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Drug-Drug Interactions Pharmacokinetic Models with Extravascular Administration: Estimation of Elimination and Absorption Rate Constants

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ABSTRACT

One and two-compartment pharmacokinetic models with drug-drug interactions are proposed. Two drugs are given orally simultaneously, so that their interaction affects the drug absorption process and subsequently the elimination process. The aim of this paper is to estimate the elimination and absorption rate constants by evaluating the data set of time and drug concentration. This data set was divided into two time phases: large-time elimination phase to estimate the elimination rate constant, and small-time absorption phase to estimate the absorption rate constant. Since the models are nonlinear, the Taylor expansion is employed to so that the Wagner-Nelson and the Loo-Riegelman methods can be used for estimation. Finally, simulations were performed using the generated arbitrary data set of time and concentration, instead of an actual data set, to derive the solution of drug concentration concerning time numerically. In these simulations we compared the original parameter values with their estimates for the one and two-compartment models, and we concluded that the two-compartment model produced better estimates than the one-compartment model. Qualitatively, the two-compartment model gives smaller drug concentration curve deviations between the original and the estimated curve compared with the one-compartment model.

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A. INTRODUCTION

Pharmacokinetics study the activity of drugs over time. There are three activities or processes occur once they enter the body: absorption, distribution, and elimination, successively. All three fundamental processes occur when drugs are administered orally, while the case that drugs are administered intravenously, the absorption process is omitted since the drugs enter directly to the blood. To investigate the drug dynamics in the body, one can consider the body as a number of compartments, starting from a simple single compartment to a complex multi compartments (Hedaya, 2012; Gössling, 1993). The single-compartment or one-compartment model means all organs or tissues in the body are assumed to have rapid drug distribution. But when a drug is distributed rapidly to some parts of the body and slowly to the other parts, the two-compartment model better describes the drug dynamics. The compartment with rapid distribution is commonly called central compartment, while the slow one is called peripheral compartment (Shargel, 2022; Hedaya, 2012; Gössling, 1993; Gibaldi, 1982).

A compartment model can be represented mathematically by fractional-order system Mtshali & Jacobs (2023); Angstmann et al. (2019); Sopasakis et al. (2018); Angstmann et al. (2017) but classically it is represented by differential equations Hedaya (2012), either a single or a system, that depends on how many compartments are used. The more compartments used the more differential equations are formed. Once a compartment model is constructed, the solution of drug concentration needs to be solved by some mathematical models, basically by separation of variables or integration factor. Savva applied the superposition methods to solve one and two-compartment models to obtain the drug concentration when the drug is administered by intermittent infusion (Savva, 2022, 2021). On the other hand, Wu et al. have successfully obtained the closed form solution of the pharmacokinetic models with the Michaelis-Menten elimination (Wu et al., 2021, 2018, 2015). Laplace transform can also be implemented to obtain the exact solution from a pharmacokinetic model (Rodrigo, 2022; Siva Rama Krishna Reddy & Narayan, 2019; Khanday et al., 2017). In addition to analytical solution, the numerical approach can be used to solve the pharmacokinetic compartment model such as the nonstandard finite difference method (Sa'adah et al., 2020; Egbelowo, 2018; Egbelowo et al., 2017).

In addition to find a solution, an estimation to some parameters in a compartment model is also another pharmacokinetics problem to look for, where the constant of absorption rate and elimination are the most common parameters to estimate. The estimation can be performed when time-concentration data points are given. There are some methods of how to do the estimation, and the two very classic and well-known methods are the residual and the Wagner-Nelson method Wagner & Nelson (1963), but these methods only apply for one-compartment model. The estimation methods have then developed to allow parameter estimation for two-compartment models, namely Loo-Riegelman method (Loo & Riegelman, 1968). The application of these two methods can be found in some articles (Zeng et al., 2021; Mahmood, 2004; Sanaka et al., 2004). For another method used to parameter estimate or make predictions from the pharmacokinetics model, one can look in the following articles (Qiao et al., 2021; Sánchez-Dengra et al., 2021; Zeng et al., 2020; Deng & Li, 2017).

The parameter estimations of the constant rate of elimination and absorption for one-compartment model can be conducted by applying the Wagner-Nelson method. Meanwhile the Loo-Riegelman method is employed for the two-compartment model. But when two distinct drugs are given simultaneously and drug-drug interactions (DDIs) occur, the absorption, distribution or elimination processes might be affected (Neves et al., 2022; Babak et al., 2019; Kennedy-Dixon et al., 2015; Palleria et al., 2013). Furthermore, the presence of DDIs makes the model to become nonlinear which implies that the Wagner-Nelson and Loo-Riegelman cannot be used directly. In this article we established the one and two-compartment pharmacokinetic models with oral administration where DDIs occurs. The absorption and elimination rate constants were estimated from these models by applying Taylor expansion to the Wagner-Nelson and the Loo-Riegelman methods. Finally, the simulations were given to compare the results of drug concentration dynamics between the one and two-compartment models.

