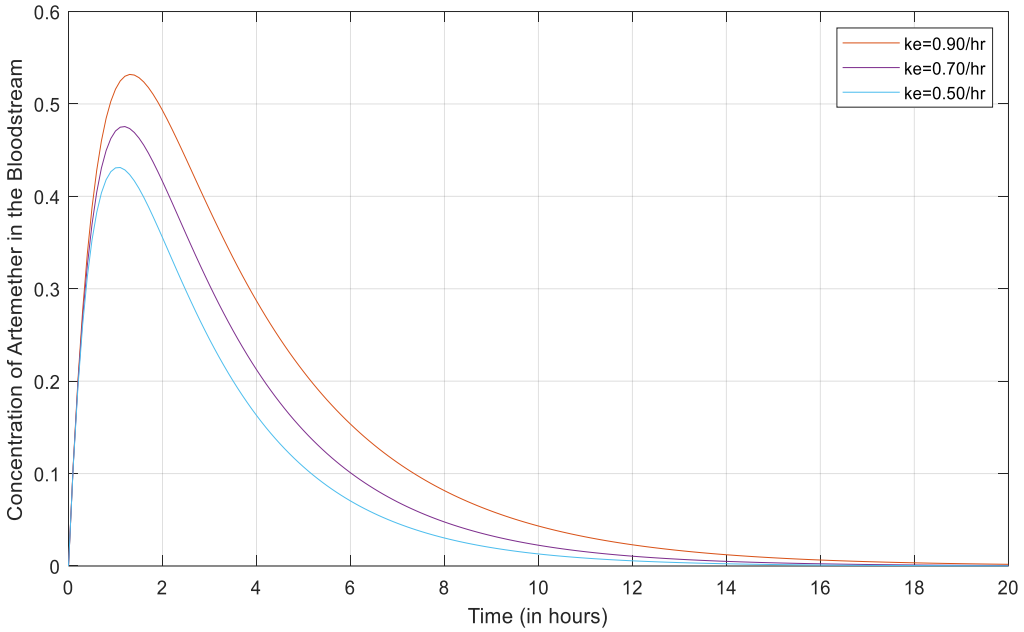

Figure 6: Graph showing the variation of Artemether drug in the Bloodstream with varying rate of k_e

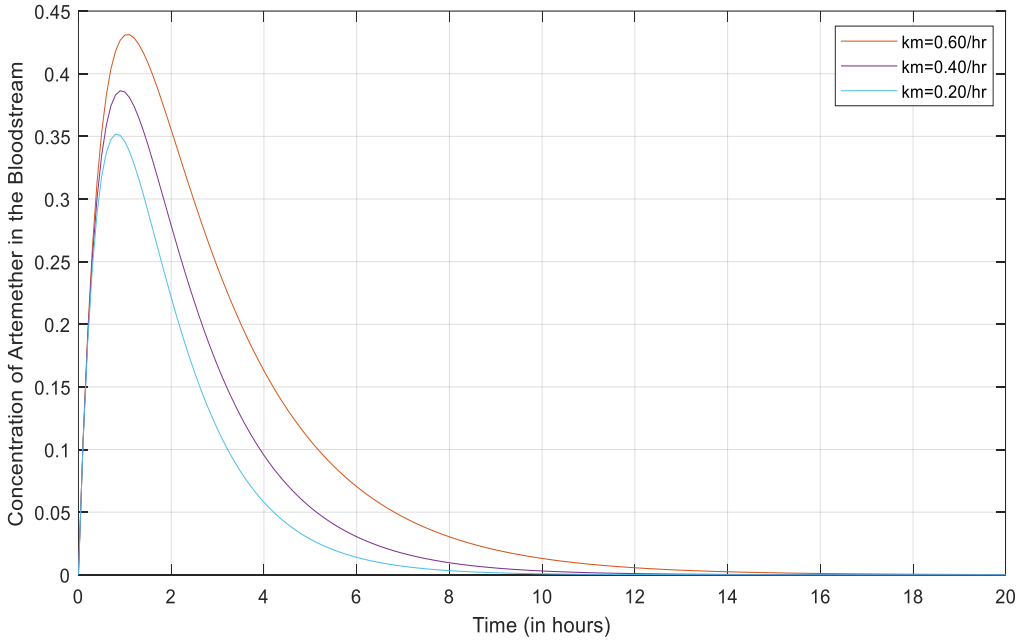

Figure 7: Graph showing the variation of Artemether drug in the Bloodstream with varying rate of k_m

