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Numerical Simulations of One-Directional Fractional Pharmacokinetics Model

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Abstract: In this paper, we present a three-compartment of pharmacokinetics model with irreversible rate constants. The compartment consists of arterial blood, tissues and venous blood. Fick's principle and the law of mass action were used to develop the model based on the diffusion process. The model is modified into a fractional pharmacokinetics model with the sense of Caputo derivative. The existence and uniqueness of the model are investigated and the positivity of the model is established. The behaviour of the model is investigated by implementing numerical algorithms for the numerical solution of the system of fractional differential equations. MATLAB software is used to plot the graphs for illustrating the variation of drug concentration concerning time. Therefore, the numerical simulations of the model are presented for different values of α which verified the theoretical analysis. Besides, we also observed the pattern of the simulations at the three-compartment of the model by using different values of initial conditions.

Keywords: Pharmacokinetics model; Irreversible rate; Fractional order; Numerical simulations

1 Introduction

Physical chemistry is the study of phenomena in a chemical system using the concept of physics. There are several branches related to this field namely thermochemistry, quantum chemistry, electrochemistry, spectroscopy, and chemical kinetics. Chemical kinetic is the understanding of chemical reaction rates widely used in research related to many aspects of cosmology, geology, biology, engineering, and even psychology. In this paper, we focus on the pharmacokinetics model one of the models in the biological field. Pharmacokinetics is a process involving the absorption, distribution, bioavailability, metabolism, and elimination of a drug through the body's biological systems. Bioavailability is the fraction of a drug absorbed into the systemic circulation, the volume of distribution and refers to measures of the apparent space in the body available to contain the drug, while clearance indicates the body's ability to eliminate the drug [1].

Various mathematical models have been developed to approximate the concentration of drugs in the body's system as found in [2–5]. Bischoff et al. [2] studied the mathematics of a two-compartment model based on a well-perfused viscera region and a poorly perfused tissue region which can simulate many of the general features of drug distribution kinetics such as concentration peaks that may occur at short times. The two-compartment model has also been discussed by Feizabadi et al. [6] where the model interacts with dynamic anti-cancer agents. In [4], the model described the mechanisms of how the human body handles the ingestion of nicardipine-cyclodextrin complexes in the gastrointestinal tract (GI), distribution in plasma, and their metabolism in the liver. Hrydziuszko et al. [7] created a two-compartment mathematical model to study cholesterol transport in the circulatory system and its de novo synthesis in the liver. Three compartments of the pharmacokinetic model (drug infusion into, and drug elimination from the central compartment) were studied by [3] because of their complexity and usefulness. Results obtained show that the model required extra computational effort at each data point. Three mathematical models ranging from one-compartment to three-compartment models were established in [8] to understand the distribution of drug administration in the human body through oral and intravenous routes. The models were formulated based on the diffusion process present in Fick's principle and the law of mass action. Based on the literature, we intend to study the diffusion of drugs in blood and tissue using a three-compartment model [8] which requires the irreversible rate constants as shown in Fig. 1.
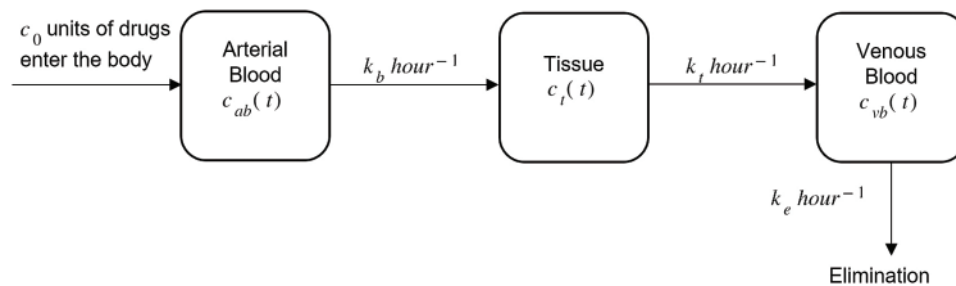

Figure 1: Drug administration through arterial blood, tissue, and venous blood with initial drug intake c_0