B. METHOD

In this article, we propose two different models of drug-drug interactions. One is the model with one compartment, and the second is the two-compartment model. For each compartment model the two parameters, which are the absorption and elimination rate constants, are quantitatively estimated using the data set of time versus drug concentration. Here, the data set is divided into two parts: the data with large time and small time. The large-time data set is employed first to estimate the elimination rate constant using the least square method. Then the small-time data set is applied for the estimation of the absorption rate constant by combining the Taylor expansion with the Wagner-Nelson method for the one-compartment model or with the Loo-Riegelman method for the two-compartment model. The reason for applying the Taylor expansion is to transform the nonlinear model formed by DDIs into a linear model so that the Wagner-Nelson and the Loo-Riegelman method can be used for the estimation.

1. One-compartment DDIs Model

In a one-compartment model, body is assumed to have a rapid and homogeneous drug distribution. Once the drug enters the body, the absorption process occurs in the Gastrointestinal Tract (GIT) followed by the distribution and elimination processes. When two drugs are administered orally and simultaneously, they first enter the GIT for absorption before coming into the blood plasma, where the distribution process occurs followed by the elimination process. Suppose two drugs are given by single doses, denoted by D_1 for drug one and D_2 for drug two, and notice that not the entire dose is completely absorbed, but there is a fraction $0 < F < 1$ of administered doses that will be absorbed into the systemic circulation. Thus, when two drugs are given, the amount of each drug that enters the systemic circulation can be calculated by $A_{a1,0} = FD_1$ and $A_{a2,0} = FD_2$. These two drugs will interact to each other with the constant of interaction rate k_i, then are transported (by absorbing) into the blood plasma as a unite A by the constant k_a, and finally this unite drug is eliminated from the body by the constant k. These systemic processes can be easily understood through the diagram given in Figure 1.

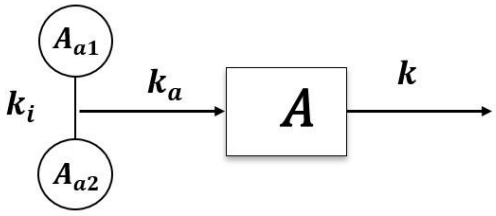


Figure 1. One-compartment model of drug-drug interactions.

From this diagram, the construction of the drug dynamics mathematical model can be divided into two phases based on where the process takes place: The model of the two drugs dynamics before they enter the systemic circulation (in GIT), and the model of the unite drug that enters the systemic circulation, that is in the blood plasma. Begin with the first phase, the rate of change of the drug amount for drug one and drug two can be modelled as

$$\frac{dA_{a1}}{dt} = -k_a A_{a1} - k_i A_{a1} A_{a2} \tag{1}$$

$$\frac{dA_{a2}}{dt} = -k_a A_{a2,} \tag{2}$$

Respectively, where the initial values are given by $A_{a1,0}$ and $A_{a2,0}$. Here, we use grams (gr) for the drug amount so that $\{A_{a1,0}, A_{a2,0}\} < 1$. We assume that $0 < \{k_i, k_a\} < 1$ and both drugs have the same constant of absorption rate, where only one drug (i.e. drug one) is affected by the presence of DDIs, shown by the term $k_i A_{a1} A_{a2}$ in (1). This means drug one is absorbed faster into the blood plasma than drug two. The next phase is when the two drugs have entered the blood plasma and become unite. The mathematical model for this stage can be specified as

$$\frac{dA}{dt} = k_a(A_{a1} + A_{a2}) - kA, \tag{3}$$

where $A(0) = 0$ since no drug in the plasma initially but in the GIT, and $0 < k < k_a$. In this one-compartment model we estimate only the parameters of the absorption rate constant k_a and the elimination rate constant k by separating the data points of time-concentration into two phases: large and small-time phases. First, the data points at large time are used to estimate k, followed by the k_a estimation using the small-time data points.

a. Large-time phase

   When the time is large, the drug is considered to have completed the absorption phase, and only the elimination phase occurs. Therefore, the first term of the righthand side in equation (3) vanishes and it becomes

$$\frac{dA}{d\hat{t}} = -kA. \tag{4}$$

   Here we use the notation $\hat{t}$ to indicate that this equation holds only for large time t. To estimate k in (4), we apply the least square method (Giordano et al., 2014), but the analytical solution must be done first. Thus, by integrating both sides of (4), we obtain

$$A(\hat{t}) = \hat{A}_0 e^{-k\hat{t}}. \tag{5}$$

   Since the data set consists of time and drug concentration instead of drug amount, the solution given in (5) should be in the concentration form. Knowing that $A = V_d C$, where V_d is the volume of distribution and C denotes the drug concentration, the solution in (5) can be rewritten as

$$C(\hat{t}) = \hat{C}_0 e^{-k\hat{t}}. \tag{6}$$

   Note that $\hat{C}(0)$ represents the concentration values at the initial large time $\hat{t}$. Taking the logarithm of both sides of (6), the equation now becomes

$$\ln C(\hat{t}) = \ln \hat{C}_0 - k\hat{t}, \tag{7}$$

which has linear relationship between $\hat{t}$ and $\ln C(\hat{t})$. The least square method now can be applied to estimate the elimination rate constant as well as the initial concentration, respectively as