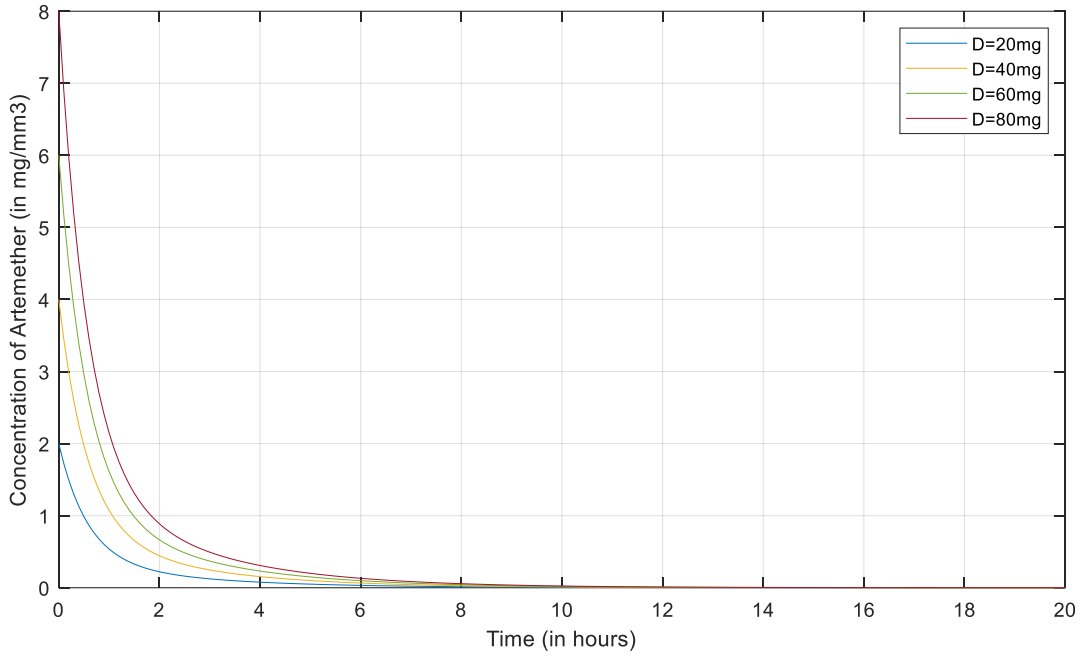

Figure 8: Graph showing the concentration of Artemether drug in the GI tract at different dosage

4. Discussion

Figure 3 is the dynamics of Artemether drugs in human body through oral administration. The result reveals the behavior of the concentration of Artemether drugs in both GI tract and the bloodstream. The graph shows that 20mg of Artemether in the GI tract decreases and almost tends to zero within 16 to 18 hours due to absorption of the drug in the bloodstream. It also shows that the drug concentration in the bloodstream will initially increase (due to availability and rapid adsorption) and then decrease with time. Finally figure 3 also show that 20mg of Artemether drug will take 20 hours (approximately) to clear from the blood stream.

Figure 4 – 7, the result shows the impact of each rate constants on the drug concentration and the result reveals that the concentration of Artemether drug is directly proportional to the rate constants k_1, k_2, k_e and k_m. the result also show that the variation of the rate parameter has little or no effect in the total time taken to clear the drug from the whole body.

Figure 8 shows the concentration level of Artemether drug in the GI tract at different dosage. The graph reveals that each dose is converted to mg/mm^3 and with 80mg, the drug concentration level decreases to almost zero at a duration of 18 to 20 hours, and when 60mg of drugs is administered, the drug concentration tends to zero within 15 to 17 hours and if 20mg is administered, the duration reduces to 7 to 8 hours. The result also shows that to maintain a certain threshold level of concentration of the drug in the bloodstream over a given time interval, high dose of the drug is require in the first administration. This result agrees with the

finding of the pharmacokinetics of Artemether drugs by Swapnil *et al.*, (2024).

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