A principle based on the law of mass conservation known as balance law is applied in the mathematical model (Fig. 1) where $c(t)$ is the concentration of drug in the compartment at time, $t(hour)$. Hence, the balance law applied is presented as follows:

$$\frac{dc}{dt} = \text{input rate of drug} - \text{output rate of drug} \tag{1}$$

where $\frac{dc}{dt}$ is the rate of change of $c(t)$. By referring to [8], the mathematical formulation of the pharmacokinetic model (Fig. 1) with the concentration of drug in arterial blood, c_{ab}, tissue, c_t and venous blood, c_{vb} is presented as follows:

$$\frac{dc_{ab}(t)}{dt} = -k_b c_{ab}(t),$$

$$\frac{dc_t(t)}{dt} = k_b c_{ab}(t) - k_t c_t(t),$$

$$\frac{dc_{vb}(t)}{dt} = k_t c_t(t) - k_e c_{vb}(t), \tag{2}$$

where c_0 is the initial dosage of drug inserted into the body. The consumption of drugs through arterial blood towards the tissue is assumed to flow at the rate of k_b and from the tissue compartment to the venous blood at the rate of k_t. Let k_e be the drug clearance rate from the venous blood as the level of drug in the venous blood increases with time and ultimately reaches zero when the kidneys and liver excrete the drug from the body.

This paper will present the numerical simulations of the pharmacokinetics model (2) using the generalised fractional order derivatives. According to [9], fractional order calculus is found to be more appealing in modelling a real-world problem in comparison to a classical integer order, as it provides a tool for the description of memory effects and genetic properties of various materials in the recent years. Fractional order differential equations are a generalisation of classical integer order to non-integer order derivative equations, which are used as a basis of mathematical models in physical models, neural networks models, system control models, social networks models, biological models and chaotic systems to investigate the underlying dynamics of the systems [10]. The presence of fractional order derivative in the pharmacokinetics model is necessary as it generalises the results obtained in the case of the standard derivative. The memory effects obtained through fractional order derivatives can measure the concentration rate of drugs in the body. Furthermore, the fractional order system can be adjusted to fit real data by selecting a suitable value of non-integer order to better predict the reaction of the drugs. Thus, some researchers are interested to study the simulations of the fractional pharmacokinetics model [1,11–14]. Some studies concentrate on providing the solutions to the fractional pharmacokinetics model dealing with the Mittag–Leffler, Riemann–Liouville, and Caputo fractional derivatives [15–18]. Therefore, we extend our understanding by modifying the model (2) by incorporating the fractional order α, and the general formula of the fractional three-compartment pharmacokinetic model is formed as follows:

$$^{C}D^{\alpha}c_{ab}(t) = -k_b^{\alpha}c_{ab}(t),$$
$$^{C}D^{\alpha}c_{t}(t) = k_b^{\alpha}c_{ab}(t) - k_t^{\alpha}c_{t}(t),$$
$$^{C}D^{\alpha}c_{vb}(t) = k_t^{\alpha}c_{t}(t) - k_e^{\alpha}c_{vb}(t),\tag{3}$$

with the following initial conditions

$$c_{ab,0} = c_0 \geq 0,\quad c_{t,0} = 0,\quad c_{vb,0} = 0.\tag{4}$$

For simplicity [19], Eq. (3) can be rewritten in the form of

$$^{C}D^{\alpha}c_{ab}(t) = -k_b c_{ab}(t),$$
$$^{C}D^{\alpha}c_{t}(t) = k_b c_{ab}(t) - k_t c_{t}(t),$$
$$^{C}D^{\alpha}c_{vb}(t) = k_t c_{t}(t) - k_e c_{vb}(t),\tag{5}$$

The purpose of the study is to investigate the behaviour of the fractional three-compartment pharmacokinetic model (5) since the fractional pharmacokinetics model has only been studied up to a two-compartment model. The model was recently established to characterise the temporal history of pharmaceuticals in the human body that follow an abnormal diffusion mechanism. The three-compartmental fractional model has been proposed and studied to consider different fractional order transmission processes by adopting Caputo's definition. Thus, this paper is organised as follows: Several definitions related to fractional derivatives will be presented in Section 2. The existence and uniqueness of the mathematical model will be discussed in Section 3. Section 4 will present

the positivity of the model and the numerical simulations will be discussed in Section 5. Lastly, a conclusion about this research will be made in Section 6.

