Numerical Simulations of Drug Dynamics in Blood Using Compartment Modelling

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***Abstract*—The study of pharmacokinetics is crucial in the modern world due to the need for advanced drugs to improve healthcare and combat diseases. To represent drug behavior within a patient's body, mathematical modelling can be used and the derived system can be easily solved using numerical techniques, instead of relying solely on traditional clinical trials. This paper presents how various parameters affect drug behavior in the human body through compartment modelling which is a technique commonly used in pharmacokinetic modelling. The study used exact solution techniques like variable separation, eigenvalue method and integration factor method to solve model equations in each compartment. Since the complexity of the models can lead to challenging scenarios, this paper investigates the applicability and importance of using the fourth-order Runge-Kutta (RK4) method for pharmacokinetic modeling as a numerical solving method. Additionally, the study will present how drug dynamics relate to the route of administration and how the maximum concentration varies as per the slight changes in the pharmacokinetic parameters used within the model under the assumptions. The findings of this study will contribute to the field of clinical science and biomedical engineering by expediting the drug development process and improving the quality of drugs.**

***Keywords*—compartment modelling, eigenvalue method, fourth-order Runge-Kutta method (RK4), mathematical modelling, numerical method, numerical simulation, pharmacokinetic**

I. Introduction

Pharmaceuticals have always been essential for improving human health and combating certain diseases. In developing sophisticated drugs that meet the demands of the modern world, research in the field o f p harmacokinetic modelling plays a crucial role by enabling scientists to comprehend how a drug behaves inside a patient's body. Traditional clinical methods make observing drug behaviour within a patient's body challenging, which prompted mathematicians to develop pharmacokinetic modelling, a sub-branch of mathematical modelling that simplifies t he e ntire t rial p rocess. T here are various approaches to pharmacokinetic modelling, with compartment modelling being the most common and efficient.

Compartmental modelling simplifies a complex dynamic system by dividing it into separate compartments. This modelling approach originated from studies on tracer-labeled compound metabolism in the 1920s [1]. The most basic form of compartment modelling is the one-compartment model, which treats the entire system as a single-compartment. The number of compartments can be increased as necessary to achieve a more precise and accurate understanding of substance movement. A set of differential equations can be used to determine the concentration of a specific substance in a compartment based on its input and output flow. Consequently, increasing the number of compartments complicates the model, making it challenging to solve using known exact methods.

Despite the complexity of the mathematical models, due to the challenges associated with clinical trials in every stage of a drug development process, creating a more realistic version of the compartment model is required, which can simply represent the complex human body and solves the differential equations derived from it. Therefore, mathematicians used several analytical methods such as the Eigenvalue Method and Laplace Transformation (LT) to solve these differential equations [2]. However, due to the complexity, numerical solving methods are found to be more easier and efficient in solving which helps to approximate the solutions rather than finding the exact solutions without doing complex calculations which consumes more time and resources.

Considering the previous studies, it was found that G.A. Koch-Noble discussed one-compartment and two-compartment models as an application of mathematical modelling [3]. Tadeusz Władysław Hermann discussed the concentration of drugs in the central compartment using LT and inverse operation along with the partial fraction theorem [4]. Furthermore, Andrea McNally discussed how a drug moves and changes in the body to find the best dosage and timing with a single-compartment and two-compartment model using LT [5]. Also, enterohepatic circulation was analysed using

the Fast Inversion of LT [6]. Moreover, Eliete B. Hauser explored how to quantify the pharmacokinetic processes of a tracer which is a radiopharmaceutical using the LT method [7]. Recent studies by Prathvi Shenoy analyzed morphine and fentanyl distribution patterns using a two-compartment model, Runge–Kutta method and non-linear ordinary differential equations [10]. Two-compartmental models were also analyzed using Eigenvalues and eigenvector method [11]. Koyel Chakravarty discussed the stability analysis of drug dynamics model using Quasi Steady State Approximation [12]. Moreover, a recent study used the Particle Swarm Optimization (PSO) Algorithm for parameters estimation of a three compartment model [13].

