Drug Elimination in Two-Compartment Pharmacokinetic Models with Nonstandard Finite Difference Approach

Niswatus Sa'adah A.M, Widodo, and Indarsih

Abstract—We use the nonstandard finite difference (NSFD) method to solve the two-compartments pharmacokinetic models of drug elimination. Pharmacokinetic models are commonly used to predict drug concentrations in the body. These models are modeled by nonlinear ordinary differential equations. We apply the NSFD rules, based on Mickens' idea of transferring nonlinear models into discrete schemes. The method used was compared with other established methods to verify its efficiency and accuracy. Two-compartment pharmacokinetic models are considered for different routes of administration: I.V. bolus injection and I.V. bolus infusion.

Index Terms—pharmacokinetics, intravenous bolus injection, intravenous bolus infusion, nonstandard finite difference, Michaelis-Menten elimination.

I. INTRODUCTION

PHARMACOKINETICS is the study of the dynamics of drugs in the body. The dynamics or behavior of drugs in the body can be described mathematically into a pharmacokinetic model. This model is very helpful in understanding the biological processes that occur in a drug that is inserted into the human body.

The pharmacokinetic model has three types namely, compartment, physiological and non-compartmental. The model that uses compartments is known as a very simple and very useful tool in describing pharmacokinetic dynamics. Drugs have various dosage forms and ways of administration according to function and purpose. Drugs that are inserted into the body, will be released from its dosage form and will be absorbed into the surrounding tissue. Parts of the human body are classified into several parts called compartments. In the case of pharmacokinetics, the number of compartments in the model depends on the rate of distribution of the drug to various parts of the body. Once distributed, the drug will be eliminated from the body, which means the drug levels in the bloodstream and tissues decrease at the same rate due to the rapid distribution balance. Drugs that follow this behavior are called one compartment pharmacokinetic models. If the speed of drug distribution differs from one tissue to another, the pharmacokinetic model follows two or more compartments [1].

The distribution and elimination of drugs in the body varies greatly between one patient to another, depending on the body condition of each patient, but the distribution and elimination of these drugs can be characterized using mathematical models and statistics. This characterization is very needed in determining the dosage, dosage form and method of drug administration to patients, so that drug administration can be carried out appropriately and the treatment goals can be achieved. In general, the method of drug administration can be divided into two. The first is intravascularly, namely the drug will be directly inserted into blood vessels. The second is extravascularly, the drug is not put directly into blood vessels, so the drug must be absorbed before entering the blood vessels [2].

Drugs put into the body are generally carried by blood. Blood vessels act as a place for blood flow to spread throughout the body, allowing drugs to enter the target tissue that requires treatment. This process describes the process of drug distribution, which is when a drug spreads in blood vessels, and the process of elimination is when a drug comes out of the blood into the target tissue. In this process, the blood vessels act as the main compartment as a place for changes in drug concentration due to the elimination process. Generally the drug concentration uses units of mg/dL which describe the amount of drug (mg) in 1 dL of blood. The compartment model formed is a one compartment model because it only considers blood vessels as the only compartment. This compartment model is assumed that there is a fast and perfect distribution of the drug in each part of the blood vessels that illustrates the concentration of the drug in the main compartment. A simple pharmacokinetic model is based on the assumption of a linear relationship between the amount of drug concentration and the change of its concentration per unit time. But in actual conditions in the body, biological processes that occur in drugs form nonlinear relationships due to absorption, distribution, metabolism and drug elimination [3]. A model that has a non-linear relationship is difficult to obtain a solution so numerical methods are used as an approach.

Pharmacokinetic models can be presented in the form of differential equations. There are a number of articles that have used numerical methods to solve the pharmacokinetic model [4], [5], [6].The numerical method that is commonly used to solve a differential equation is the standard finite difference (SFD). The SFD scheme is carried out by replacing the derivative form in the differential equation with the difference quotient formula [7]. Although SFD is often used, this scheme has several deficiencies so that it can cause numerical instability. These shortcomings include: producing unnecessary oscillations, providing false solutions that are not in corresponding with the analytical solution and the results given are converging to fixed point solutions that are not in corresponding with the model [8]. This limitation has led Mickens to develop alternative methods that can produce

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approximate solutions for various differential equations, both of which the analytic solutions are easy to obtain or difficult to obtain, and reduce the numerical instability that can be generated by the SFD scheme [8]- [11]. This method is known as the nonstandard finite difference (NSDF). Apart from being an alternative method for the SFD method, NSDF schemes can be used when exact finite difference schemes cannot be formed because there is no information related to analytical solutions from the differential equation model.