2 Preliminaries

There are various definitions of derivative and integration in the literature. Since we are using the approach of Caputo derivative in this paper, the following definitions related to the study are given. The advantage of implementing the Caputo derivative is that the initial conditions for fractional order differential equations with the Caputo derivative are the same for integer differential equations, hence avoiding solvability difficulties and its advantages in applied problems [9]. Besides, many experts choose to utilise the Caputo definition because one may typically have a well-intelligible physical meaning that can be measured when using Caputo's idea [20].

Definition 1. *The Riemann-Liouville differential operator of fractional order $\alpha > 0$ is given by*

$$^{RL}D^\alpha y(t) = \frac{1}{\Gamma(n-\alpha)} \frac{d^n}{dt^n} \int_0^t \frac{y(\tau)}{(t-\tau)^{\alpha-n+1}} d\tau \tag{6}$$

where n is the integer defined by $n - 1 < \alpha \leq n$.

Definition 2. *The Caputo differential operator of order $\alpha > 0$ is given by*

$$^{C}D^\alpha y(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{y^{(n)}(\tau)}{(t-\tau)^{\alpha-n+1}} d\tau \tag{7}$$

where n is the first integer which is greater than α and $\Gamma(\cdot)$ is the Euler gamma function.

3 Existence and Uniqueness of the Pharmacokinetics Model

Some qualitative behaviours of the proposed fractional order model (5) are investigated in this section. By considering the following lemma,

Lemma 1. *Consider the system*

$$^{C}_{t_0}D^\alpha_t C(t) = f(t, C), t > t_0 \tag{8}$$

with the initial condition x_0, where $\alpha \in (0, 1]$, $f : [t_0, \infty) \times \Omega \to \mathbb{R}^n$ if $f(t, C)$ satisfies the locally Lipschitz condition with respect to C, then exists a unique solution of (5) on $[t_0, \infty) \times \Omega$,

we begin with the investigation of the existence and uniqueness of the solution (5) in the region $\Omega \times [t_0, T]$, where $\Omega = \{(c_{ab}, c_t, c_{vb}) \in \mathbb{R}^2 : \max|c_{ab}|, |c_t|, |c_{vb}| \leq M\}$ and $T < +\infty$. We denote $C = (c_{ab}, c_t, c_{vb})$ and $\overline{C} = (\overline{c_{ab}}, \overline{c_t}, \overline{c_{vb}})$. Consider a mapping $K(C) = (K_1(C), K_2(C), K_3(C))$ and

$$K_1(C) = -k_b c_{ab}(t),$$

$$K_2(C) = k_b c_{ab}(t) - k_t c_t(t),$$

$$K_3(C) = k_t c_t(t) - k_e c_{vb}(t), \tag{9}$$

For any $C, \overline{C} \in \Omega$, it follows from (5)

$$
\begin{aligned}
\left\| K(C) - K\left(\overline{C}\right) \right\| &= \left| K_1(C) - K_1\left(\overline{C}\right) \right| + \left| K_2(C) - K_2\left(\overline{C}\right) \right| + \left| K_3(C) - K_3\left(\overline{C}\right) \right| \\
&= \left| -k_b c_{ab}(t) + k_b \overline{c_{ab}(t)} \right| + \left| k_b c_{ab}(t) - k_t c_t(t) - \left(k_b c_{ab}(t) - k_t \overline{c_t(t)}\right) \right| \\
&\quad + \left| k_t c_t(t) - k_e c_{vb}(t) - \left(k_t c_t(t) - k_e \overline{c_{vb}(t)}\right) \right| \\
&= \left| -k_b \left(c_{ab}(t) - \overline{c_{ab}(t)}\right) \right| + \left| k_b(c_{ab}(t) - c_{ab}(t)) - k_t\left(c_t(t) - \overline{c_t(t)}\right) \right| \\
&\quad + \left| k_t(c_t(t) - c_t(t)) - k_e\left(c_{vb}(t) - \overline{c_{vb}(t)}\right) \right| \\
&\leq k_b \left| c_{ab}(t) - \overline{c_{ab}(t)} \right| + k_t \left| c_t(t) - \overline{c_t(t)} \right| + k_e \left| c_{vb}(t) - \overline{c_{vb}(t)} \right| \\
&\leq \tau \left\| C - \overline{C} \right\|
\end{aligned}
\tag{10}
$$

where $\tau = \max\{k_b, k_t, k_e\}$. Thus, $K(C)$ satisfies the Lipschitz condition with respect to C. It follows from Lemma that there exists a unique solution $C(t)$ of system (5) with the initial condition $C_{t_0} = \left(C_{ab,0}, C_{t,0}, C_{vb,0}\right)$.