Accordingly, compared to the recent studies, it has been proved that not much attention has been focused on having a comprehensive study to output more useful insights related to drug behavior in the human body as per the changes in the dosage of a drug, absorption rate or elimination rate and other parameters. Additionally, there were fewer studies to determine how changes in pharmacokinetic characteristics can affect a drug's maximum concentration in the human body. Therefore, this identified gap will be filled through this study using numerical simulations following validation with other exact solution techniques instead of using LT method.

II. Methodology

A. Model 1 – Single Compartment

In this model, the entire body was considered as a single compartment of blood and it is assumed that the drug is distributed uniformly throughout the body and eliminated at a single rate. Depending on how the drug is administered, this model can be analyzed using different methods. Here, the following two types of methods of administration were considered for this study;

1) Intravenous (IV) administration: When a drug is administrated through IV, it is considered that the whole concentration of the injected drug is exposed to the blood compartment. Therefore, only the elimination process of the drug is considered when forming the equation.

According to the Fig. 1 and based on the law of conservation of mass, the following equation was formed.

$$\frac{dx}{dt} = -x \cdot K_e \tag{1}$$

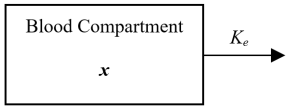

Fig. 1. Single-compartment model for an IV drug. Here, K_e is the elimination rate and x is the drug concentration of the blood compartment.

By using the variable separation method with the initial drug concentration of the blood as x_0, the following solution was obtained.

$$x = x_0 e^{-K_e t} \tag{2}$$

2) Oral administration: When a drug is administered orally, it's important to consider the rate at which the drug is absorbed in the gastrointestinal (GI) tract. As a result, in addition to the previous setup, GI tract compartment was included before the blood compartment. Although this may appear similar to a two-compartment model, the absorption of the drug into the blood compartment was taken as an input flow, which allowed the model to be represented with a single compartment.

In order to proceed with the model, the concentration of the drug in the blood compartment was calculated using the administered drug dose. This involved the volume of distribution (V_d) of the drug, which is a critical parameter in PK modelling. [3] The volume of distribution provides insight into the typical volume in which the drug is distributed within the body. By dividing the total mass of the drug in the blood compartment by its V_d, we can calculate the concentration of the drug in the blood compartment.

Therefore, according to the Fig. 2, the following differential equations are formed;

$$\frac{dA}{dt} = -A \cdot K_a \tag{3}$$

$$\frac{dx}{dt} = K_a \cdot (\frac{A}{V_d}) - x \cdot K_e \tag{4}$$

Equation (3) can be solved to give the following equation, using the initial drug dose as A_0.

$$A = A_0 e^{-K_a t} \tag{5}$$

Accordingly, equation (4) can be solved using the integrating factor method with the initial drug dose, A_0 as per below;

$$x = \left[\frac{K_a A_0}{V_d(K_e - K_a)e^{K_e t}}\right]\left\{e^{(K_e - K_a)t} - 1\right\} \tag{6}$$

B. Model 2 – Two compartment - IV administration

Two-compartment models are used to have a more realistic understanding of drug behavior by incorporating two distinct compartments as central and peripheral. Here, the central

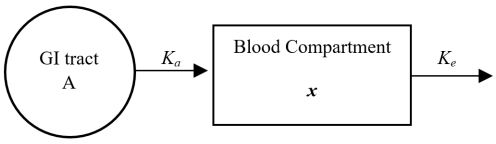

Fig. 2. Single-compartment model for an oral drug. Here, K_e is the elimination rate, K_a is the absorption rate and x is the drug concentration of the blood compartment. The drug mass in the GI tract is denoted by A

compartment represents the blood, while the peripheral compartment represents the tissues. This can also be represented as the simplified version of the human body, as blood works as the main transportation medium for the drug.

Increasing the number of compartments yields a more accurate and realistic model of the human body, leading to more precise results during calculations and providing more precise values during the solving process.

