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Pharmacokinetic Consideration to Formulate Sustained Release Drugs: Understanding the Controlled Drug Diffusion through the Body Compartment of the Systemic Circulation and Tissue Medium-A Caputo Model

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Abstract:

The aim of this study is to provide an overview of various models to study drug diffusion for a sustained period into and within the human body. Emphasized the mathematical compartment models using fractional derivative (Caputo model) approach to investigate the change in sustained drug concentration in different compartments of the human body system through the oral route or the intravenous route. Law of mass action, first-order kinetics, and Fick's perfusion principle were used to develop mathematical compartment models representing sustained drug diffusion throughout the human body. To adequately predict the sustained drug diffusion into various compartments of the human body, consider fractional derivative (Caputo model) to investigate the rate of concentration changing depending upon the change in the order of fractional differentiation in all the possible compartments of the body, i.e., systemic circulation and tissue compartments. Also, assigned a numerical parameter value to the rate of drug flow in different compartments to estimate the drug concentration. Results were calculated and figures were depicted by using MATLAB software (version R2020a). Illustrated graphical effects of change in concentration rate by assuming various intermediate values according to the fractional derivative (Caputo model). The resultant graphical representation concludes that considering the order of the differential equation values, the drug concentration varies depending upon its rate of constants in compartments concerning time. Considering the initial case for rough estimation where the body is indicated as a whole compartment, following division of the body into two model compartments. Whereas, the model I represents stomach, liver, and systemic blood, and model II consider arterial blood, liver tissue, and venous blood.

Keywords: Caputo model, Compartment model, Drug diffusion, Fractional-order derivative, Mathematical modeling.

Introduction:

The complexity of the human body is simplified by designing into compartments and studying pharmacokinetic parameters to understand the better role of the drug and its pharmacological process[1]. Model development and graphical evaluation are essential to understand the relationship between sustained drug consumption, its corresponding concentration, and its rate constant in different body compartments following the pharmacokinetic parameter of controlled drug absorption and distribution in the body compartment[2]. The controlled drug diffusion within compartment models of the body determines to sustain drug concentration locally in tissue or blood compartments, with its rate constant concerning time[3]. The dosage beyond the therapeutic index or its continual exposure and its flow rate in the body estimate the adverse effects. So, to overcome such conditions based on ADME parameters, the

scientist depicted the behavioral outcome of the administered drug, considering its route of administration and its chemical entities, which get distributed throughout the body compartments over a scale of time[4]. It assists in understanding the interrelation between the rate constant during absorption, diffusion, and the elimination route of the drug throughout the body compartments and aids in the formulation and development of effective dose-dependent sustain therapeutic formulations[5]. Mathematical analysis of the body compartment models constitutes a significant predictive and accurate quantitative tool in understanding complex drug action during its bio-transport in body compartments. Once the method and model are validated, applying the mathematical concept is a theoretical prediction; consequently, the illustrated results contribute to representative, reliable, and realistic related outcomes while drug development[1,6]. In the absence of expensive and sophisticated experimental tools, the development of alternative mathematical compartment models and software-based in silico simulations was conducted with logical, predictable, and potent results. Such kinds of research methodologies are adopted by many scientists working in P.K. and P.D. models[6,7]. Drug distribution is meant to transfer through the complex vascular system of arteries and venous that further combines to make the human circulatory system where the drug can effectively come in contact with physiological tissues. Such extensive drug pharmacokinetics contributes to the design of blood and tissue as a different compartment model to study drug diffusion and distribution pattern in an individual compartment using various mathematical methods[3,8]. In light of the increasing significance of mathematical tools and techniques, developing a compartment model represents and describes the characteristics of biological and pharmacological kinetics of drugs in each body compartment. The compartments of the body are organized sequentially or in parallel order considering the pharmacokinetics of drug entities[5,7]. To understand the drug kinetic path, the human body is regarded as a whole single compartment or divided into multiple compartment models[7].