II. THE NONSTANDARD FINITE DIFFERENCE METHOD

Numerical approaches have been frequently used in continuous models. It is well known that traditional schemes like forward Euler and others, sometimes fail generating oscillations, bifurcations, chaos and false steady states. One alternative to prevent these classes of numerical instabilities is the construction of numerical schemes using nonstandard finite difference method. The NSFD procedures, developed by Mickens [10], [11], are based on following rules,

1) the discrete first-derivative has the representation

$$\frac{du}{dt} \longrightarrow \frac{u_{k+1} - \psi u_k}{\phi}$$

where ψ and ϕ depends on *step-size* $\Delta t = h$ and satisfy the conditions

$$\psi = 1 + \mathcal{O}(h), \quad \phi = h + \mathcal{O}(h^2).$$

The functions of ψ and ϕ can differ from one another. While no general principles currently exist for selecting the functions $\psi(h)$ and $\phi(h)$, particular forms for a specific equation can easily be determined. Functional forms commonly used for $\psi(h)$ and $\phi(h)$ are

$$\phi(h) = \frac{e^{\lambda h} - 1}{\lambda}, \quad \psi(h) = 1,$$

where λ is some parameter appearing in the differential equations.

2) both linear and nonlinear terms may require a nonlocal representation on the discrete computational; for example,

$$x \Longrightarrow 2x_k - x_{k+1},$$
$$x^3 \Longrightarrow \left(\frac{x_{k+1} + x_{k-1}}{2}\right) x_k^2,$$
$$x^3 \Longrightarrow 2x_k^3 - x_k^2 x_{k+1},$$
$$x^2 \Longrightarrow \left(\frac{x_{k+1} + x_k + x_{k-1}}{3}\right) x_k.$$

There are some preliminary rules for constructing denominator functions for system of coupled, first-order, ordinary differential equations:

1) Form an initial, finite difference model by replacing all first-derivatives by discrete forward-Euler terms.
2) For a particular discrete equation, in general, its dependent variable will occur linearly in its evaluation at the $(k+1)$-th time step. Solve for this dependent variable, at the $(k+1)$-th time step, in terms of all other dependent variables evaluated at the k-th time step.
3) If a factor in a particular discrete equation contains an expression of the form $(1 + \lambda h)$, where λ is composed

of one or more parameters appearing in the original differential equations, then the denominator function can be selected as

$$\phi(h, \lambda) = \frac{e^{\lambda h} - 1}{\lambda}.$$

4) In the discrete finite-difference schemes, constructed in (1), replace h by the appropriate $\phi(h, \lambda)$.
5) For the case where $\lambda = 0$, use as the denominator function $\phi(h) = h$.

III. PHARMACOKINETIC MODEL OF TWO COMPARTMENTS

In the pharmacokinetic model of one compartment, the drug that is inserted into the body is assumed to be mixed and spread quickly and evenly so that the body is considered as one compartment. This assumption is a simplification of the actual event. The distribution of drugs in the body is actually not equal, depending on the nature of the drug and the structure of the place or tissue where the drug is spread. In this study, it is assumed that the body is divided into two parts or compartments, namely the compartment with a rapid spread or called the central compartment, and compartments with a relatively slower spread or called the peripheral compartment. The central compartment consists of blood flow and tissues that are mostly passed through the bloodstream such as the kidneys and liver, while the peripheral compartments include fat and muscle where these tissues are slightly passed through the bloodstream so the spread of drugs in them is relatively low [1]. Another assumption applied is that drug elimination occurs only in the central compartment, so drugs in the peripheral compartment must be transferred back to the central compartment [5]. This assumption is given because most drugs are eliminated by tissues that are in the central compartment. These assumptions produce a pharmacokinetic model with two compartments.

The drug that is put into the body will dissolve in the appropriate compartment fluid so that the drug in the body is expressed in terms of concentration, i.e. the amount of the drug divided by the volume of compartmental fluid, or $C = A/V$ with A is the amount of drug in mg, V is the volume of compartments in units of mL, and C is the concentration of drugs in the compartment (mg/mL).

The drug is given in small quantities so the concentration in the body will also be small, so that its elimination from the central compartment will also be linear. Drugs given in large quantities will result in high concentration in the body. Each tissue has a different ability to eliminate drugs. Tissues that have low elimination ability will be saturated when the concentration of drugs in the body is high. This saturation results in elimination occurring nonlinearly following the Michaelis-Menten kinetics. Whereas for tissue with fast elimination capabilities, elimination remains linear [1].