4 Positivity of the Pharmacokinetics Model

In this section, the positivity of the solution for the fractional order model (5) is established by considering the following theorem.

Theorem 1. *All the solutions of system (5) which start in C_+ are non-negative and uniformly bounded.*

Referring to [21], the property of positivity is a fractional differential system (5) satisfying the positivity property for all initial conditions $x_0 \in \mathbb{R}_+^m$, the solution $y_t(x_0)$ passing through x_0 at time $t = 0$ remains positive for all $t > 0$.

Establishing the positivity of the solution is important following the fractional order model (5) we have

$$
{}^C D^\alpha c_{ab}(t) \big|_{c_{ab}=0} = 0,
$$

$$
{}^C D^\alpha c_t(t) \big|_{c_t=0} = 0,
$$

$$
{}^C D^\alpha c_{vb}(t) \big|_{c_{vb}=0} = 0.
\tag{11}
$$

The integer order case of model (5) can be formed as

$$
\frac{dc_{ab}}{dt} = c_{ab} f_1(c_{ab}, c_t, c_{vb}), \quad \frac{dc_t}{dt} = c_t f_2(c_{ab}, c_t, c_{vb}), \quad \frac{dc_{vb}}{dt} = c_{vb} f_3(c_{ab}, c_t, c_{vb})
\tag{12}
$$

where

$$
f_1(c_{ab}, c_t, c_{vb}) = 0,
$$

$$
f_2(c_{ab}, c_t, c_{vb}) = k_b c_{ab}(t),
$$

$$
f_3(c_{ab}, c_t, c_{vb}) = k_t c_t(t).
\tag{13}
$$

It follows that

$$c_{ab}(t) = c_{ab}(0) \, e^{\int_0^t f_1\left(c_{ab}(u),c_t(u),c_{vb}(u)\right)du},$$

$$c_t(t) = c_t(0) \, e^{\int_0^t f_2\left(c_{ab}(u),c_t(u),c_{vb}(u)\right)du},$$

$$c_{vb}(t) = c_{vb}(0) \, e^{\int_0^t f_3\left(c_{ab}(u),c_t(u),c_{vb}(u)\right)du}, \tag{14}$$

Therefore, the solution of the integer order model with initial conditions $C(0) = (c_{ab}(0), c_t(0), c_{vb}(0)) \in \mathbb{R}_+^3$ remains positive and satisfies Theorem 1. In addition, the solution of model (5) also fulfils the positivity theorem as mentioned in [22].

5 Simulations of the Pharmacokinetics Model

In this section, we demonstrate the numerical simulations of c_{ab}, c_t and c_{vb} in (5) at different values of α to confirm the theoretical findings obtained before. Using an approach of the PECE method from Diethelm et al. [22], the model (5) is solved using a MATLAB code fde12.m established by Garrappa [23]. Tab. 1 shows the parameters from [8] which will be used to plot the graphs in this paper. Note that the value of $k_e < k_t < k_b$.

Table 1: Parameters used in simulations of the fractional pharmacokinetic model

Parameter	Description	Case 1	Case 2
$c_{ab,0}$	Initial condition of the drug concentration in the arterial blood	500	500
$c_{t,0}$	Initial condition of the drug concentration in the tissue	0	0
$c_{vb,0}$	Initial condition of the drug concentration in the venous blood	0	0
k_b	The drug consumption by arterial blood toward tissue	0.9776	0.5000
k_t	The drug consumption from the tissue compartment to the venous blood	0.3293	0.2500
k_e	The clearance rate of the drug from the blood	0.2213	0.0500

We set $t \in [0, 24]$ hours long to stimulate the data for monitoring the behaviour of drugs in the body within one day and the step size, $h = 0.1$. Since we only focus on the pattern of the model, a control value of h is not necessary because it does not lead to a significantly different or better result.

