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TWO-COMPARTMENT PHARMACOKINETIC MODELS WITH SINGLE AND DOUBLE ELIMINATION RATES FOR ORAL ADMINISTRATION OF TWO DRUGS

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Abstract. This paper presents two pharmacokinetic models with two compartments, incorporating both single and double elimination rates for the oral administration of two drugs. The models allow for the estimation of the absorption, distribution, and elimination rate constants. This estimation is performed in two phases based on the time intervals. The first phase estimates the distribution and elimination rates using concentration data from larger time data points, employing residual techniques and least squares error. In contrast, the absorption rate estimation is conducted using the Wagner-Nelson method for smaller time intervals. Prior to these estimations, an analytical solution is required, for which Laplace transform is utilized. Finally, graphical simulations are performed to observe the dynamics of drug concentrations in plasma and tissues throughout the processes of absorption, distribution, and elimination. A comparison between actual data and estimated results from both models is also presented. The findings suggest that the double-elimination model offers a more accurate estimation of the drug concentration in plasma, closely aligning with the observed data. Meanwhile, the single elimination-rate model provides a more reliable estimation of drug concentration in tissues.

Keywords: Pharmacokinetics model, Wagner-Nelson method, parameter estimation, Laplace transform.

I. INTRODUCTION

Pharmacokinetics is a branch of medical science that specifically studies the changes in the amount or concentration of a drug in plasma as a function of time. This study analyzes the drug changes through three fundamental processes: absorption, distribution, and elimination [2]. Initially, a drug is absorbed and transported to the circulatory system, where it is then distributed throughout tissues and organs, and finally eliminated from the body. The last process is divided into two type of processes: excretion and metabolism. There are two common routes for administering drugs, the first is the intravascular route, such as injection and infusion, and the second is the extravascular route, which includes oral and intramuscular administration. The intravascular route refers to the direct entry of the drug into the bloodstream, while the extravascular route involves an absorption process before the drug enters the circulatory system.

To analyze the changes in drug concentration within the body, mathematical models can be employed, which may take the form of differential equations [10] or fractional order equations [7, 8, 15]. Different routes of drug administration yield distinct mathematical models. In pharmacokinetics, these mathematical models are typically referred to as compartment models, with the number of compartments depending on how body tissues are classified based on blood

flow rate, namely affinity. If the affinity for each tissue is considered homogeneous, a one-compartment model can be represented by a single differential equation. On the other hand, if two different affinities—fast and slow—are classified within body tissues, a two-compartment model, consisting of a central compartment (fast affinity) and a peripheral compartment (slow affinity), would be appropriate for depicting the dynamics of drug changes within the body, where it is characterized by a system of two differential equations. This approach can similarly be extended to three compartments and more.

The discussion about compartment models in pharmacokinetics has been extensively explored, including studies by Mahmood [6] who estimated absorption rate constant using the Wagner-Nelson method [16], the Loo-Riegelman method [5], and statistical moments for oral administration. One should be note that the Wagner-Nelson method is commonly used to estimate absorption rate parameters in a one-compartment model, whereas the Loo-Riegelman method is typically employed for two-compartment models. In addition to these methods, Zulkarnaen et al.[19, 21, 20] also estimated parameters using a residual method as a comparative approach and introduced an integral-based method [4] for estimating parameters in intravenous models. Another approach utilized is the Nonstandard Finite Difference method, as reported by Sa'adah et al.[11]. Notably, Rodrigo [9] analyzed drug dynamics using the Laplace transform in a multi-compartment model. Additional references include foundational texts by Shargel & Yu [14], Gibaldi & Perrier [2], and Hedaya [3], which serve as excellent resources for understanding the fundamentals of pharmacokinetics.

Several papers have discussed pharmacokinetic models for drug administration via intravascular by injection [21, 1] and infusion [12, 13, 18], which are applicable to one or two-compartment models. While these articles introduce the model with a single drug, this paper proposes two-compartment models in which two drugs are administered via extravascular oral route. Two scenarios are developed to formulate the models: first, when only the central compartment undergoes drug elimination, and second, when both the central and peripheral compartments experience elimination. Parameter estimation for these models is conducted using the Wagner-Nelson method. Additionally, graphical simulations are performed using Scilab software to observe the concentration changes throughout the processes of absorption, distribution, and elimination. A comparison of the estimated graphs with theoretical data will also be presented, alongside calculations of the root mean square error.

II. TWO-COMPARTMENT MODEL

In this section, two models for oral drug administration are constructed: a two-compartment model with a single elimination rate and a two-compartment model with double elimination rates. From these two models, parameters in the form of absorption rate constants are estimated using the Wagner-Nelson method, while the elimination rate constants are estimated using the least squares and the residual methods. It should be noted that we employ the least squares method as an optimization technique to ease the parameter estimation in linear regression, aiming to achieve the best fit by minimizing the sum of squared errors.

2.1. Model I: Single Elimination Rate

In contrast to the model presented in [2, 3, 6, 10] which considers the administration of a single drug, this paper assumes the simultaneous administration of two drugs in equal doses.

The dynamics of drug changes occurring within the body can be illustrated in the diagram shown in Figure 1.