According to the Fig. 3, the following differential equations (DE) are formed;

$$\frac{dx_1}{dt} = -(K_1 + K_e) \cdot x_1 + K_2 \cdot x_2 \tag{7}$$

$$\frac{dx_2}{dt} = K_1 \cdot x_1 - K_2 \cdot x_2 \tag{8}$$

Here, two approaches are considered to get a solution for the drug concentrations of each compartment. Initially, the Eigenvalue method is used to obtain the exact solution. Afterwards, the Fourth Order Runge-Kutta Method (RK4) was used to obtain the numerical solution for the same model.

C. Model 2 - Solution using Eigenvalue Method

Using the equations 7 and 8, the coefficient matrix was written as per follows;

$$A = \begin{pmatrix} -K_1 - K_e & K_2 \\ K_1 & -K_2 \end{pmatrix} \tag{9}$$

Therefore, the Eigenvalues (λ) were obtained by solving the following equation.

$$det(A \ - \ \lambda \, I) = 0 \tag{10}$$

By simplifying the above, the following quadratic equation was obtained.

$$\lambda^2 \ + \ (K_1 \ + \ K_2 \ + \ K_e)\lambda \ + \ K_2 K_e = 0 \tag{11}$$

Since the above equation tends to give a real solution, the λ values were obtained as follows;

$$\lambda_1 = \frac{1}{2}(-(K_1+K_2+K_e)+\sqrt{(K_1+K_2+K_e)^2-4K_2K_e}) \tag{12}$$

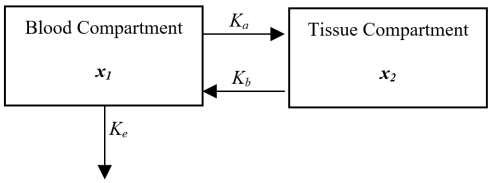

Fig. 3. Two-compartment model for an IV drug. Here, x_1 and x_2 are the drug concentration of the blood compartment and tissue compartment respectively. K_a is the transfer rate from blood compartment to tissue compartment and K_b is the transfer rate from tissue compartment to blood compartment. K_e is the elimination rate of the drug from the blood compartment.

$$\lambda_2 = \frac{1}{2}(-(K_1+K_2+K_e)-\sqrt{(K_1+K_2+K_e)^2-4K_2K_e}) \tag{13}$$

By finding the corresponding Eigenvectors to this Eigenvalues, the following was obtained;

$$for\ \lambda_1;\ \begin{pmatrix} n_1 \\ n_2 \end{pmatrix} \ \ \& \ \ for\ \lambda_2;\ \begin{pmatrix} n_3 \\ n_4 \end{pmatrix} \tag{14}$$

Using the above Eigenvectors and Eigenvalues, the general solution for the drug concentration at each compartment was obtained as per follows;

$$x_1(t) = C_1 e^{\lambda_1 t}(n_1) \ + \ C_2 e^{\lambda_2 t}(n_3) \tag{15}$$

$$x_2(t) = C_1 e^{\lambda_1 t}(n_2) \ + \ C_2 e^{\lambda_2 t}(n_4) \tag{16}$$

Here, the arbitrary constants, C_1 and C_2 can be calculated using the initial conditions of the used compartment model.

Due to the complexity of solving a two or more-compartments model using the Eigenvalues method, particularly, when increasing the number of compartments, we considered the RK4 method to calculate the numerical solution.

D. Model 2 - Solution using RK4 Method

The RK4 method is widely recognized as the most reliable numerical solution technique among other numerical methods such as Euler Method and also other variations of the RK method. Similar to other numerical methods, RK4 use numerical calculation method that can be easily done. However, the main significance of RK4 method compared to other numerical methods, is the accuracy of the results. It offers approximate solutions that align more closely with the exact results [14]. Furthermore, the simplicity of implementation of the RK4 method to a complex problem is another significance. As a result, this method was employed to determine the solution for the two-compartment model.