By using MATLAB R2021b, we plot the fractional pharmacokinetics model (5) with a classical integer value of α and the information in Tab. 1 as shown in Fig. 2. Fig. 2a shows the concentration of drugs for Case 1 with the rate constant within $[0.2213, 0.9776]$. Meanwhile, Fig. 2b shows the concentration of drug for Case 2 with the rate constant within $[0.05, 0.50]$. As presented, we can see that as the drugs start to enter the body, the concentration rate of drugs in arterial blood, c_{ab} is going to drop from 500 units approaching 0 units in 24 h. In the meantime, the concentration rate of drugs in tissue, c_t and venous blood, c_{vb} are going to increase then decrease with time, t. This explains the physician's standard suggestions of taking a medicine every 4 to 6 h for better results. From the graphs, we found that a larger value of the rate constants will accelerate the absorption of the drug within the body. Meanwhile, at a smaller value, some amount of drug will remain within the body as a residue and this may trigger side effects experienced by the patient.
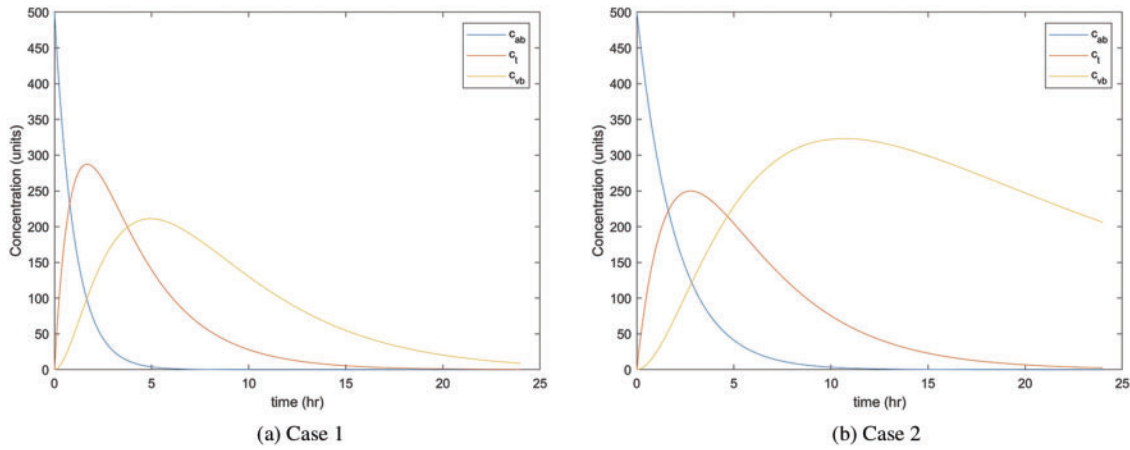
(a) Case 1 (b) Case 2

Figure 2: Concentration rate of drugs in three compartments of the body

As mentioned earlier, the different values of α will be considered in this research to illustrate the concentration rate of drugs in c_{ab}, c_t and c_{vb}. As shown in Fig. 2a, compared to Case 2, $\alpha = 0.80, 0.85$, 0.90 and 0.95 are used to solve Case 1 since it is more efficient, and the following figures are plotted. Referring to Figs. 3–5, the concentration rate of drugs in three compartments slowly approaches zero as the values of α become smaller. However, it still follows the pattern of the model as presented in Fig. 2. The results indicate that the curve with the larger value of α respond efficiently and the drug will be absorbed faster within the body as compared to the small value of α.
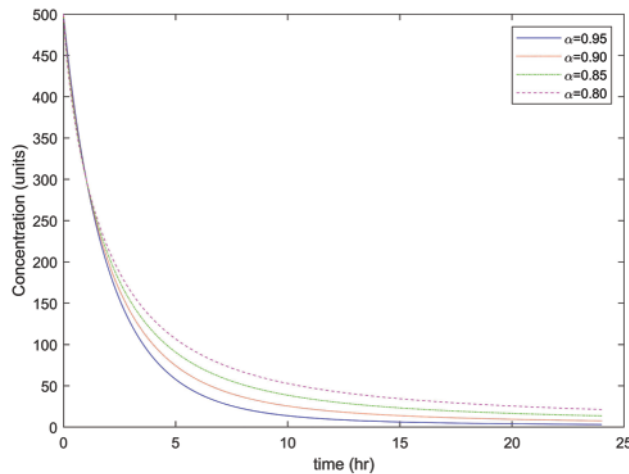