The process of elimination in the two compartment pharmacokinetic model with nonlinear elimination will be reviewed in the following two administration methods:

A. I.V. Bolus Injection

At I.V. injection, all doses of the drug will enter directly into the bloodstream or central compartment and will then enter the peripheral compartment. Apart from entering into
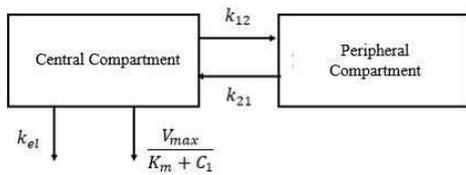
Fig. 1. Illustration of drug movement in the case I.V. bolus injection scheme with nonlinear elimination in the two compartment model

the peripheral compartment, the drug will also be eliminatied from the central compartment which in this case elimination occurs nonlinearly. Figure 1 provides an illustration of the movement of drugs in two-compartment. In Figure 1 it appears that the concentration of the drug available in the central compartment will enter the peripheral compartment at the speed of k_{12}. Because the assumption was given that elimination only occurs in the central compartment, the concentration of the drug in the peripheral compartment will return to the central compartment with speed k_{21}. Furthermore, the drug will be eliminated from the central compartment in two ways, namely linearly with a speed of k_{el} and non-linearly following the kinetics of Michaelis-Menten, $\frac{V_{max}}{K_m + C_1}$, with V_{max} is the maximum elimination capacity, K_m is the Michaelis coefficient and C_1 is the concentration in the central compartment. From Figure 1, a system of differential equations can be formed which illustrates the change of drug concentration in the body as follows,

$$\frac{dC_1}{dt} = -k_{el}C_1 - \frac{V_{max}}{K_m + C_1}C_1 - k_{12}C_1 + k_{21}C_2, \quad (1)$$

$$C_1(0) = C_{1,0}$$

$$\frac{dC_2}{dt} = -k_{21}C_2 + k_{12}C_1, \quad (2)$$

$$C_2(0) = 0$$

where C_2 is the concentration of the drug in the peripheral compartment. Analytical solutions for the (1)-(2) system are difficult to obtain, so solutions will be observed around the equilibrium point. The equilibrium point is the point when there is no change in concentration in a compartment, or the rate of concentration that enters the compartment is the same as the rate that exits the compartment. The equilibrium point is the point that satisfies $\frac{dC_1}{dt} = 0$ and $\frac{dC_2}{dt} = 0$ so that it is obtained

$$-k_{el}C_1 - \frac{V_{max}}{K_m + C_1}C_1 - k_{12}C_1 + k_{21}C_2 = 0, \quad (3)$$

$$-k_{21}C_2 + k_{12}C_1 = 0. \quad (4)$$

The Equation (4) is then substituted into the (3) equation so that it is obtained

$$-\left(k_{el} + \frac{V_{max}}{K_m + C_1}\right)C_1 = 0.$$

The result obtained is $C_1 = 0$ or

$$k_{el} + \frac{V_{max}}{K_m + C_1} = 0$$

$$\iff C_1 = -\left(\frac{V_{max}}{k_{el}} + K_m\right). \quad (5)$$

The first possibility is $C_1 = -\left(\frac{V_{max}}{k_{el}} + K_m\right)$. All parameters in this model are positive, so C_1 in Eqs. (5) produces

a negative value. A negative C_1 value does not reflect the condition of drug concentration in the body, so this point is not used. The second possibility is $C_1 = 0$ and produce $C_2 = 0$. So the equilibrium point of the (1)-(2) system is $(C_1^*, C_2^*) = (0, 0)$.

Furthermore, linearization is conducted at $(0, 0)$. The first step is to determine the Djacobian matrix of the nonlinear (1)-(2) system, i.e.,

$$D(C_1, C_2) = \begin{pmatrix} -k_{el} - \frac{V_{max}}{K_m + C_1} - k_{12} & k_{21} \\ k_{12} & -k_{21} \end{pmatrix},$$

So the linearization of the (1)-(2) system at point $(0, 0)$ is

$$\begin{pmatrix} \frac{dC_1}{dt} \\ \frac{dC_2}{dt} \end{pmatrix} = \begin{pmatrix} -k_{el} - \frac{V_{max}}{K_m} - k_{12} & k_{21} \\ k_{12} & -k_{21} \end{pmatrix} \begin{pmatrix} C_1 \\ C_2 \end{pmatrix}$$

or

$$\frac{dC_1}{dt} = -\left(k_{el} + \frac{V_{max}}{K_m} + k_{12}\right)C_1 + k_{21}C_2 \quad (6)$$

$$\frac{dC_2}{dt} = k_{12}C_1 - k_{21}C_2 \quad (7)$$

Analytical solutions for concentration in the central compartment, C_1, and the peripheral compartment, C_2, are obtained using the Laplace transformation, $\mathcal{L}$, as follows.

- Eqs. (6)

$$\mathcal{L}\left[\frac{dC_1}{dt}\right] = \mathcal{L}\left[-k_{el}C_1 - \frac{V_{max}}{K_m} - k_{12}C_1 + k_{21}C_2\right]$$

$$\Leftrightarrow \left(s + k_{el} + \frac{V_{max}}{K_m} + k_{12}\right)\mathcal{L}[C_1] - k_{21}\mathcal{L}[C_2] = C_{1,0}$$

$$\Leftrightarrow \left(s + k_{el} + \frac{V_{max}}{K_m} + k_{12}\right)Q_1 - k_{21}Q_2 = C_{1,0}, \quad (8)$$

where $Q_1 = \mathcal{L}[C_1]$ and $Q_2 = \mathcal{L}[C_2]$.