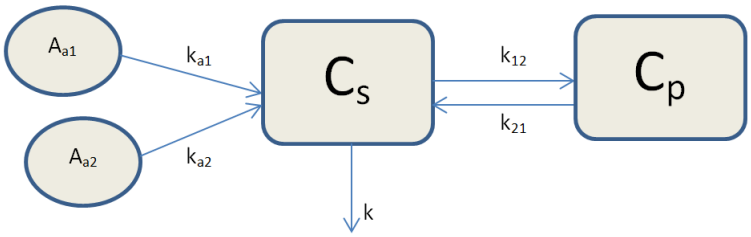


Figure 1. Two-compartment model diagram with single elimination rate

Based on the figure, the central compartment, representing plasma, is denoted as C_s, while the peripheral compartment, representing body tissues, is denoted as C_p. For the amount of drug administered to the body, the notations A_{a1} and A_{a2} are used. Using the relationship between concentration, amount of drug, and volume of distribution $C = \frac{A_a}{V_d}$, the two-compartment model with single elimination rate can be represented by

$$\begin{aligned} \frac{dC_s}{dt} &= -(k_{12}+k)C_s + k_{21}C_p + \frac{k_{a1}A_{a1}}{V} + \frac{k_{a2}A_{a2}}{V}, \\ \frac{dC_p}{dt} &= k_{12}C_s - k_{21}C_p. \end{aligned} \tag{1}$$

where k_{12} and k_{21} represent the distribution rate constants between the central and peripheral compartments, k represents the elimination rate, and k_{a1} and k_{a2} denote the absorption rates of drugs one and drug two into the bloodstream. Since the drugs initially have not yet entered the circulatory system but are still in the gastrointestinal tract (GIT), we can consider that $C_s(0) = C_p(0) = 0$. For the changes in drug concentration occurring in the GIT, the model can be specified as

$$\begin{aligned} \frac{dA_{a1}}{dt} &= -k_{a1}A_{a1}, \\ \frac{dA_{a2}}{dt} &= -k_{a2}A_{a2}, \end{aligned} \tag{2}$$

with $A_{a1}(0) = A_{a10}$ and $A_{a2}(0) = A_{a20}$. Our goal from the model given in (3) is to find its solution, which can then be incorporated into model given in (1) to ultimately estimate the required parameters. The solution of the model can be easily obtained as

$$\begin{aligned} A_{a1}(t) &= A_{a10}e^{-k_{a1}t}, \\ A_{a2}(t) &= A_{a20}e^{-k_{a2}t}. \end{aligned} \tag{3}$$

Estimation of Elimination and Distribution Rate Parameters

We begin with large time where the absorption process is considered complete, and only the elimination process continues. In other words, for $t \to \infty$, the model represented in equation (1)

can be rewritten as

$$\begin{aligned}\frac{dC_s}{dt} =& -(k_{12}+k)C_s + k_{21}C_p,\\ \frac{dC_p}{dt} =& k_{12}C_s - k_{21}C_p.\end{aligned} \tag{4}$$

To estimate the distribution and elimination parameters in (4), the initial step we need to take is to determine its analytical solution using Laplace transform. It involves forming the matrix

$$\begin{bmatrix} C_s' & C_p' \end{bmatrix} = \begin{bmatrix} -(k_{12}+k) & k_{21}\, k_{12} & -k_{21} \end{bmatrix} \begin{bmatrix} C_s & C_p \end{bmatrix}$$

From this matrix, we can express the Laplace transformat simply as

$$\begin{aligned}\mathcal{L}(C'(t)) =& \mathcal{L}\big[K, C(t)\big],\\ \hat{C}(s) =& (sI-K)^{-1}C(0),\end{aligned}$$

where $\hat{C} = \mathcal{L}(C(t))$ and

$$(sI-K)^{-1} = \frac{1}{(s+\alpha)(s+\beta)} \begin{bmatrix} s+k_{21} & k_{21}\, k_{12} & s+k_{12}+k \end{bmatrix},$$

with

$$\begin{aligned}\alpha+\beta =& k_{21}+k_{12}+k,\\ \alpha\beta =& kk_{21}.\end{aligned} \tag{5}$$

By taking the inverse of the Laplace transformation, we obtain the solutions for each compartment as:

$$\begin{aligned}C_s(t) =& \frac{(\alpha-k_{21})C_0}{\alpha-\beta}e^{-\alpha t} + \frac{(k_{21}-\beta)C_0}{\alpha-\beta}e^{-\beta t},\\ C_p(t) =& \frac{-k_{12}C_0}{\alpha-\beta}e^{-\alpha t} + \frac{k_{21}C_0}{\alpha-\beta}e^{-\beta t}.\end{aligned} \tag{6}$$

Next, to simplify the parameter estimation calculations, we can denote the last equations as

$$\begin{aligned}A(t) =& Ve^{-\alpha t} + We^{-\beta t},\\ B(t) =& Xe^{-\alpha t} + Ye^{-\beta t}.\end{aligned} \tag{7}$$

It should be noted that α and β represent the elimination and distribution phases, respectively, with $\alpha < \beta$ since the distribution process is faster than the elimination process.