$$k = -\frac{n\sum_{i=1}^{n}\hat{t}_i \ln C_i - \sum_{i=1}^{n}\hat{t}_i \sum_{i=1}^{n}\ln C_i}{n\sum_{i=1}^{n}\hat{t}_i^2 - (\sum_{i=1}^{n}\hat{t}_i)^2}, \tag{8}$$

$$\hat{C}_0 = \exp\left(\frac{\sum_{i=1}^{n}\hat{t}_i^2 \sum_{i=1}^{n}\ln C_i - \sum_{i=1}^{n}\hat{t}_i \ln C_i \sum_{i=1}^{n}\hat{t}_i}{n\sum_{i=1}^{n}\hat{t}_i^2 - (\sum_{i=1}^{n}\hat{t}_i)^2}\right). \tag{9}$$

b. Small-time phase

Recall that the absorption phase occurs at the beginning time drug enters the body. Thus, in this part the Wagner-Nelson and the Taylor expansion are implemented to estimate k_a using the small-time data points. Wagner and Nelson have calculated the fraction of the absorbed drug as

$$\frac{A_b}{A_b^\infty} = \frac{C + k[AUC]_0^t}{k[AUC]_0^\infty} \tag{10}$$

and the unabsorbed drug by

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

Here A_b and A_b^∞ represent the respective absorbed drug over time t and at infinite time (drug has been absorbed completely), while $[AUC]_0^t = \int_0^t C\ dt$ interpret the area under curve over time t. To see the derivation of (10) please see (Hedaya, 2012; Wagner & Nelson, 1963). Now we implement the Wagner-Nelson method to our proposed model for absorption phase with small t. Revisited to equation (2), we find the solution of the amount of drug two as

$$A_{a2}(t) = A_{a2,0}e^{-k_a t}. \tag{12}$$

Inserting this solution to equation (1), we have

$$\frac{dA_{a1}}{dt} = -k_a A_{a1} - k_i A_{a1} A_{a2,0} e^{-k_a t}. \tag{13}$$

Furthermore, separating the variables Aa1 and t to each side then integrating them, we obtain the solution as

$$A_{a1}(t) = A_{a1,0} \exp\left(-k_a t + \frac{k_i A_{a2,0}}{k_a}(e^{-k_a t} - 1)\right). \tag{14}$$

Next, we need to calculate the fraction of drug remaining in the GIT, that is by determining the formula $(A_{a1} + A_{a2})/(A_{a1,0} + A_{a2,0})$. Since a linear form is what we need to ease the parameter estimation by least square method, the Taylor expansion must be done first. We begin with

$$A_{a1} + A_{a2} = A_{a10} \exp\left(-k_a t + \frac{k_i A_{a20}}{k_a}(e^{-k_a t} - 1)\right) + A_{a20} e^{-k_a t} \tag{15}$$

from (12) and (13). By the Taylor expansion, the exponential term in the latter equation can be expanded as

$$e^{-k_a t} = 1 - k_a t + \frac{k_a^2 t^2}{2!} - \frac{k_a^3 t^3}{3!} + \cdots. \tag{16}$$

Suppose that k_a is defined small so that $k_a t \ll 1$ since t is also small. This means we can consider that $(k_a t)^n \approx 0$, for $n = 2, 3, \cdots$. As a result, the equation (16) can be truncated and becomes $e^{-k_a t} \approx 1 - k_a t$. The equation given in (15) now can be simplified as

$$A_{a1} + A_{a2} = A_{a1,0}(1 - (k_a + k_i A_{a20})t) + A_{a2,0}(1 - k_a t). \tag{17}$$

Recall that $k_i < k_a$, t is small and $A_{a2,0} < 1$. This implies their multiplication $k_i A_{a2,0} t \ll 1$, so as the term $(k_a + k_i A_{a2,0})t \ll 1$ in (17). Therefore, the Taylor expansion can be used again to equation (17) to obtain the more simplified equation and then make the equation rearrangement, we obtain

$$\frac{A_{a1} + A_{a2}}{A_{a1,0} + A_{a2,0}} = 1 - \left(k_a + \frac{k_i A_{a1,0} A_{a2,0}}{A_{a1,0} + A_{a2,0}}\right) t. \tag{18}$$

Thus, this equation defines the fraction of drug remaining in the GIT, which has the same meaning as the fraction of the unabsorbed drug, defined previously in (11). Consequently, we can combine the latter equation and (11) to obtain

$$1 - \frac{C + k[AUC]_0^t}{k[AUC]_0^\infty} = 1 - \left(k_a + \frac{k_i A_{a1,0} A_{a2,0}}{A_{a1,0} + A_{a2,0}}\right) t. \tag{19}$$

As can be seen here, the equation is linear, so the least square method can be used here toestimate the rate constant of absorption, formulated by

$$k_a = -\frac{n\sum_{i=1}^{n} t_i\left(1-\frac{C+k[AUC]_0^t}{k[AUC]_0^\infty}\right)-\sum_{i=1}^{n} t_i\sum_{i=1}^{n}\left(1-\frac{C+k[AUC]_0^t}{k[AUC]_0^\infty}\right)}{n\sum_{i=1}^{n} t_i^2-\left(\sum_{i=1}^{n} t_i\right)^2}-\frac{k_i A_{a1,0}A_{a2,0}}{A_{a1,0}+A_{a2,0}}. \quad (20)$$

2. Two-compartment DDIs Model

In the two-compartment model, the absorbed drugs are transported into the systemic circulation which has two classes of distribution speed. One class is the tissues or organs that have rapid distribution, represented by central compartment. The other one is the group of tissues with slow distribution, represented by peripheral compartment. The entire process of two orally given drugs from absorption to elimination is shown by the diagram in Figure 2.