- Eqs. (7)

$$\mathcal{L}\left[\frac{dC_2}{dt}\right] = \mathcal{L}[k_{12}C_1 - k_{21}C_2]$$

$$\iff s\mathcal{L}[C_2] - C_2(0) = k_{12}\mathcal{L}[C_1] - k_{21}\mathcal{L}[C_2]$$

$$\iff -k_{12}\mathcal{L}[C_1] + (s + k_{21})\mathcal{L}[C_2] = 0$$

$$\iff -k_{12}Q_1 + (s + k_{21})Q_2 = 0. \quad (9)$$

Next, Eqs. (9) is substituted into Eqs. (8), so that it is obtained

$$Q_2 = \frac{k_{12}C_{1,0}}{(s + \lambda_1)(s + \lambda_2)}, \quad (10)$$

where

$$\lambda_{1,2} = \frac{1}{2}\left(\left(k_{el} + \frac{V_{max}}{K_m} + k_{12} + k_{21}\right)\right.$$

$$\left. \pm \sqrt{\left(k_{el} + \frac{V_{max}}{K_m} + k_{12} + k_{21}\right)^2 - 4\left(k_{el} + \frac{V_{max}}{K_m}\right)k_{21}}\right).$$

The solution for the peripheral compartment is obtained by using the inverse Laplace transform in Eqs.(10), so that it is

obtained

$$C_2(t) = \mathcal{L}^{-1}[Q_2]$$
$$= \mathcal{L}^{-1}\left[\frac{k_{12}C_{1,0}}{(s+\lambda_1)(s+\lambda_2)}\right]$$
$$= \frac{k_{12}C_{1,0}}{\lambda_2 - \lambda_1}\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right). \qquad (11)$$

Eqs.(11) is then substituted into Eqs.(7) to get the solution from the central compartment, $C_1(t)$. The results given are as follows,

$$C_1(t) = \frac{(k_{21}-\lambda_1)C_{1,0}}{\lambda_2-\lambda_1}e^{-\lambda_1 t} + \frac{(\lambda_2-k_{21})C_{1,0}}{\lambda_2-\lambda_1}e^{-\lambda_2 t}.$$

So the concentration of the drug in the central compartment, $C_1(t)$, and the peripheral compartment, $C_2(t)$, around the equilibrium point, $(C_1^*, C_2^*) = (0,0)$ are

$$C_1(t) = \frac{(k_{21}-\lambda_1)C_{1,0}}{\lambda_2-\lambda_1}e^{-\lambda_1 t} + \frac{(\lambda_2-k_{21})C_{1,0}}{\lambda_2-\lambda_1}e^{-\lambda_2 t}$$
$$C_2(t) = \frac{k_{12}C_{1,0}}{\lambda_2-\lambda_1}\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right).$$

Next will be determined numerical solutions of Eqs. (6)-(7) in the form of NSFD and SFD for comparison. Using a forward-Euler schemes to construct The SFD schemes, Equation (6)-(7) becomes

$$\frac{C_{1,k+1}-C_{1,k}}{h} = -\left(k_{el} + \frac{V_{max}}{K_m + C_{1,k}} + k_{12}\right)C_{1,k}$$
$$+ k_{21}C_{2,k} \qquad (12)$$
$$\frac{C_{2,k+1}-C_{2,k}}{h} = k_{12}C_{1,k} - k_{21}C_{2,k}. \qquad (13)$$

To construct the NSFD schemes, using a forward-Euler schemes for the first derivative and nonlocal representations for other terms, Equation (1) becomes

$$\frac{C_{1,k+1}-C_{1,k}}{h} = -\left(k_{el} + \frac{V_{max}}{K_m + C_{1,k}} + k_{12}\right)C_{1,k+1}$$
$$+ k_{21}C_{2,k}.$$

Solving for $C_{1,k+1}$ gives the expression

$$C_{1,k+1} = \frac{C_{1,k} + k_{21}hC_{2,k}}{1 + (k_{el}+k_{12})h + \frac{V_{max}h}{K_m+C_{1,k}}}.$$

Since $(1+(k_{el}+k_{12})h)$ occurs, based on point (3) [11], it follows that the denominator function should be selected to have the form

$$\phi(h, k_{el}, k_{12}) = \frac{e^{(k_{el}+k_{12})h}-1}{k_{el}+k_{12}}.$$

Thus, the NSFD schemes of Equation (1) is

$$\frac{C_{1,k+1}-C_{1,k}}{\phi} = -\left(k_{el} + \frac{V_{max}}{K_m + C_{1,k}} + k_{12}\right)C_{1,k+1}$$
$$+ k_{21}C_{2,k}$$