The general formula for the RK4 method is as follows;

$$y_{n+1} = y_n + \frac{(k_1 + 2k_2 + 2k_3 + k_4)}{6} \tag{17}$$

Here k_1, k_2, k_3 and k_4 can be calculated using the following equations;

$$k_1 = hf(t_n, y_n) \tag{18}$$

$$k_2 = hf(t_n + \frac{h}{2}, y_n + \frac{k_1}{2}) \tag{19}$$

$$k_3 = hf(t_n + \frac{h}{2}, y_n + \frac{k_2}{2}) \tag{20}$$

$$k_4 = hf(t_n + h, y_n + k_3) \tag{21}$$

Here, h is the step size of the RK4 method. We can vary this value to get the optimum solution for the model which is more closer to the exact solution.

To solve the system of differential equations (DE) consisting of eq.7 and eq.8, the above RK4 method was applied to both compartments independently but simultaneously.

All the above simulations were executed using MATLAB software. The pseudocode of the written MATLAB code for the RK4 method can be expressed as in algorithm 1.

Algorithm 1 Pseudocode of MATLAB code for RK4 Method

$t = 0$ **to** t_{end}
while until t reaches the t_{end} **do**
  $Find\ RK\ coefficients\ for\ the\ central\ compartment$
  $Find\ RK\ coefficients\ for\ the\ peripheral\ compartmen$
  $Find\ concentration\ for\ the\ central\ compartment$
  $Find\ concentration\ for\ the\ peripheral\ compartment$
  $Store\ calculated\ values$
  $Increase\ t\ by\ the\ step\ size(h)$
end while
Plot *the result*

III. Results and Discussion

This study was based on several assumptions. It was assumed that only the variables considered within the study affect the concentration of a drug inside the body and rates such as absorption, elimination and other transfer rates do not change over time. Additionally, the patient's physical conditions or drug charactersitcs were not considered in developing these models.

However, in real-world scenarios, the absorption rate is influenced by the route of administration, while the elimination rate is affected by various factors and the condition of the internal organs associated with circulation. Moreover, both of these are directly affected by the drug characteristic. Typically, these rates exhibit a proportional relationship. However, when attempting to solve the system of differential equations (DE) formulated for the model, incorporating proportional and dynamic rates can introduce significant complexity, making it challenging to utilize standard solving methods.

Hence, this study assumed these rates to be constant to simplify the model's solving process. Considering all the conditions that affect the model would result in significantly more complex equations, making them challenging to solve using standard methods. However, considering these things are needed to create more realistic simulation of the drug behavior. Therefore, to gain a more realistic understanding of the drug's behavior inside the body, the study can be extended incorporating other parameters.

Within this study, the behaviour of the same drug under different conditions was observed before proceeding to solve the two-compartment model using the RK4 Method.

Initially, the behaviour of a drug concentration in a single-compartment model was observed when the drug was administered orally and intravenously. (*see Fig. 4*)

For the simulation in Fig. 4, we considered an intravenously administered drug with an initial concentration of $0.8mgl^{-1}$ and an orally administered drug with an initial dose of $80mg$ and a V_d of $100l$. The simulation plot indicated that the intravenously administered drug experiences exponential decay over time, whereas the orally administered drug demonstrates both growth and decay, reaching a peak concentration of $0.4mgl^{-1}$ which was reported 7 hours after the dose was given. Furthermore, it was noted that the oral drug reached maximum concentration at the half-life of the IV drug, which