Missel *et al*. developed a compartmental model to understand the physiologically based pharmacokinetics modeling using the computational method and mathematical simulation[9]. Niederalt *et al*. designed a generic physiologically based pharmacokinetic (PBPK) that signified the whole human body into multiple parallel compartments explaining protein diffusion from arterial blood to venous blood surpassing via the liver, portal drain organs, large organs (heart, brain, muscles, kidney, etc.), and lung[10]. Sa'adah A.M. *et al*. explained two-compartment pharmacokinetics of different routes of administration through I.V. bolus injection and infusion. They solved equations with the mathematical approach of the nonstandard finite difference (NSFD) method[11]. Brady and Enderling formulated a mathematical model of cancer to predict the treatment strategy and treatment regimen depending on the severity of the cancer[12]. Using a mathematical approach, they explained the concept of chronic inflammation as an essential initiator and cause of cancer development[12]. Scientist Hashida explained drug diffusion through the skin using an organ perfusion experiment. The model represented statistical moment analysis and understanding of drug disposition at the organ and cellular level via dermal absorption. They have studied one compartment comprising of stratum corneum, the viable epidermis or the dermis, and blood; the two-compartment model describes the first skin compartment as stratum corneum, viable epidermis, and serum[13].

Literature reports of Khanday et al. explained drug diffusion expressed by designing all possible approximate compartment models[8]. Extended our research investigation to understand drug diffusion's compartment models by the innovative approach of mathematical analysis using the Caputo-model, fractional derivative method. As to date, the fractional derivative order is applied for estimating epidemiological studies to tract particular infectious diseases outbreak in society[14]. Some such research highlights given by scientist Khan *et al*. traced the Zika viral dynamic in the community using Caputo-Fabrizio fractional derivative[15], using the same derivative model Moore et al. presented HIV/AIDS epidemic analysis in society[16]. The present scenario of the novel coronavirus (2019-nCoV) outbreak causing respiratory disorder, epidemiology of the unique coronavirus pandemic estimated by a fractional order approach by scientists. They summarized brief information on inter-relationship among the viral carrier species and unknown hosts spreading infection among the people[17]. According to drug kinetics, the human body is differentiated into two different compartments models[8,18]. The first case considers the entire body as one compartment model where administered drug immediately diffuses throughout the body. In the first model, the body is divided into two compartments assuming that the delivered drug transports from the stomach through the liver and central compartment of blood. Then, Model II describes intravenous drug diffusion where the body is divided into four compartments:

arterial blood, liver, tissue compartment, and venous blood. Summarized the possible factors to distinguish two different approximations of mathematical models considered to generate multiple graphical plots representing plots of concentration and rate constant vs. time assuming different parameter values and fractional order[14]. The numerical analysis was executed using fractional derivative (Caputo model) describing more possible assumptions of rate and concentration of sustained drug diffusion in different compartments of the body. Intend to use fractional derivative (Caputo model) by assuming the condition of fractional order ($0 < \alpha \leq 1$) anywhere in between the intervals irrespective of integer assumptions, adequately to estimate sustain drug concentration through the compartment of the human body.

Material and methods:

Overview of drug pharmacokinetics in the human body:

Drug pharmacokinetics through the human body compartment plays a crucial role in finding the sustained rate of drug absorption, distribution, and elimination assuming fractional derivative simulation; during this ADME process, the aliquots of sustain drug concentration concerning time in different body compartments give insight into the information of drug pharmacology. The sustained concentration of drugs in the body compartments depends on two parameters[11]. First, considering the route of drug administration describes the period required for drug transport from the site of administration to systemic blood circulation; the second parameter which depends on drug elimination explains the time needed to sustain drug distribution to tissue and its elimination rate from the site of tissue. Once the drug is absorbed into the blood, controlled drug bio-transport exclusively into peripheral organs through tissue cells by passive diffusion, further implicit its pharmacology by binding to its receptor site[4]. Here, in Model II, assuming that the tissue cells do not present any barrier for drug transport into the tissue compartment helps to estimate drug concentration adequately in tissue[2]. According to the drug's physicochemical characterization, its diffusion will be slow due to its reduced permeability, so assume excellent drug permeability but in a controlled sustain period. A quantitative analysis of drug concentration is essential to understand the bio-transport kinesis of sustain release drugs. A drug is said to be effective only if it results in therapeutic efficacy with a low or nil toxicity index. Overall, to obtain substantial drug concentration at the target tissue site, the administered drug and its distribution rate should be balanced with its elimination rate[1,11].