In the same way, we have the NSFD scheme for Equation (2) becomes

$$\frac{C_{2,k+1}-C_{2,k}}{\phi} = k_{12}C_{1,k+1} - k_{21}C_{2,k+1}.$$
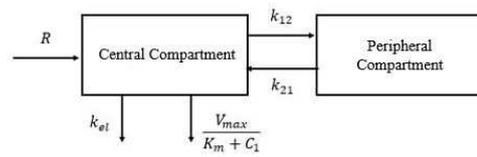
Fig. 2. Illustration of drug movement in the case I.V. bolus infusion scheme with nonlinear elimination in the two compartment model

So that the NSFD scheme is obtained as follows

$$\frac{C_{1,k+1}-C_{1,k}}{\phi} = -\left(k_{el} + \frac{V_{max}}{K_m + C_{1,k}} + k_{12}\right)C_{1,k+1}$$
$$+ k_{21}C_{2,k}, \qquad (14)$$
$$\frac{C_{2,k+1}-C_{2,k}}{\phi} = k_{12}C_{1,k+1} - k_{21}C_{2,k+1}, \qquad (15)$$

B. I.V. Bolus Infusion

The second method of drug administration is intravenous infusion, where the drug is inserted into blood vessels or central compartment slowly at a constant rate that is equal to the speed of drug infusion. After entering the central compartment, the drug will undergo the same process as the IV injection case, which is entered into the peripheral compartment and also eliminated. Figure 2 provides an illustration of the movement of drugs in compartment two with nonlinear elimination. From the Figure 2, a system of differential equations can be formed which illustrates the changes in drug concentration in the body as follows,

$$\frac{dC_1}{dt} = R - k_{el}C_1 - \frac{V_{max}}{K_m + C_1}C_1 - k_{12}C_1 + k_{21}C_2,$$
$$(16)$$
$$C_1(0) = 0$$
$$\frac{dC_2}{dt} = -k_{21}C_2 + k_{12}C_1, \qquad (17)$$
$$C_2(0) = 0$$

where R represents the drug flow rate and C_2 is the drug concentration in the peripheral compartment. Furthermore, using a forward-Euler schemes to construct The SFD schemes, Equations (16)-(17) becomes

$$\frac{C_{1,k+1}+C_{1,k}}{h} = R - k_{el}C_{1,k} - \frac{V_{max}}{K_m + C_{1,k}}C_{1,k}$$
$$- k_{12}C_{1,k} + k_{21}C_{2,k}, \qquad (18)$$
$$\frac{C_{2,k+1}+C_{2,k}}{h} = -k_{21}C_{2,k} + k_{12}C_{1,k}, \qquad (19)$$

To construct the NSFD schemes, using a forward-Euler schemes for the first derivative and nonlocal representations for other terms, Equation (16) becomes

$$\frac{C_{1,k+1}-C_{1,k}}{h} = R - k_{el}C_{1,k+1} - \frac{V_{max}}{K_m + C_{1,k}}C_{1,k+1}$$
$$- k_{12}C_{1,k+1} + k_{21}C_{2,k}.$$

Solving for $C_{1,k+1}$ gives the expression

$$C_{1,k+1} = \frac{Rh + C_{1,k} + k_{21}hC_{2,k}}{1 + (k_{el}+k_{12})h + \frac{V_{max}h}{K_m+C_{1,k}}}.$$

Since $(1+(k_{el}+k_{12})h)$ occurs, it follows that the denominator function should be selected to have the form

$$\phi(h, k_{el}, k_{12}) = \frac{e^{(k_{el}+k_{12})h}-1}{k_{el}+k_{12}}.$$
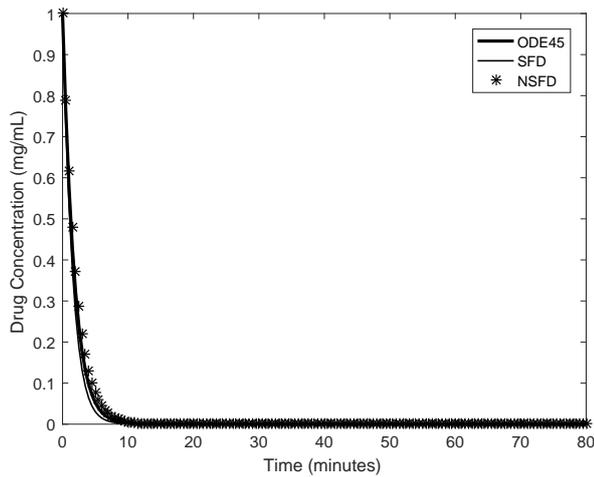
Fig. 3. The concentration of drug in the central compartment where $h = 0.5$ (I.V. bolus injection). The SFD scheme (12) and NSFD scheme (14) plotted against ODE45 of (1)
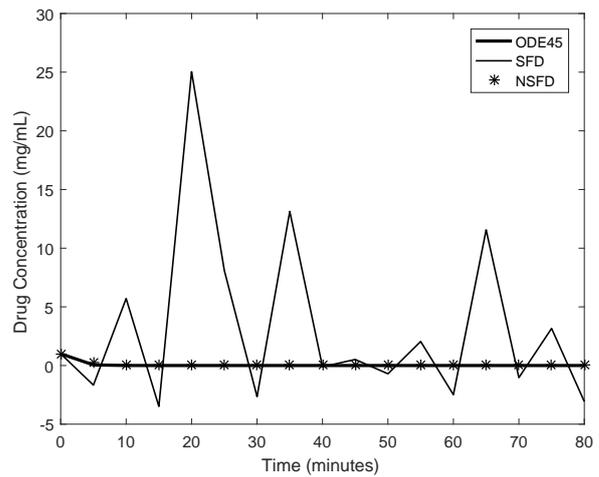
Fig. 4. The concentration of drug in the central compartment where $h = 5$ (I.V. bolus injection). The SFD scheme (12) and NSFD scheme (14) plotted against ODE45 of (1)