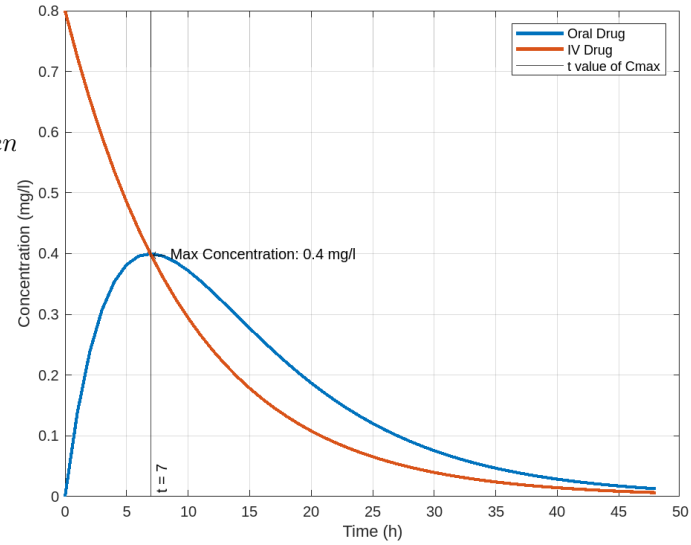

Fig. 4. Drug concentration in the single-compartment model over time for an oral administration along with an IV administration of the same drug. Here the parameter values of the oral drug are $K_a = 0.2h^{-1}$, $K_e = 0.1h^{-1}$, $V_d = 100l\ and\ A_0 = 80mg$. The parameter values of the IV drug are $x_0 = 0.8mgh^{-1}\ and\ K_e = 0.1h^{-1}$.

is the time taken for the concentration of the drug to reach half of its initial value.

In order to gain a better understanding of the behavior of an oral drug, we conducted simulations in which we varied each variable while keeping others constant.

The simulation depicted in Fig. 5 revealed that a reduction in the absorption rate of an oral drug led to a decrease in the maximum concentration of the drug while resulting a increase the time required to reach that concentration.

Through the simulation of Fig. 6, it was observed that when the elimination rate of an oral drug decreases, the maximum concentration of that specific drug along with the half-life of that drug varies inverse proportionally by increasing the value.

Based on simulations from the Fig. 7 and Fig. 8, it is evident that the maximum concentration of an oral drug is influenced by the V_d and the initial drug dose. Meanwhile, the half-life along with the time it need to reach the maximum concentration of the drug remains unaffected by changes in these rates.

Our study aimed to evaluate the suitability of using the RK4 method for pharmacokinetic compartment modelling of intravenously administered drugs compared to more complex exact methods. In our simulation in Fig. 9, we found that the RK4 method yields a solution equivalent to the Eigenvalue method for the two-compartment model. Moreover, compared to Fig. 4, concentration-time profile of Fig. 9 indicates rapid initial distribution followed by slower elimination which better reflects the reality of drug distribution in the human body. Furthermore, the concentration decay in the central compartment and the growth along with the decay of the peripheral compartment exhibited consistent patterns across

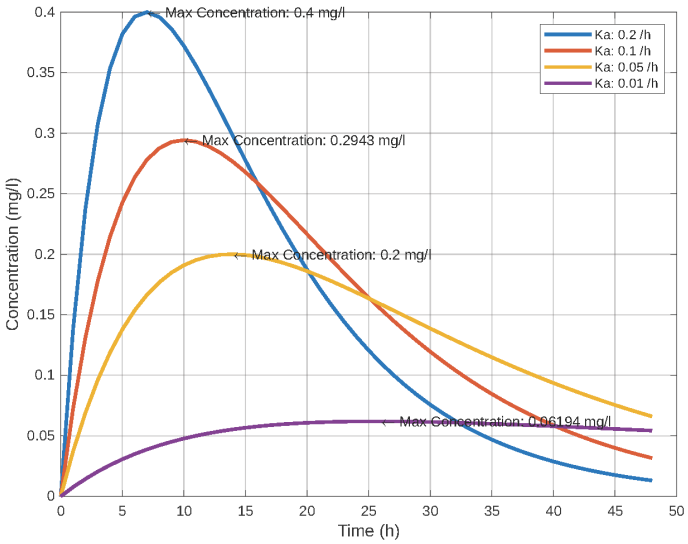

Fig. 5. Drug concentration in the single-compartment model over the time for an orally administered drug. Here, the absorption rate (K_a) was changed as 0.2, 0.1, 0.05 and 0.01 h^{-1} while having other rates at a constant of $A_0 = 80mg$, $K_e = 0.1h^{-1}$ and $V_d = 100l$. This indicates that a decrease in the absorption rate lowers the maximum concentration of the drug.