Now, to estimate the parameters k, k_{12}, and k_{21}, we only need to use the solution of equation $A(t)$. For large t and $\alpha < \beta$, we have $e^{-\beta t} \approx 0$. This implies that the solution $A(t)$ in (7) can be rewritten as

$$C_{se}(t) = Ve^{-\alpha t}. \tag{8}$$

From this equation, we can easily calculate the values of α and V using the least squares method

as

$$\begin{aligned}\alpha &= -\frac{n\sum_{i=1}^{n} t_i \ln C_{sei}(t) - \sum_{i=1}^{n} t_i \sum_{i=1}^{n} \ln C_{sei}(t)}{n\sum_{i=1}^{n}(t_i)^2 - (\sum_{i=1}^{n} t_i)^2},\\ V &= \exp\Big(\frac{n\sum_{i=1}^{n} t_i^2 \sum_{i=1}^{n} \ln C_{sei}(t) - \sum_{i=1}^{n} t_i \ln C_{sei}(t) \sum_{i=1}^{n} t_i}{n\sum_{i=1}^{n}(t_i)^2 - (\sum_{i=1}^{n} t_i)^2}\Big).\end{aligned} \tag{9}$$

Next, for β and W, the parameter estimation can be performed using the residual technique by subtracting $A(t)$ in (7) from C_{se} in (8), yielding

$$R_{es} = We^{-\beta t}$$

Using the same approach as before, the least squares method yields

$$\begin{aligned}\beta &= -\frac{n\sum_{i=1}^{n} t_i \ln R_{esi} - \sum_{i=1}^{n} t_i \sum_{i=1}^{n} \ln R_{esi}}{n\sum_{i=1}^{n}(t_i)^2 - (\sum_{i=1}^{n} t_i)^2},\\ W &= \exp\Big(\frac{n\sum_{i=1}^{n} t_i^2 \sum_{i=1}^{n} \ln R_{esi} - \sum_{i=1}^{n} t_i \ln R_{esi} \sum_{i=1}^{n} t_i}{n\sum_{i=1}^{n}(t_i)^2 - (\sum_{i=1}^{n} t_i)^2}\Big).\end{aligned} \tag{10}$$

With the values of V, W, α, and β obtained, and using the formula given in (5), we can compute the parameters k_{12}, k_{21}, k as follows

$$\begin{aligned}k_{21} &= \frac{V\beta + W\alpha}{V + W},\\ k &= \frac{\alpha\beta}{k_{21}},\\ k_{12} &= \alpha + \beta - k_{21} - k.\end{aligned}$$

Estimation of Absorption Rate Parameters

To calculate the absorption rate constants, we consider short time period where the absorption process is more dominant than the elimination process. The Wagner-Nelson method is implemented to determine the absorption rate constants k_{a1} and k_{a2} by first calculating the fraction of the drug that has been absorbed as

$$\frac{A_b}{A_b^{\infty}} = \frac{C_s + C_p + k[AUC]_0^t}{k[AUC]_0^{\infty}},$$

where AUC denotes the Area Under Curve of the drug concentration in the plasma, defined analytically as

$$\big[AUC\big]_0^t = \int_0^t C_s(t)\, dt,$$

from which we can express the amount of unabsorbed drug as

$$1 - \frac{A_b}{A_b^{\infty}} = 1 - \frac{C_s + C_p + k[AUC]_0^t}{k[AUC]_0^{\infty}}. \tag{11}$$

Here, the notations A_b and A_b^∞ denote the amount of drug absorbed at time t and the total amount that has been fully absorbed, respectively.

Next, we need to calculate the fraction of the drug remaining in the gastrointestinal tract (GIT) by evaluating the formula $\frac{A_{a1}+A_{a2}}{A_{a10}+A_{a20}}$ for the administration of two drugs. We refer back to the previously provided solution in Equation (3). Given that the time used is $t \ll 1$, the exponential forms in the solution can be simplified using Taylor expansion. As a result, the sum of the two solutions can be expressed as

$$A_{a1} + A_{a2} = A_{a10}(1 - k_{a1}t) + A_{a20}(1 - k_{a2}t).$$

By performing algebraic manipulation, this equation can be rearranged to

$$\frac{A_{a1} + A_{a2}}{A_{a10} + A_{a20}} = 1 - \frac{1}{2}(k_{a1} + k_{a2})t.$$

This equation represents the amount of drug present in the GIT, which also indicates the amount that has not been absorbed. Therefore, by combining the latter equation with equation (11), we obtain

$$1 - \frac{A_b}{A_b^\infty} = \frac{A_{a1} + A_{a2}}{A_{a10} + A_{a20}} = 1 - \frac{1}{2}(k_{a1} + k_{a2})t.$$

It is evident that this equation is linear, where the slope of the line can be calculated as

$$(k_{a1} + k_{a2}) = -2\left(\frac{n\sum_{i=1}^n t_i(1 - A_b/A_b^\infty) - \sum_{i=1}^n t_i \sum_{i=1}^n (1 - A_b/A_b^\infty)}{n\sum_{i=1}^n (t_i)^2 - (\sum_{i=1}^n t_i)^2}\right). \tag{12}$$

Notice that the value of $(1 - A_b/A_b^\infty)$ in the formula can be calculated based on equation (11).