Thus, the NSFD schemes of Equation (16) is

$$\frac{C_{1,k+1} - C_{1,k}}{\phi} = R - k_{el}C_{1,k+1} - \frac{V_{max}}{K_m + C_{1,k}}C_{1,k+1} - k_{12}C_{1,k+1} + k_{21}C_{2,k}$$

In the same way, we have the NSFD scheme for Equation (17) becomes

$$\frac{C_{2,k+1} - C_{2,k}}{\phi} = k_{12}C_{1,k+1} - k_{21}C_{2,k+1}.$$

So that the NSFD scheme is obtained as follows

$$\frac{C_{1,k+1} - C_{1,k}}{\phi} = R - k_{el}C_{1,k+1} - \frac{V_{max}}{K_m + C_{1,k}}C_{1,k+1} - k_{12}C_{1,k+1} + k_{21}C_{2,k}, \quad (20)$$

$$\frac{C_{2,k+1} + C_{2,k}}{h} = -k_{21}C_{2,k+1} + k_{12}C_{1,k+1}, \quad (21)$$

IV. NUMERICAL SIMULATIONS

In this simulation the result of the case of drug administration by I.V. bolus injection methods were shown which were eliminated nonlinearly. In this case the drug Sisomycin has $V_{max} = 3{,}33$ mg/dL, $K_m = 5{,}56$ mg/L, $k_{el} = 0{,}0078$/mnt, $k_{12} = 0{,}0187$/mnt, $k_{21} = 0{,}0157$/mnt and the dose for I.V. bolus injection is 1 mg [12], [13].