Figure 3: Concentration rate of drugs in arterial blood with different values of α
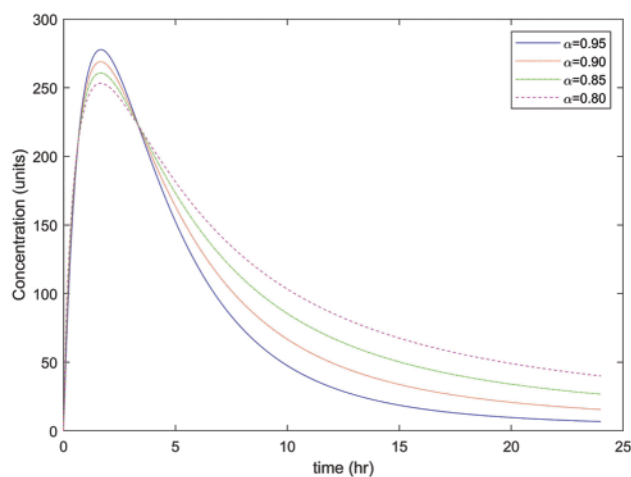
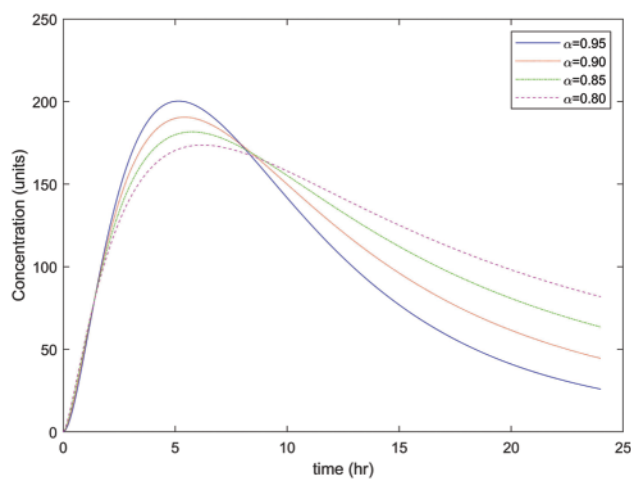**Figure 4:** Concentration rate of drugs in tissue with different values of α

Figure 5: Concentration rate of drugs in venous blood with different values of α

Next, we observe the fractional order pharmacokinetics model (5) by approximating the solutions with $\alpha = 0.70$ and $\alpha = 0.90$ as presented in Fig. 6. These figures reveal the pattern of drug distribution in the three-compartment model of the body. We can conclude that the fractional model with $\alpha = 0.90$ accelerates the absorption of drugs in the body and the full excretion by the kidneys compared to $\alpha = 0.70$ within 24 h.

We consider the initial condition of $c_0 = 200, 300, 400$ and 500 to explore the behaviour of the system of the fractional order model (5). As presented in Figs. 7–9, as less drug concentration enters the body, the faster it will be absorbed by the body, thus avoiding an excess of the drug in the body.
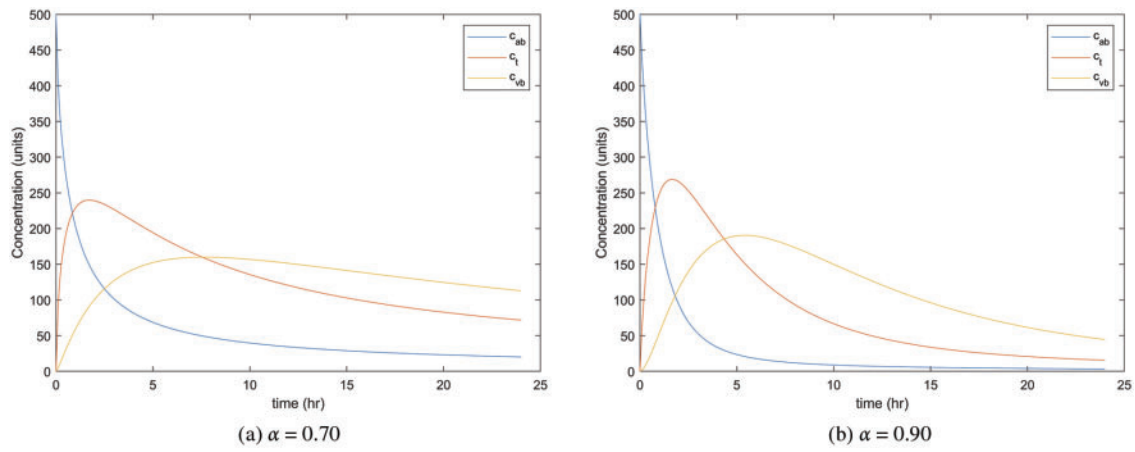
(a) $\alpha = 0.70$ (b) $\alpha = 0.90$