2.2. Model II: Double Elimination Rates

In the subsequent model, the two-compartment model with double elimination rates assumes that two drugs entering the body will be eliminated by each compartment, as illustrated in Figure 2. Similar to the previous model, the doses of the two drugs are considered equal. However, the elimination process in this model occurs not only in the central compartment but also in the peripheral compartment, with corresponding rate constants of k_1 and k_2. Based on

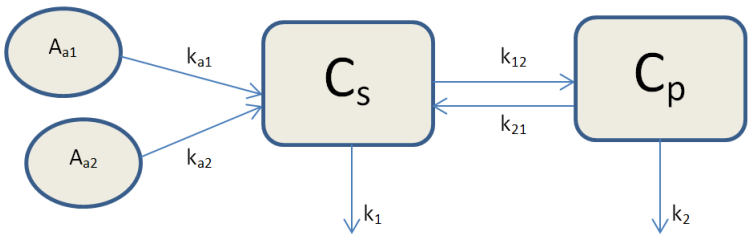


Figure 2. Two-compartment model with double elimination rates

the diagram, this model can be specified as

$$\begin{aligned}\frac{dC_s}{dt} =& -(k_{12}+k_1)C_s + k_{21}C_p + \frac{k_{a1}A_{a1}}{V_d} + \frac{k_{a2}A_{a2}}{V_d},\\ \frac{dC_p}{dt} =& k_{12}C_s - (k_{21}+k_2)C_p,\end{aligned} \tag{13}$$

where A_{a1} and A_{a2} have the same solution as in the previous model, as shown in equation (3).

To analyze the model, we start by considering large time, assuming $t \to \infty$ to derive the distribution and elimination rates. Since the absorption process is assumed to finish at large time, equation (13) simplifies to

$$\begin{aligned}\frac{dC_s}{dt} =& -(k_{12}+k_1)C_s + k_{21}C_p,\\ \frac{dC_p}{dt} =& k_{12}C_s - (k_{21}+k_2)C_p,\end{aligned} \tag{14}$$

with initial conditions $C_s(0) = C_p(0) = 0$. To estimate the parameters k_{12}, k_{21}, k_1, k_2, the first step is to find the analytical solution. Using the Laplace transform, the system of equations in (14) can be represented in matrix form as

$$\begin{bmatrix} C_s' \\ C_p' \end{bmatrix} = \begin{bmatrix} -(k_{12}+k_1) & k_{21} \\ k_{12} & -(k_{21}+k_2) \end{bmatrix} \begin{bmatrix} C_s \\ C_p \end{bmatrix}$$

Following the same procedure as in the previous model, we obtain the solution:

$$\begin{aligned}C_s(t) =& \frac{(\alpha - k_{21} - k_2)C_0}{(\alpha-\beta)}e^{-\alpha t} + \frac{(k_{21}+k_2-\beta)C_0}{(\alpha-\beta)}e^{-\beta t},\\ C_p(t) =& -\frac{k_{12}C_0}{(\alpha-\beta)}e^{-\alpha t} + \frac{k_{21}C_0}{(\alpha-\beta)}e^{-\beta t}.\end{aligned}$$

This can also be expressed in a simpler form as:

$$\begin{aligned}C_s(t) =& Ve^{-\alpha t} + We^{-\beta t},\\ C_p(t) =& Xe^{-\alpha t} + Ye^{-\beta t},\end{aligned} \tag{15}$$

where $\alpha < \beta$ and

$$\begin{aligned}\alpha + \beta =& k_{12} + k_1 + k_{21} + k_2,\\ \alpha\beta =& k_{21}k_1 + k_2k_{12} + k_2k_1.\end{aligned}$$

In this model, to determine the distribution and elimination rate constants, we use both the solution $C_s(t)$ and $C_p(t)$. Consequently, the estimates of α and β in the central and peripheral compartments in equation (15) may differ because they rely on distinct datasets—namely, the drug concentration data in the central compartment and the drug concentration data in the

peripheral compartment. Thus, equation (15) can be reformulated as:

$$\begin{aligned} C_s(t) =& Ve^{-\alpha_1 t} + We^{-\beta_1 t}, \\ C_p(t) =& Xe^{-\alpha_2 t} + Ye^{-\beta_2 t}. \end{aligned} \tag{16}$$

Using the same methodology as in the previous model, for large t, the first equation in (16) can be simplified to:

$$C_{se1}(t) = Ve^{-\alpha_1 t}$$

allowing the estimation of α_1 and V using the least squares method, as

$$\begin{aligned} \alpha_1 =& -\frac{n\sum_{i=1}^{n} t_i \ln C_{se1i}(t) - \sum_{i=1}^{n} t_i \sum_{i=1}^{n} \ln C_{se1i}(t)}{n\sum_{i=1}^{n}(t_i)^2 - (\sum_{i=1}^{n} t_i)^2}, \\ V =& \exp\left(\frac{n\sum_{i=1}^{n} t_i^2 \sum_{i=1}^{n} \ln C_{se1i}(t) - \sum_{i=1}^{n} t_i \ln C_{se1i}(t) \sum_{i=1}^{n} t_i}{n\sum_{i=1}^{n}(t_i)^2 - (\sum_{i=1}^{n} t_i)^2}\right). \end{aligned} \tag{17}$$