A. I.V. Bolus Injection: Simulations

The following is a comparison figure between the SFD scheme in Equations (12)-(13), the NSFD scheme in Equations (14)-(15) and MATLAB built-in function ODE45 of (1)-(2). Figure 3, 4, 5 and 6 shows the concentration profile of Sisomicin drug in the central and peripheral compartment with the initial dose given is 1 mg and is plotted for 0 minutes (0) until the 80th minute for $h = 0.5$ and $h = 5$. The results show that the NSFD scheme is stable and closer to the results obtained via the built-in ODE45. The SFD scheme does not match the dynamics of the system for higher step sizes; we observe oscillations of the SFD method for large h.
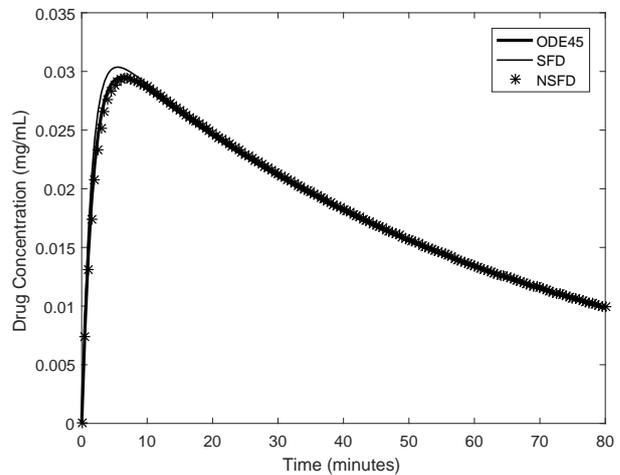
Fig. 5. The concentration of drug in the peripheral compartment where $h = 0.5$ (I.V. bolus injection). The SFD scheme (13) and NSFD scheme (15) plotted against ODE45 of (2)
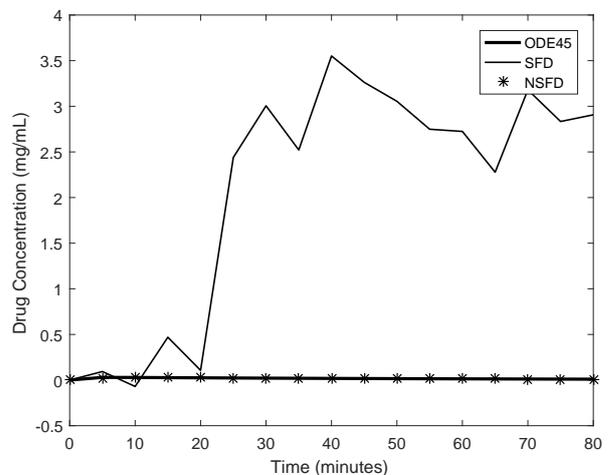
Fig. 6. The concentration of drug in the peripheral compartment where $h = 5$ (I.V. bolus injection). The SFD scheme (13) and NSFD scheme (15) plotted against ODE45 of (2)
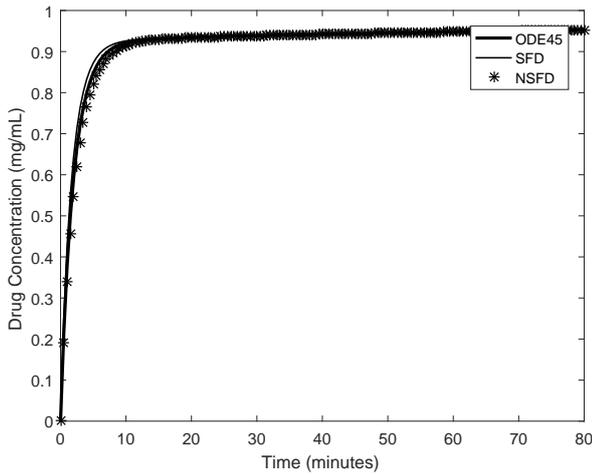
Fig. 7. The concentration of drug in the central compartment where $h = 0.5$ (I.V. bolus infusion). The SFD scheme (18) and NSFD scheme (20) plotted against ODE45 of (16)
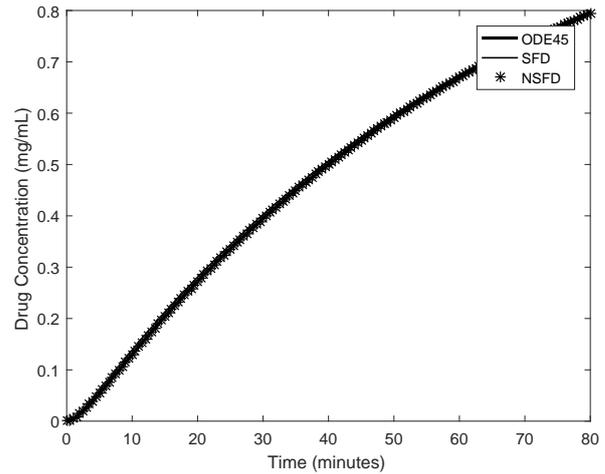
Fig. 9. The concentration of drug in the peripheral compartment where $h = 0.5$ (I.V. bolus infusion). The SFD scheme (19) and NSFD scheme (21) plotted against ODE45 of (17)
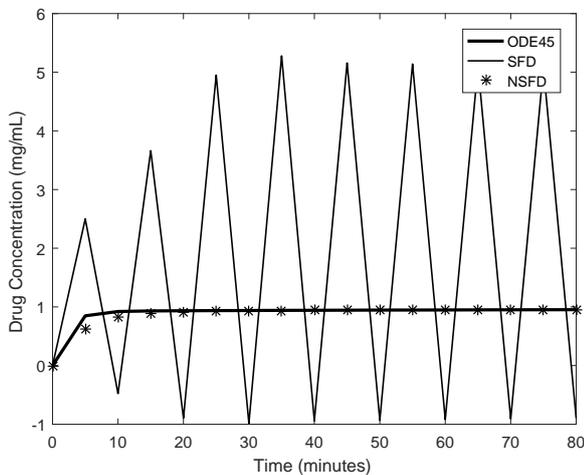
Fig. 8. The concentration of drug in the central compartment where $h = 5$ (I.V. bolus infusion). The SFD scheme (18) and NSFD scheme (20) plotted against ODE45 of (16)
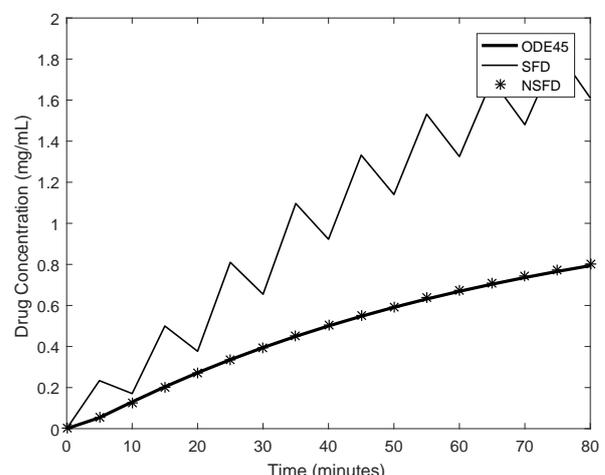
Fig. 10. The concentration of drug in the peripheral compartment where $h = 5$ (I.V. bolus infusion). The SFD scheme (19) and NSFD scheme (21) plotted against ODE45 of (17)