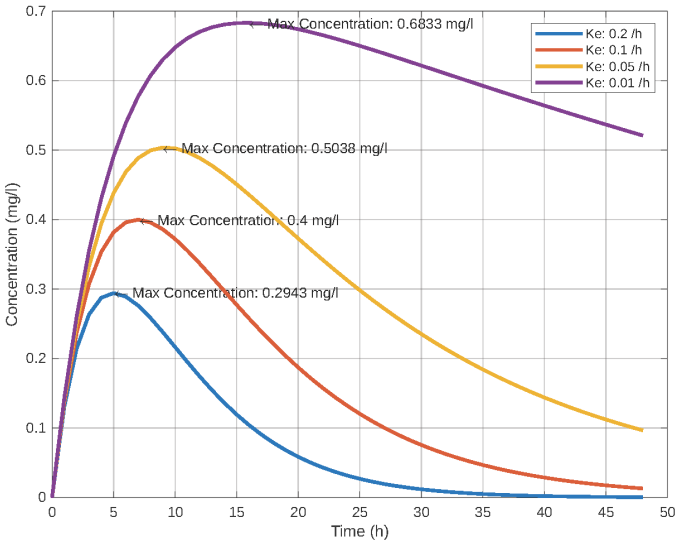

Fig. 6. Drug concentration in the single-compartment model over the time for an orally administered drug. Here, the elimination rate (K_e) was changed as 0.2, 0.1, 0.05 and 0.01 h^{-1} while having other rates at a constant of $A_0 = 80mg$, $K_a = 0.2h^{-1}$ and $V_d = 100l$. The decrease in the absorption rate leads to a higher maximum concentration of the drug.

both methods.

Additionally, both methods resulted in a maximum concentration of $0.1699mgl^{-1}$ in the peripheral (tissue) compartment, reported at the same time after the drug is administrated in both oral and IV methods.

Moreover, it was determined that the percentage error between the values derived from the two methods was 0.004385%, which highlighted the significance of accuracy in the results. The study also observed that the drug concentration reached it's stable equilibrium state of zero concentration at

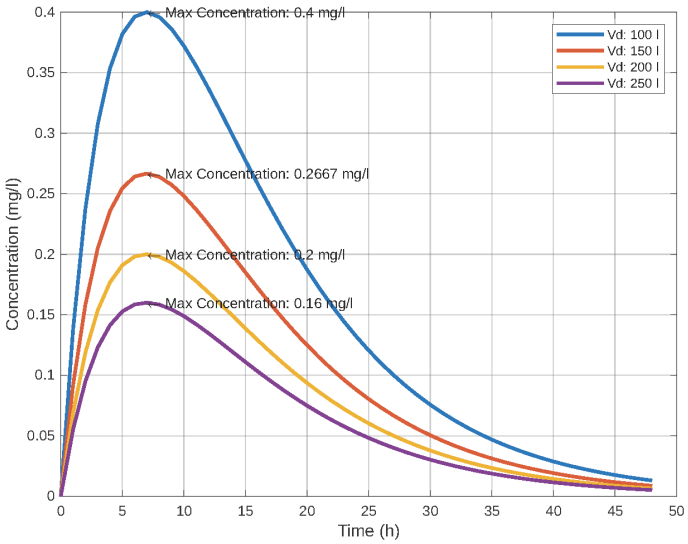

Fig. 7. Drug concentration in the single-compartment model over the time for an orally administered drug. Here, the volume of distribution (V_d) was changed as 100, 150, 200 and 250 l while having other rates at a constant of $A_0 = 80mg$, $K_a = 0.2h^{-1}$ and $K_e = 0.1h^{-1}$. This indicates that as the volume of distribution increases, the maximum concentration of the drug decreases.