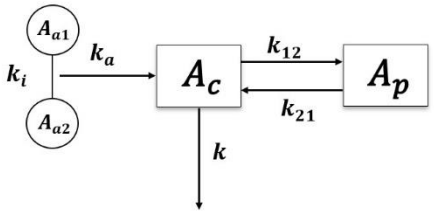


Figure 2. Two-compartment model of drug-drug interactions.

From this diagram, the mathematical model for the elimination phase can be established as a system of two differential equations, governed by

$$\begin{aligned}\frac{dA_c}{dt} &= -(k_{12}+k)A_c + k_{21}A_p + k_a(A_{a1}+A_{a2}),\\ \frac{dA_p}{dt} &= k_{12}A_c - k_{21}A_p,\end{aligned} \quad (21)$$

where $A_c(0) = A_p(0) = 0$. In this model k_{12} and k_{21} denote the transfer rate constant from central to peripheral compartment and from peripheral to central compartment, respectively, A_c and A_p represent the drug amount in the central and peripheral compartment, respectively. Meanwhile the mathematical model for absorption phase remains unchanged, given by (1) and (2). Like in the one-compartment model, in this part we estimate k and k_a, whereas k_i is given. On the other hand, k_{12} and k_{21} are also estimated as the requirement to estimate k. Now the data points of time-concentration are broken down into large and small-time phases.

a. Large-time phase

The goal of this part is finding the formula for the transfer rate constants k_{12} and k_{21} so that k can be estimated. Note that the steps for estimation follow the reference (Giordano et al., 2014; Shargel L, Wu-Pong S, 2022). Therefore, the explanation given here will not be detailed as this reference are clear enough to understand the step-by-step estimation. As explained earlier that there is only an elimination process when the time is large. This makes the model given in (21) become

$$\begin{aligned} \frac{dA_c}{d\hat{t}} &= -(k_{12}+k)A_c + k_{21}A_p \\ \frac{dA_p}{d\hat{t}} &= k_{12}A_c - k_{21}A_p, \end{aligned} \tag{22}$$

where $\hat{t}$ indicates the large time t. Note that when the elimination phase begins, there will be some amount of drugs that has entered the systemic circulation, and here we assume that some amount of drugs has entered the central compartment, but not yet the peripheral compartment. Hence, we have $A_c(0) = A_{c,0}$ and $A_p(0) = 0$ as the initial values for the system (22). The first step we need to take for estimation is to find an analytical solution of (22) using the Laplace transform. Representing the system (22) into the matrix

$$\begin{bmatrix} A_c' \\ A_p' \end{bmatrix} = \begin{bmatrix} -(k_{12}+k) & k_{21} \\ k_{12} & -k_{21} \end{bmatrix} \begin{bmatrix} A_c \\ A_p \end{bmatrix}, \tag{23}$$

or simply writing $A'(t) = KA(t)$ with $A(t) = \begin{bmatrix} A_c \\ A_p \end{bmatrix}$ and $K = \begin{bmatrix} -(k_{12}+k) & k_{21} \\ k_{12} & -k_{21} \end{bmatrix}$, we can express its Laplace transform as

$$\mathcal{L}\big(A(s)\big) = (s-K)^{-1}\mathcal{L}\big(A(0)\big), \tag{24}$$

Where

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

The parameters α and β in the latter equation are called the hybrid constants, where their addition and multiplication can be calculated by

$$\begin{aligned} \alpha + \beta &= k_{12} + k_{21} + k \\ \alpha\beta &= k_{21}k. \end{aligned} \tag{25}$$

Performing the inverse Laplace transform of equation (24), we obtain the solution as

$$\begin{aligned} A_c(\hat{t}) &= \frac{\hat{A}_0(\alpha - k_{21})}{(\alpha-\beta)} e^{-\alpha\hat{t}} + \frac{\hat{A}_0(k_{21}-\beta)}{(\alpha-\beta)} e^{-\beta\hat{t}}, \\ A_p(\hat{t}) &= \frac{\hat{A}_0 k_{12}}{(\alpha-\beta)} e^{-\alpha\hat{t}} + \frac{\hat{A}_0 k_{21}}{(\alpha-\beta)} e^{-\beta\hat{t}} \end{aligned} \tag{26}$$

or in terms on concentration, we have

$$C_c(\hat{t}) = Pe^{-\alpha\hat{t}} + Qe^{-\beta\hat{t}}, \qquad C_p(\hat{t}) = Re^{-\alpha\hat{t}} + Se^{-\beta\hat{t}}. \tag{27}$$

Where

$$P = \frac{\hat{C}_0(\alpha - k_{21})}{(\alpha - \beta)}, \qquad Q = \frac{\hat{C}_0(k_{21} - \beta)}{(\alpha - \beta)}, \qquad R = \frac{\hat{A}_0 k_{12}}{(\alpha - \beta)}, \qquad S = \frac{\hat{A}_0 k_{21}}{(\alpha - \beta)}. \quad (28)$$