B. I.V. Bolus Infusion: Simulations

The following is a comparison figure between the SFD scheme in Equations (18)-(19), the NSFD scheme in Equations (20)-(21) and MATLAB built-in function ODE45 of (16)-(17). Figure 7, 8, 9 and 10 shows the concentration profile of Sisomicin drug in the central and peripheral compartment with the drug flow rate is 0.5 and is plotted for 0 minutes (0) until the 80th minute for $h = 0.5$ and $h = 5$. As in the simulation results of the infusion model, the results in this model also show that the NSFD scheme is stable and closer to the results obtained via the built-in ODE45. The SFD scheme does not match the dynamics of the system for higher step sizes; we observe oscillations of the SFD method for large h.

V. CONCLUSION

In this work, we structured two systems of two-compartment pharmacokinetic models. The first model is an I.V. bolus injection two-compartment model while the second model is an I.V. infusion two-compartment model.

We presented numerical results with the NSFD scheme for each of the developed models and compared it with the SFD method and the built-in function ODE45 in MATLAB, paying particular attention to the efficiency of the NSFD method in comparison to standard methods. From the results obtained, we observe that the stability of the NSFD scheme is independent of the chosen step-size. This is not the case with standard methods. The numerical simulations conducted verify that NSFD schemes are efficient and accurate for the solution of the problems of modelling pharmacokinetic processes. Importantly, as pointed out through test cases in this work, the NSFD method is able to generate numerical schemes that are dynamically consistent with the original equations.

REFERENCES

[1] L. Shargel and A. B. C. Yu, *Applied Biopharmaceutics and Pharmacokinetics, 7th ed.*, McGraw-Hill, 2017.
[2] M. J. Mycek, R. A. Harvey, and P. C. Champe, *Pharmacology Pictorial Reviews, 2nd ed.,* Widya Medika, 2001.

[3] J. T. DiPiro, et al., *Pharmacotherapy: A Pathophysiologic Approach, 7th ed.,* McGraw-Hill, 2008.

[4] Glen Atlas, and Sunil Dhar, "Development of a Recursive Finite Difference Pharmacokinetic Model from an Exponential Model: Application to a Propofol Infusion," *IAENG International Journal of Applied Mathematics*, vol. 40, no. 1, pp. 13-25, 2010.

[5] O. Egbelowo, C. Harley and B. Jacobs, "Nonstandard Finite Difference Method Applied to a Linear Pharmacokinetics Model," *Bioengineering*, vol. 4, no. 40, 2017.

[6] O. Egbelowo, "Nonlinear Elimination of Drug in One-Compartment Pharmacokinetic Models: Nonstandard Finite Difference Approach for Various Routes of Administration," *Mathematical and Computational Applications*, vol. 23, no. 27, 2018.

[7] R. J. LeVeque, *Finite Difference Methods for Ordinary and Partial Differential Equations,* Society for Industrial and Applied Mathematics, 2007.

[8] R. E. Mickens, "Lie methods in mathematical modelling: Difference equation models of differential equation," *Math. Comput. Modelling*, vol. 11, pp. 528-530, 1988.

[9] R. E. Mickens, "Nonstandard Finite Difference Schemes for Differential Equations," *Journal of Difference Equations and Applications*, vol. 8, no. 9, pp. 823-847, 2002.

[10] R. E. Mickens, "Dynamic consistency: a fundamental principle for constructing nonstandard finite difference schemes for differential equations," *Journal of Difference Equations and Applications*, vol. 11, no. 7, pp. 645-653, 2005.

[11] R. E. Mickens, "Calculation of Denominator Functions for Nonstandard Finite Difference Schemes for Differential Equations Satisfaying a Positivity Condition," *Numerical Methods for Partial Differential Equations*, vol. 23, no. 3, pp. 672-691, 2006.

[12] H. Lode, B. Kemmerich and P. Koeppe, "Comparative Clinical Pharmacology of Gentamicin, Sisomicin, and Tobramycin," *Antimicrobial Agent and Chemotherapy*, vol. 8, no. 4, pp. 396-401, 1975.

[13] K. Radika and D. B. Northrop, "Correlation of Antibiotic Resistance with V_{max}/K_m Ratio of Enzymatic Modification of Aminoglycosides by Kanamycin Acetyltransferase," *Antimicrobial Agent and Chemotherapy*, vol. 25, no. 4, pp. 479-482, 1984.