Subsequently, by calculating the residual of the drug concentration in the central compartment, we can determine the values of β_1 and W from the residual equation

$$R_{es1} = We^{-\beta_1 t}$$

with the formula:

$$\begin{aligned} \beta_1 =& -\frac{n\sum_{i=1}^{n} t_i \ln R_{es1i} - \sum_{i=1}^{n} t_i \sum_{i=1}^{n} \ln R_{es1i}}{n\sum_{i=1}^{n}(t_i)^2 - (\sum_{i=1}^{n} t_i)^2}, \\ W =& \exp\left(\frac{n\sum_{i=1}^{n} t_i^2 \sum_{i=1}^{n} \ln R_{es1i} - \sum_{i=1}^{n} t_i \ln R_{es1i} \sum_{i=1}^{n} t_i}{n\sum_{i=1}^{n}(t_i)^2 - (\sum_{i=1}^{n} t_i)^2}\right). \end{aligned} \tag{18}$$

Perform the same steps for the peripheral compartment in equation (16) to obtain estimates for α_2 and X as

$$\begin{aligned} \alpha_2 =& -\frac{n\sum_{i=1}^{n} t_i \ln C_{se2i}(t) - \sum_{i=1}^{n} t_i \sum_{i=1}^{n} \ln C_{se2i}(t)}{n\sum_{i=1}^{n}(t_i)^2 - (\sum_{i=1}^{n} t_i)^2}, \\ X =& \exp\left(\frac{n\sum_{i=1}^{n} t_i^2 \sum_{i=1}^{n} \ln C_{se2i}(t) - \sum_{i=1}^{n} t_i \ln C_{se2i}(t) \sum_{i=1}^{n} t_i}{n\sum_{i=1}^{n}(t_i)^2 - (\sum_{i=1}^{n} t_i)^2}\right). \end{aligned} \tag{19}$$

Similarly, for β_2 and Y, which are obtained from the residual concentrations, it is formulated as:

$$R_{es2} = Ye^{-\beta_2 t}$$

the formulas are given by

$$\begin{aligned} \beta_2 =& -\frac{n\sum_{i=1}^{n} t_i \ln R_{es2i} - \sum_{i=1}^{n} t_i \sum_{i=1}^{n} \ln R_{es2i}}{n\sum_{i=1}^{n}(t_i)^2 - (\sum_{i=1}^{n} t_i)^2}, \\ Y =& \exp\left(\frac{n\sum_{i=1}^{n} t_i^2 \sum_{i=1}^{n} \ln R_{es2i} - \sum_{i=1}^{n} t_i \ln R_{es2i} \sum_{i=1}^{n} t_i}{n\sum_{i=1}^{n}(t_i)^2 - (\sum_{i=1}^{n} t_i)^2}\right). \end{aligned} \tag{20}$$

Based on the formulas obtained in equations (17), (18), (19), and (20), we derive the estimates

for the distribution and elimination rate constants as follows

$$k_{12} = \frac{X(\beta_2 - \alpha_2)}{V + W}, \quad k_{21} = \frac{Y(\beta_2 - \alpha_2)}{V + W},$$
$$k_1 = \frac{V\alpha_1 + W\beta_1 + L(\alpha_2 - \beta_2)}{V + W}, \quad k_2 = \frac{V\beta_1 + W\alpha_1}{(V + W)k_{21}}.$$

Estimation of Absorption Rate Parameters

The formula for estimating the absorption rate is not significantly different from the previous model; however, the peripheral compartment is included in the calculations. In other words, for this model, the amount of drug that has not been absorbed can be expressed as

$$1 - \frac{A_b}{A_b^\infty} = 1 - \frac{C_s + C_p + k_1[AUC]_0^t + k_2[AUC]_0^t}{k_1[AUC]_0^\infty + k_2[AUC]_0^\infty}. \tag{21}$$

As a result, to calculate the values of k_{a1} and k_{a2}, the same formulation as in the previous model in (12) can be used; however, the value of $1 - \frac{A_b}{A_b^\infty}$ in this model is defined based on equation (21).

III. Numerical Simulation

In this section, graphical simulations are provided for both the single and double elimination rate models. These simulations aim to estimate the parameters for the absorption, distribution, and elimination rate constants when two drugs are administered orally. The data used here are theoretical, constructed based on selected parameter values. In other words, parameter values are selected and incorporated into Model I in (1) and Model II in (13), allowing the built-in numerical method in scilab to be used to solve these models by computing the drug concentrations over specified time interval, the success of these estimations is evaluated by the consistency between the initially selected parameter values and the resulting estimates. Additionally, the success of the estimation is quantified by the error generated between the theoretical data and the approximations of drug concentrations in the central and peripheral compartments using root mean square error.