The first term of each equation in (27) indicates the elimination phase, while the second term is the distribution phase. Thus α and β denote the coefficient constants of the elimination and distribution phases, where $\alpha < \beta$ since the distribution process is faster than the elimination process. To estimate k, k_{12} and k_{21}, we only use the first equation of (27) since the data collection is only available via blood plasma (central compartment). In other words, before we estimate these three rates, we first need to calculate α, β, P and Q. Observe that $\alpha < \beta$ which implies $e^{-\beta \hat{t}} \approx 0$ due to the large $\hat{t}$. Thus, we have

$$C_c(\hat{t}) = Pe^{-\alpha \hat{t}}. \quad (29)$$

Taking logarithms to both sides to linearize the equation as

$$\ln C_c(\hat{t}) = \ln P - \alpha \hat{t},$$

and applying the least square method we can calculate α and P as

$$\alpha = -\frac{n\sum_{i=1}^{n} \hat{t}_i \ln C_{c,i} - \sum_{i=1}^{n} \hat{t}_i \sum_{i=1}^{n} \ln C_{c,i}}{n\sum_{i=1}^{n} \hat{t}_i^2 - \left(\sum_{i=1}^{n} \hat{t}_i\right)^2}, \; P = \exp\left(\frac{\sum_{i=1}^{n} \hat{t}_i^2 \sum_{i=1}^{n} \ln C_{c,i} - \sum_{i=1}^{n} \hat{t}_i \ln C_{c,i} \sum_{i=1}^{n} \hat{t}_i}{n\sum_{i=1}^{n} \hat{t}_i^2 - \left(\sum_{i=1}^{n} \hat{t}_i\right)^2}\right). \quad (30)$$

Next, to calculate β and Q, the residual concentration between (29) and (27) needs to be calculated first by

$$\text{Res} = -Qe^{-\beta \hat{t}}.$$

Likewise, we can linearize the equation as

$$\ln \text{Res} = \ln(-Q) - \beta \hat{t}, \quad (31)$$

and use the least square method to calculate

$$\beta = -\frac{n\sum_{i=1}^{n} \hat{t}_i \ln \text{Res}_i - \sum_{i=1}^{n} \hat{t}_i \sum_{i=1}^{n} \ln \text{Res}_i}{n\sum_{i=1}^{n} \hat{t}_i^2 - (\sum_{i=1}^{n} \hat{t}_i)^2}, \quad (32)$$

$$Q = -\exp\left(\frac{\sum_{i=1}^{n} \hat{t}_i^2 \sum_{i=1}^{n} \ln \text{Res}_i - \sum_{i=1}^{n} \hat{t}_i \ln \text{Res}_i \sum_{i=1}^{n} \hat{t}_i}{n\sum_{i=1}^{n} \hat{t}_i^2 - (\sum_{i=1}^{n} \hat{t}_i)^2}\right). \quad (33)$$

Since the values *α, β, P, Q* have been given in (30) to (33), we can finally estimate k_{21}, k, k_{12} from the equations (25) and (28), sequentially as

$$k_{21} = \frac{P\beta + Q\alpha}{P + Q}, \qquad k = \frac{\alpha\beta}{k_{21}}, \qquad k_{12} = \alpha + \beta - k_{21} - k. \tag{34}$$

b. Small-time phase

The Wagner-Nelson method to estimate the constant absorption rate cannot be used in the two-compartment model. Instead, the development method, namely Loo-Riegelman method, is used. First of all, the fraction of unabsorbed drug is calculated by

$$1 - \frac{A_b}{A_b^{\infty}} = 1 - \frac{C_c + C_p + k[AUC]_0^t}{k[AUC]_0^{\infty}}. \tag{35}$$

Observe that this expression is similar to the one in the one-compartment model given in (11), where the blood concentration now includes the concentration in the central and peripheral compartments. The drug concentration value in the peripheral compartment is required to calculate (35), and Loo-Riegelman (Loo & Riegelman, 1968) has established the formula to calculate it by

$$C_p(t) = \frac{(k_{12}\Delta C_c \Delta \mathrm{t})}{2} + \frac{k_{12}}{k_{21}} C_c(t - \Delta t)(1 - e^{-k21\Delta t}) + C_p(t - \Delta t)e^{-k_{21}\Delta t}, \tag{36}$$

Recall that unabsorbed drug is the amount of drug that does not enter the blood systemic circulation but remains in the GIT. Since this process occurs before the drug enters the blood, the drug that remains in the GIT in this case is the same as the case in the one-compartment model. In other words, we can calculate the drug remaining in the GIT by (17). Furthermore, we can insert the equation (35) and (19) into (11) to construct a linear relationship between time and unabsorbed drug by

$$1 - \frac{C_c + C_p + k[AUC]_0^t}{k[AUC]_0^{\infty}} = 1 - \left(k_a + \frac{k_i A_{a1,0} A_{a2,0}}{A_{a1,0} + A_{a2,0}}\right)t, \tag{37}$$