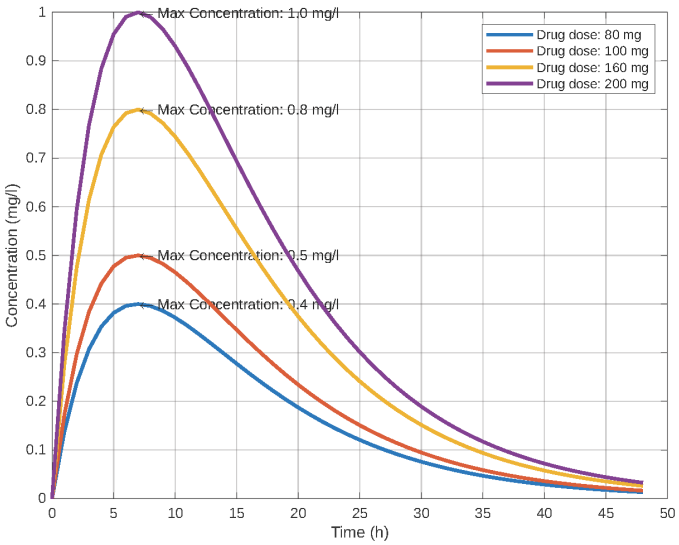

Fig. 8. Drug concentration in the single-compartment model over the time for an orally administered drug. Here, the initial drug dose (A_0) was changed as 80, 100, 160 and 200 mg while having other rates at constant of $V_d = 100l$, $K_a = 0.2h^{-1}$ and $K_e = 0.1h^{-1}$. This indicates that the maximum concentration of the drug increases in proportion to the dosage administered.

the end due to the elimination rate.

IV. Conclusion

In this paper, we observed the significance of absorption rate, elimination rate and volume of distribution due to their direct impact on the behavior of a specific drug in the human body. The study found how the maximum concentration of the drug in the blood compartment relates to these variables. Our observations also revealed that variations in absorption and

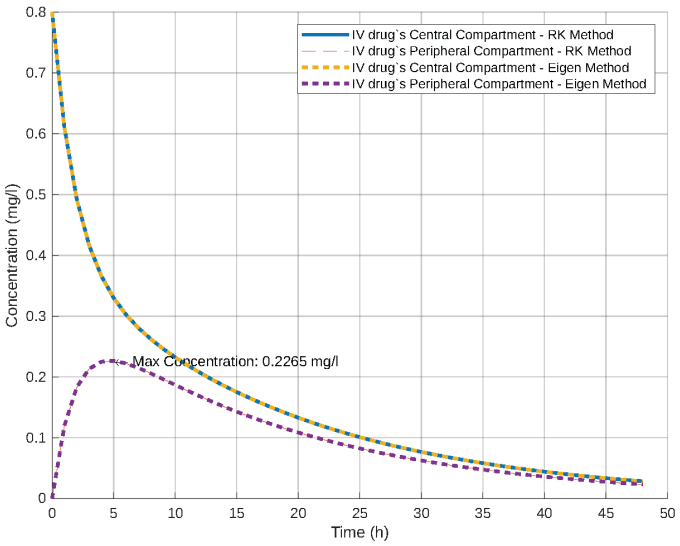

Fig. 9. Drug concentration in the two-compartment model over the time using the Eigenvalue method and the RK4 method. Here, initial drug concentration at the blood compartment $x_0 = 0.8mgl^{-1}$, $K_1 = 0.2h^{-1}$, $K_2 = 0.3h^{-1}$ and $K_e = 0.1h^{-1}$. This shows that the difference in error between these two methods is very small.

elimination rates can influence the maximum drug concentration in the blood compartment without altering the drug dose. Additionally, we found that, among the factors we examined, only the absorption and elimination rates affect the drug's half-life, making them critical considerations when designing a therapeutic process. Based on our study on the applicability of the RK4 method for solving a two-compartment model in comparison to exact methods, the RK4 method was found to be both easier and more efficient to implement. It offers simplicity and precision, yielding results comparable to exact solutions with a percentage error of less than 0.1%. The study also shows that the stability issues typically associated with the RK4 method can be effectively addressed by using a step size of 1. Furthermore, the RK4 method's straightforward implementation highlights its potential for solving compartment models with an increased number of compartments. The results of this study can be validated through clinical data and future research may extend the model by incorporating additional compartments to enhance the realism of the outcomes.

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