3.1. Graphical Simulation of Model I

Consider two drugs administered via oral route at the same dose of 2 mg/l, and consider that the absorption, distribution, and elimination rate constants are given as follows:

$$k_{21} = 0.55,\ k = 0.2,\ k_{12} = 0.4,\ k_{a1} + k_{a2} = 1. \tag{22}$$

Next, we define the time interval to observe changes in drug concentration, that is from 0 to 20 hours. Using a numerical approach to the pharmacokinetic model in system (1), we obtain the drug concentration data for both central and peripheral compartments, as illustrated in Figure 3..

To estimate the distribution and elimination rate parameters, the values of several supporting parameters need to be determined first. To find the values of α and V, we utilize the

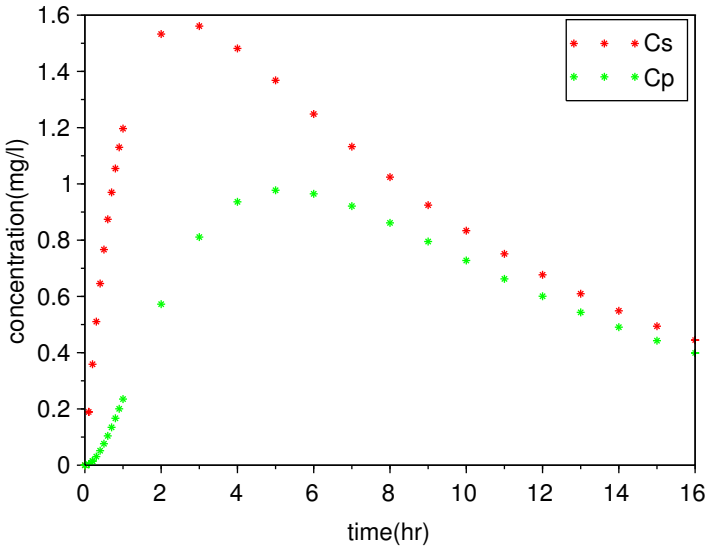
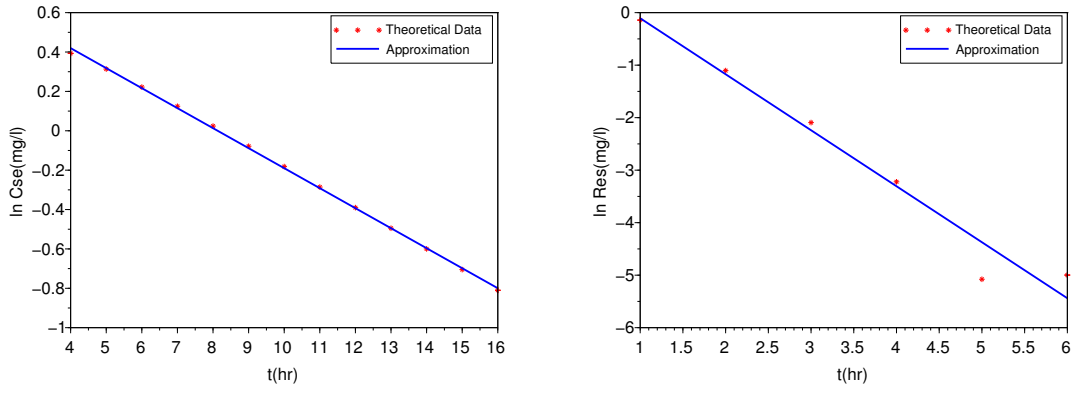


Figure 3. Graph of drug concentration data points over time for Model I.

formula in (9), yielding $\alpha = 0.1016$ and $V = 2.2845$. The approximation results based on these two values compared to the theoretical data are shown in Figure 4.a. It can be seen that the approximation of these two parameter estimates is quite close to the theoretical data points.



(a) **(b)**

Figure 4. Comparison of theoretical data points and their estimates for Model I, using (a) parameter α and V, (b) parameter β and W.

Similarly, to obtain the values of β and W, using the formula in (10), we find $\beta = 1.0665$ and $W = 2.611461$. With this estimation, we can draw a straight line that closely aligns with the theoretical data, as shown in Figure 4.b. Next, to estimate the absorption rate parameters using the Wagner-Nelson method, we utilize the data presented in Table 1. for small time t so that we can compute (11) to find the absorption rate constants of both drugs using the formula provided in (12). The result of this estimation is $k_{a1} + k_{a2} = 1.077272$.

With all parameters including the absorption, distribution, and elimination rate constants obtained, we can derive the numerical solution of the model given in (1) and then compare it

Table 1. Data points of drug concentration during the absorption phase for Model I.

t	C_s	C_p	Δt	ΔC	AUC	$1-\frac{A_b}{A_b^\infty}$
0	0	0	0	0	0	1
0.1	0.189	0.003	0.1	0.189	0.009	0.944
0.2	0.358	0.014	0.1	0.548	0.027	0.892