By this linearity, we can use the least square method to calculate the slope of (37), say α, as

$$\alpha = \frac{n\sum_{i=1}^{n} t_i \left(1 - \frac{C + k[AUC]_0^t}{k[AUC]_0^{\infty}}\right) - \sum_{i=1}^{n} t_i \sum_{i=1}^{n} \left(1 - \frac{C + k[AUC]_0^t}{k[AUC]_0^{\infty}}\right)}{n\sum_{i=1}^{n} t_i^2 - (\sum_{i=1}^{n} t_i)^2}. \tag{38}$$

Since the slope α in (38) has the value $-\left(k_a + \left(k_i A_{a1,0} A_{a2,0}\right)/\left(A_{a1,0} + A_{a2,0}\right)\right)$, the absorption rate constant k_a for the two-compartment model can be estimated by

$$k_a = -\alpha - \frac{k_i A_{a1,0} A_{a2,0}}{A_{a1,0} + A_{a2,0}}. \tag{39}$$

C. RESULT AND DISCUSSION

In this section, simulations are performed to estimate the coefficient of elimination and absorption rate using the formulas given in the previous section. These estimation values are then verified by comparing the deviation between the approximation values and the original data points through the root means squared error. These simulations are conducted to one and two-compartment models to find out which model better represents drug dynamics through the error values obtained.

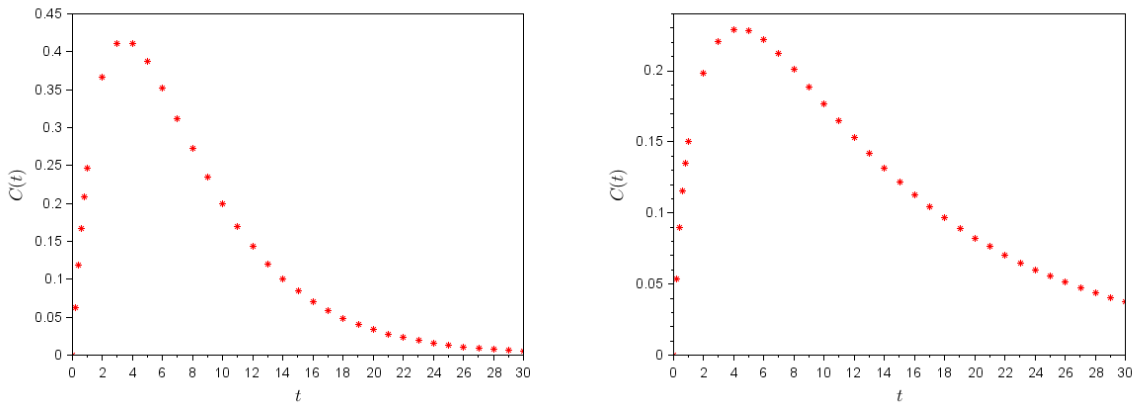
The parameter estimates require the data points of drug concentration versus time, where the data points are obtained by choosing parameter values randomly then inserting them into the DDIs model, either one or two-compartment model. By using a numerical approach, the model solution of drug concentration with respect to time is obtained. The data is then broken into two parts: small-time and large-time data points. The large-time data points are used first to estimate the elimination rate coefficient, followed by the small-time data points to estimate the absorption rate coefficient. These estimated values are then compared with the original values that were input earlier.

1. One-compartment model

In the one-compartment model we randomly select the parameter values as shown in Table 1, which are inserted into the model in equation (3) to generate drug concentration data points over time as depicted in Figure 3a (notice that dividing the equation by volume of distribution will convert the amount of drug into the concentration of drug), as shown in Table 1 and Figure 3.

Table 1. Parameter values used to obtain time-concentration data set

Parameter	$C_{a1,0}$	$C_{a2,0}$	F_1	F_2	k_a	k	k_i
Value	0.5 gr/lt	0.7 gr/lt	66%	71%	0.4049/hr	0.1896/hr	0.0932/(gr.hr)

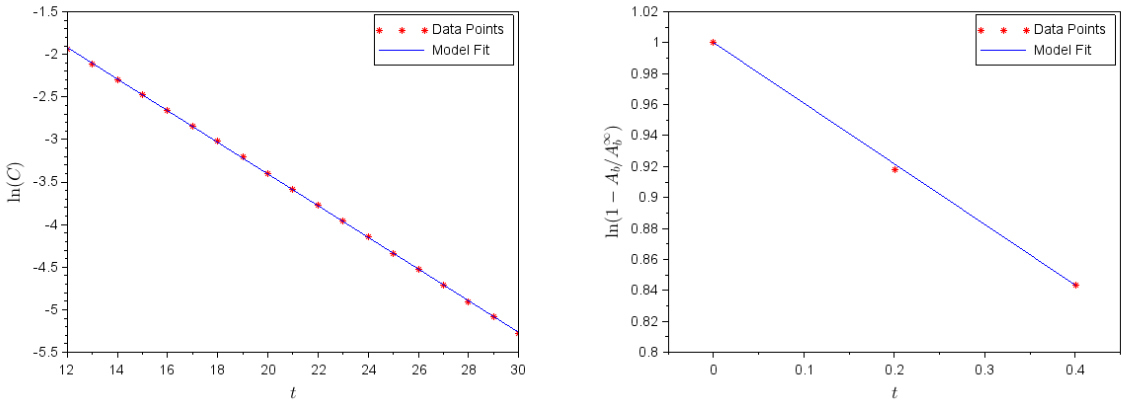


(a) (b)

Figure 3. The data set of time and drug concentration in the blood plasma for (a) one-compartment model and (b) two-compartment model.