Figure 6: Concentration rate of drugs in three parts of the body with $\alpha = 0.70$ and 0.90
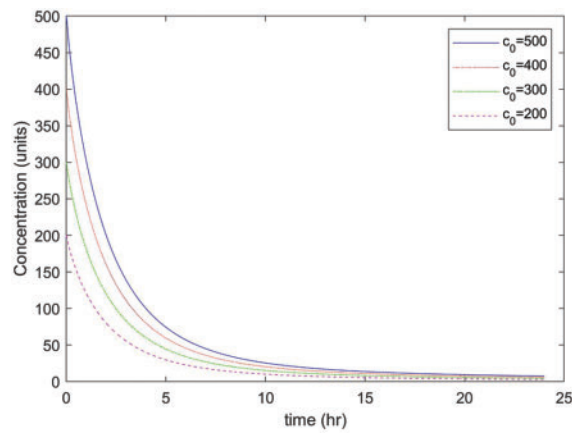

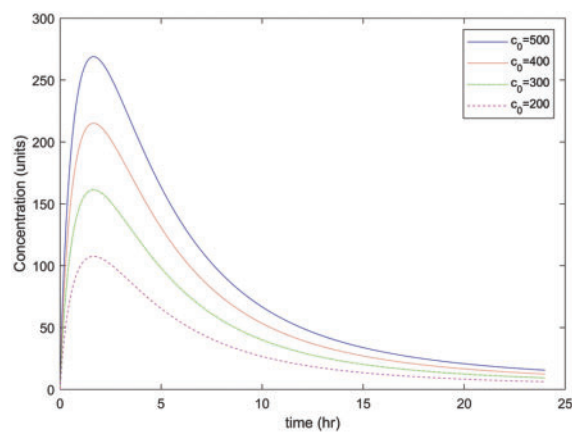**Figure 7:** Concentration rate of drugs in arterial blood with different values of the initial condition, c_0

Figure 8: Concentration rate of drugs in tissue with different values of the initial condition, c_0
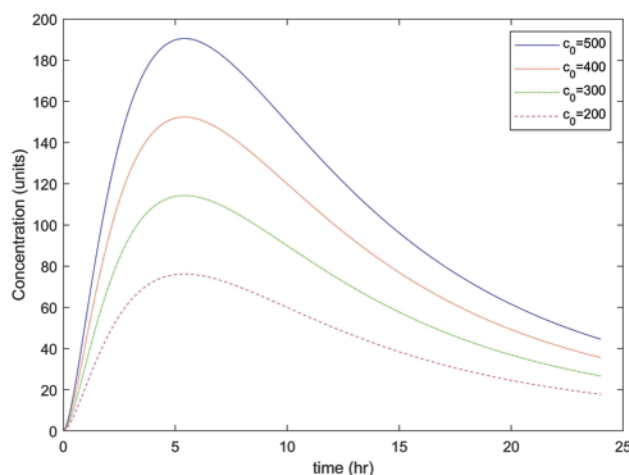
Figure 9: Concentration rate of drugs in venous blood with different values of the initial condition, c_0

6 Conclusion

In this paper, a fractional order of the three-compartment pharmacokinetic model (5) was proposed and studied. The existence and uniqueness of the solution of model (5) were examined under sufficient conditions. Non-negativity of the solution of the fractional order model (5) was conducted. Numerical simulations were presented to analyse the behaviour of the fractional order model (5). Then, we analysed the quantitative behaviour using different values of the rate constant and a few values of $\alpha \in (0, 1)$. Based on the analysis, we found that the fractional order model (5) with a larger value of the rate constant and α approaching 1 resulted in better absorption of the drug in the three-compartment model of the body. We explored the behaviour of the drug distribution in the three-compartment model by adjusting the initial value of c_0. As a result, the drugs were absorbed faster with less residue remaining in the body. Thus, we concluded that as compared to the ordinary differential equations, the fractional order of the three-compartment pharmacokinetic model (5) is more appealing and realistic in modelling drug distribution as it possesses memory. In the future, we are interested to study the modified three-compartment pharmacokinetic model into a fuzzy fractional order problem because we may overcome uncertainties or lack of accuracy by using a fuzzy environment in parameters, variables, and starting conditions instead of exact ones [24].

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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