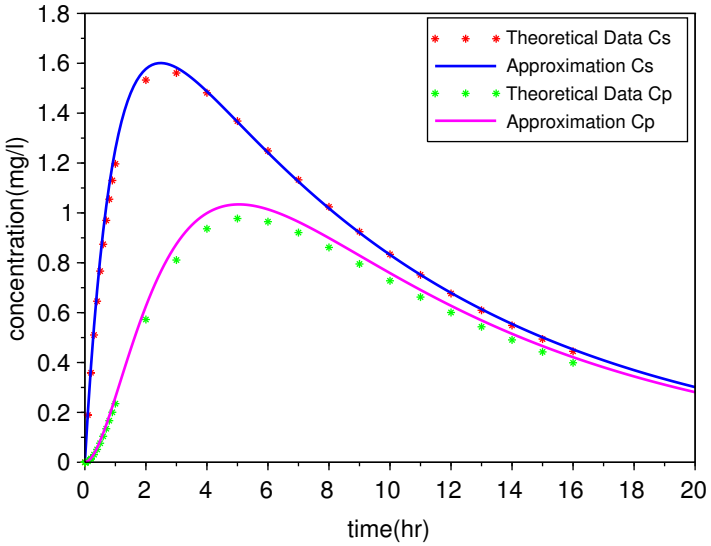


Figure 5. Comparison the drug concentration dynamics between the theoretical data and their approximations for Model I.

with the theoretical data. This comparison is illustrated in Figure 5., which shows that the drug concentration approximation in both central and peripheral compartments closely aligns with the theoretical data. Quantitatively, the errors produced in the central and peripheral compartments are 0.0734 and 0.1465, respectively.

3.2. Graphical Simulation of Model II

In this section, two drugs are administered at the same dose of 2 mg/l. We assume the absorption, distribution, and elimination rate constants are defined as:

$$k_{a1}+k_{a2}=0.9, k_{21}=0.5,\ k_1=0.8,\ k_{12}=0.2,\ k_2=0.2.$$

Using these values, drug concentration data over time can be constructed numerically based on the model specified in (13).

Similar to the Model I, we need to determine the supporting parameters before obtaining the absorption, distribution, and elimination rate constants. By employing the formulas from equations (17) to (20), we find $\alpha_1 = 0.3847, V = 2.8319, \beta_1 = 1.2546, W = 4.8219, \alpha_2 = 0.3256, X = 0.8405, \beta_2 = 1.1080, Y = 4.8219$. The results of these estimates when simulated graphically are displayed in Figure 6. It can be observed in the figures, especially in Figures 6.a and 6.c, that the theoretical data does not exhibit a linear trend, making the significant differ-

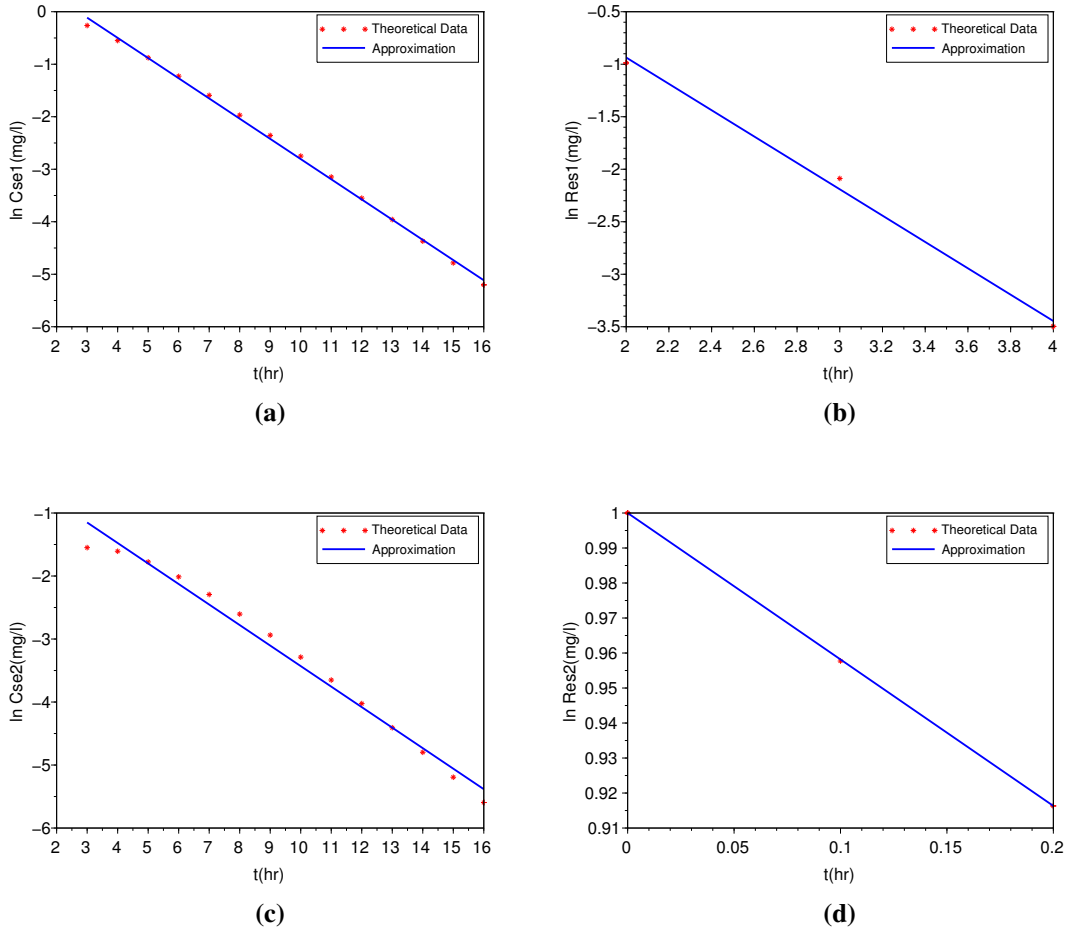


Figure 6. Comparison of theoretical data points and their estimates for Model II, using (a) parameter α_1 and V (b) parameter β_1 and W (c) parameter α_2 and X (d) parameter β_2 and Y.

ences between the theoretical data and its approximation clearly visible.