The time data points used here are up to 30 hours, or within the interval [0,30], where for the first hour there are 5 data points with the time step size of 0.2 hour followed by 1 hour step size for the rest. The data points are divided into two parts: the data with small time within the interval $0 \leq t \leq 0.4$ and the data with large time within the interval $12 \leq t \leq 30$. Large-time

data points are used first to find the value of the elimination rate coefficient k using (7) which is illustrated by Figure 4a as semi-log graph.



(a) (b)

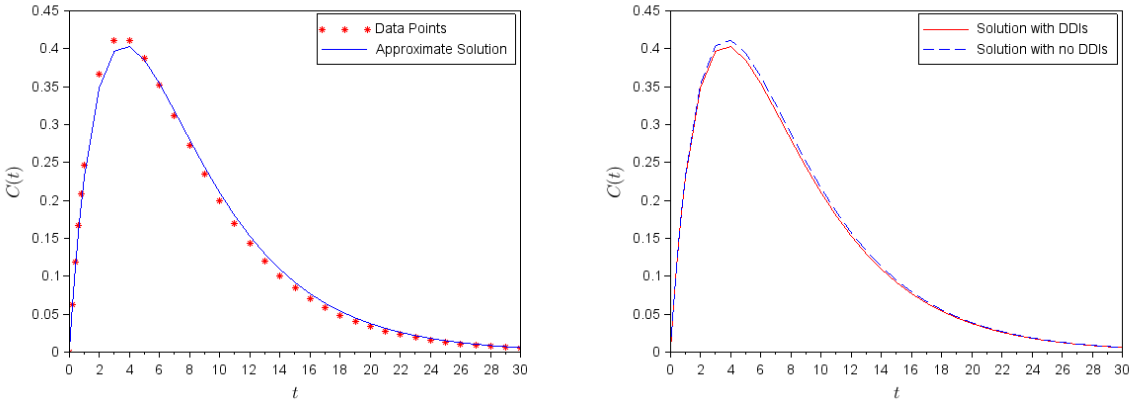
Figure 4. Comparison data set to its approximation (a) to find k using large-time data set and (b) to find ka using small-time data set for one-compartment model.

The star symbol represents the original data points, while the solid line indicates the fit model that takes the form $\ln C = -0.1860t + 0.3134$, calculated by (8) dan (9). As a result, we obtain $k = 0.1860$ which is close enough to the original value shown in Table 1. For the estimation k_a, we use small-time data points in the interval $0 \leq t \leq 0.4$. The first step we need to do is to calculate AUC using the trapezoidal rule so that the unabsorbed drug is able to be estimated by using (11), as shown in Table 2.

Table 2 : The fraction of unabsorbed drug for small-time phase for one-compartment-model

Time	**Concentration**	$\boldsymbol{\Delta t}$	$\boldsymbol{\Delta C}$	**AUC**	$\boldsymbol{1 - A_b/A_b^{\infty}}$
0.00	0.00	0.00	0.00	0.00	1.00
0.20	0.06	0.20	0.06	0.01	0.92
0.40	0.12	0.20	0.12	0.02	0.84

The results are shown in Table 2. Next, the unabsorbed drug values can be used to determine k_a through the linear fit model (see Figure 4b) presented by equation (19), where k_a is obtained from the slope of the linear fit model. By using the equation (20), the value of ka is estimated as 0.3916. The estimates k and k_a are then used to find the numerical solution of drug concentration so that it can be compared with the original data points. The comparison of these two produces root mean squared error (RMSE) of 0.0078. Graphically, the comparison can be seen clearly in Figure 5a. As we know, DDIs in this model affect the absorption process. Therefore, another simulation is performed to see the drug concentration level when DDIs are taken into account and when they are not. It can be seen in Figure 5b that the curve with DDIs is lower than the curve with no DDIs. In other words, there is a reduction in cumulative drug concentration for the model with DDIs compared with the one with no DDIs.



(a) (b)

Figure 5. Comparisons (a) the data points and the approximate solution of DDIs and (b) the drug concentrations with and without DDIs for one-compartment model.