Next, to estimate the absorption rate parameters using the Wagner-Nelson method, we require the data as recorded in Table 2. for small time t, enabling us to compute (21) to find the absorption rate constants of both drugs with the formula given in (12). The result is $k_{a1} + k_{a2} = 0.836787$.

Table 2. Data points of drug concentration during the absorption phase for Model II.

t	C_s	C_p	Δt	ΔC	AUC	$1 - \frac{A_b}{A_b^\infty}$
0	0	0	0	0	0	1
0.1	0.167	0.001	0.1	0.001	0.008	0.957
0.2	0.311	0.006	0.1	0.007	0.023	0.916

After all parameters have been obtained, we can construct the graph of the solution from the model given in (13) and subsequently compare it with the actual data. The comparison of these two graphs is shown in Figure 7., where the approximation of the drug concentration

in the central compartment is quite close to the actual data, although this is not the case for the peripheral compartment. Quantitatively, the errors produced in the central and peripheral compartments are 0.0313 and 0.2160, respectively.

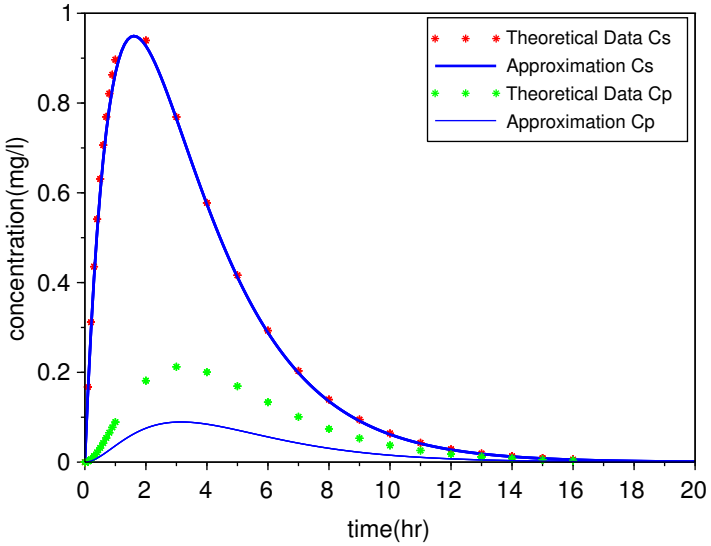


Figure 7. Comparison the drug concentration dynamics between the theoretical data and their approximations for Model II.

IV. CONCLUSIONS AND FUTURE RESEARCH DIRECTION

The estimations conducted on the pharmacokinetic models presented in this paper are deemed satisfactory. It is supported by the comparison between the initially provided parameter values and the resulting estimates.

Table 3. Comparation parameter values between the original and the estimation.

MODEL I: Single Elimination Rate				
Parameter	k	k_{12}	k_{21}	$k_{a1}+k_{a2}$
Original Value	0.2	0.4	0.55	1
Estimation	0.1964	0.4200	0.5519	1.0773
Deviation	0.0036	0.0200	0.0019	0.0773

MODEL II: Double Elimination Rate					
Parameter	k_1	k_2	k_{12}	k_{21}	$k_{a1}+k_{a2}$
Original Value	0.8	0.2	0.2	0.5	0.9
Estimation	0.8469	0.2137	0.0859	0.4929	0.8368
Deviation	0.0469	0.0137	0.1141	0.0071	0.0632

Table 3. shows the comparison between the original values and the estimated results for the absorption, distribution, and elimination rate constants for both Model I and Model II. It

can be observed from the table that the elimination rate constants in Model I yield better results compared to Model II. Conversely, for the absorption rate constant, Model II demonstrates superior performance, as indicated by the deviation between the original values and their estimates. Nonetheless, when examining the graphs shown in Figures 5. and 7., it is evident that Model I provides more accurate estimations than Model II. This is particularly noticeable in the peripheral compartment graphs, although both models exhibit similar estimations for the central compartment.

In more detail, when the errors for both graphs are calculated, the second model yields a slightly better result for the central compartment, with an error of 0.0313 compared to 0.0734 for Model I. Conversely, Model I demonstrates significantly better performance for the peripheral compartment, showing an error of 0.1465 compared to 0.2160 for Model II.

While the results obtained are considered satisfactory, there remains a need to enhance the model to improve its performance. One potential approach is the introduction of a three-compartment model, comprising blood plasma and tissues with both fast and slow perfusion rates. Such a model is expected to provide more accurate estimations, as incorporating additional compartments typically brings the model closer to real-world situations. However, this approach requires rigorous validation through complicated analysis, given that the complexity of the resulting model would surpass that of a two-compartment model.

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