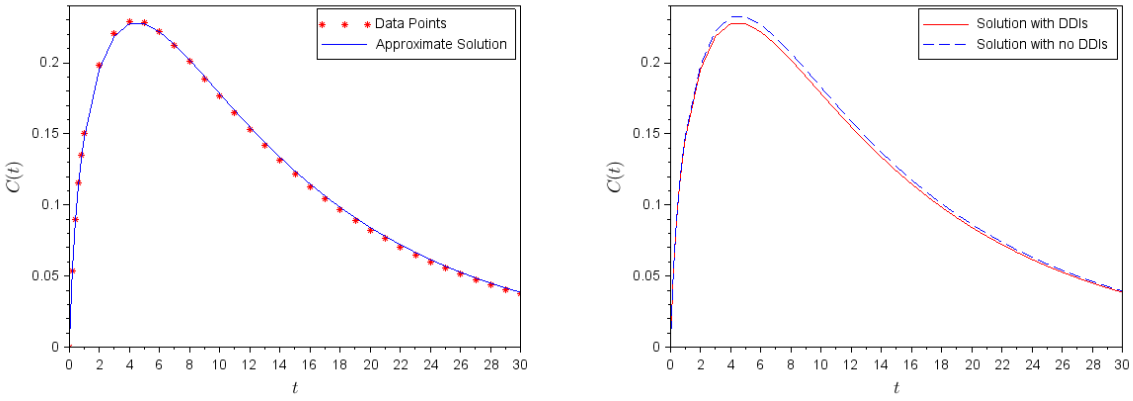
2. Two-compartment model

Estimation of the parameters k and k_a for the two-compartment model is performed using data points generated by the same parameter values as the one-compartment model given in Table 1, with the addition of parameters $k_{12} = 1.7/\text{hr}$ and $k_{21} = 1.3/\text{hr}$. We also use the same time interval, that is [0,30]. The generated data points from these parameter values can be seen in Figure 3b. Similar to the one-compartment model, in the two-compartment model the parameter k is estimated using large-time data points in the interval $12 \leq t \leq 30$, while k_a is estimated using small-time data points in $0 \leq t \leq 0.4$. To estimate k, given in (34), a number of parameters such as α, β and k_{21} must be calculated first. The parameter α can be determined based on the fit linear model in the form $\ln C = -0.0786t - 0.9273$. This fit model is associated with the calculation of the equations (30). From these calculations, we obtain $\alpha = 0.1809$ and $P = 0.3956$.

Table 3. The fraction of unabsorbed drug for small-time phase for two-compartment model

Time	C_c	C_p	Δt	ΔC_c	AUC	$1 - A_b/A_b^{\infty}$
0.00	0.00	0.00	0.00	0.00	0.00	1.00
0.20	0.05	0.01	0.20	0.05	0.01	0.91
0.40	0.09	0.03	0.20	0.14	0.02	0.83

Like α, the parameter β can also be obtained by constructing the linear fit model of the residual concentration given in (31). By using (32) and (33) equations, we obtain $\beta = 0.7504$ and $Q = 0.0114$. These four parameter values (α, β, P, Q) are then used to find k_{21} using the formula (34). Since k_{21} is now known, we can estimate k by (34) with the result $k = 0.1875$.



(a) (b)

Figure 6. Comparisons (a) the data points and the approximate solution of DDIs and (b) the drug concentrations with and without DDIs, for two-compartment model.

The parameter k_a is estimated by small-time data points, which is presented in Table 3. The linear fit model is established first as the semi-log graph between the unabsorbed drug concentration and time to obtain $k_a = 0.3943$ which is calculated from (39). The approximated parameters k, k_a, k_{12}, k_{21} along with the selected parameter $k_i = 0.0930$, are then inserted into the model (21) to obtain the approximation solution numerically. The Comparison of the approximate solution and the original data points is shown graphically in Figure 6a. From this comparison, the value of RMSE is obtained at 0.0017. Comparisons between the presence and absence of drug interactions in the two-compartment model are also performed here, and it is illustrated in Figure 6b. As can be seen in the figure, the cumulative of the drug concentrations in the blood with the presence of DDIs are smaller than the one with no DDIs.

Table 4. The comparison of the estimate parameter with the original values.

Model	k	k_a
Original	0.1896	0.4049
One-compartment	0.1860	0.3916
Two-compartment	0.1875	0.3943

From the simulations performed for the one and two-compartment DDIs models we can summarize and compare the original and the estimated parameter values as shown in Table 4. As can be seen in this table, the elimination rate constant k and the absorption rate constant k_a for the two-compartment model provide values that are closer to the original values compared to the one-compartment model. Qualitatively, the curve of the drug concentration for the two-compartment model appears to have smaller deviations from the original data points than that of the one-compartment model. We can compare them from Figures 5a and 6a.

D. CONCLUSION AND SUGGESTIONS

In this paper, the drug-drug interactions models of the one and two compartments are proposed, where the drug interaction coefficient is taken into account in the models so that it affects the absorption process. The elimination rate constant k and the absorption rate constant

k_a are the parameters to be estimated using the data set of time and drug concentration. We do not use the actual data points, instead the data points are generated from the input parameters including k and k_a. Using the Wagner-Nelson method for one-compartment model and the Loo-Riegelman method for the two-compartment model, the simulations show good estimation for both models as shown graphically by Figure 5a and 6a. Furthermore, comparing the estimated and the original values as given in Table 4, the two-compartment model gives a better approximate than the one-compartment model since both k and k_a for one-compartment model have closer values from the original one. This conclusion is consistent with the fact that organs and tissues in the body have different perfusion levels. The more the perfusion level is classified, the more it reflects the real situation of the body. In other words, a body with two different levels of perfusion more closely reflects the real situation than a body with only one level. This work can be extended to a model of three or more compartments, then see comparisons with the smaller compartment. Other factors such as drug-protein binding and circadian rhythm can also be considered in the model as well as investigating the DDIs effect on the drug delivery process when other routes of administration are performed.

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