Compartment models of the Human body:

Consider the human body into two models Model-I and Model-II. Model-I illustrates the human body expressed into three compartments: stomach, liver, and blood; followed by drug intake by the oral route. Consequently, Model-II explains the human body into four divisions as showing arterial blood, liver, tissue, and venous blood followed by intravenous drug infusion.

The overall view is to estimate sustained drug concentration in different model compartments by executing the mathematical simulation of the Caputo model.

Mathematical analysis:

The mathematical simulations and estimations help to find a realistic solution to numerous severe problems related to human biology. The interdisciplinary research of numerical simulation and drug PK/PD parameters simplified, solved, and more reliable results obtained irrespective need for complex, sophisticated instrumentation[19]. The aid in applying a mathematical approach using fractional derivative (Caputo model) analysis to find the drug concentration in the controlled pattern at different tissue compartments and the blood compartment[5]. The drug distribution pattern varies according to the route of drug administration. Oral drug delivery allows drug absorption into the blood through the intestinal system; through the liver to the blood, it further delivers to the target tissue site. Oral drug intake undergoes first-pass metabolism, where the drug is metabolized in the liver and eliminated through the kidney, followed by its distribution to the target tissue[20]. An intravenous drug infusion directly enters into arterial blood, distributes to the target tissue, and is eliminated after venous blood. According to the literature review, the intravenous drug also follows a very low amount through the first-pass metabolism. So, the liver is also considered as one compartment in Modell II. The rate of drug flow throughout the body is described by dividing the body parts as a compartment and tracing the drug concentration as it flows into and out of the individual compartment[3]. The flow rate of the drug leaving and arriving in the next compartment is directly proportional to the drug concentration present in the previous compartment. First-order kinetics was executed to explain the rate of drug transport within the model compartments.

The proportionality rate of constant is estimated by drug concentration, the type of

compartment model, and the health condition of the human body in concern with time. The rate of change in concentration of a drug is equal to the difference between the input and output rate of medication. The drug concentration in the compartment models is estimated based on the law of conservation of mass principle (Balance law).

Mathematical Model I:

The human body in the model I divided into three compartments describes the drug flow through the intestinal system (stomach), liver, and its absorption into systemic blood circulation followed by the administration's oral route. The first-pass metabolism of the orally administered drug is represented by considering the liver as one among the compartment in Model-I. The drug enters into the stomach and then diffuses further into blood circulation, as illustrated in Fig.1. Mathematical simulation using the fractional derivative Caputo model is applied which helps to understand PK for designing sustain formulations.

Here, obtained three differential equations from the Fig. 1. as follows:

$$\frac{dc_s(t)}{dt} = -(k_1+k_s)c_s(t) + k_l c_l(t); \qquad c_s(0) = c_0 \qquad 1$$

$$\frac{dc_b(t)}{dt} = k_1 c_s(t) - k_e c_b(t)\,; \qquad c_b(0) = 0 \qquad 2$$

$$\frac{dc_l(t)}{dt} = k_s c_s(t) - k_l c_l(t)\,; \qquad c_l(0) = 0 \qquad 3$$

In the model I, considered c_0, $c_s(t)$, $c_b(t)$, and $c_l(t)$ represent drug concentration as the initial value, the internal compartment of GIT (stomach), liver, and systemic blood circulation respectively. Whereas, k_1, k_s, k_l, and k_e are considered the rate constant of drug flow through compartment 1 (stomach), compartment 2 (liver), compartment 3 (blood), and drug elimination rate respectively.

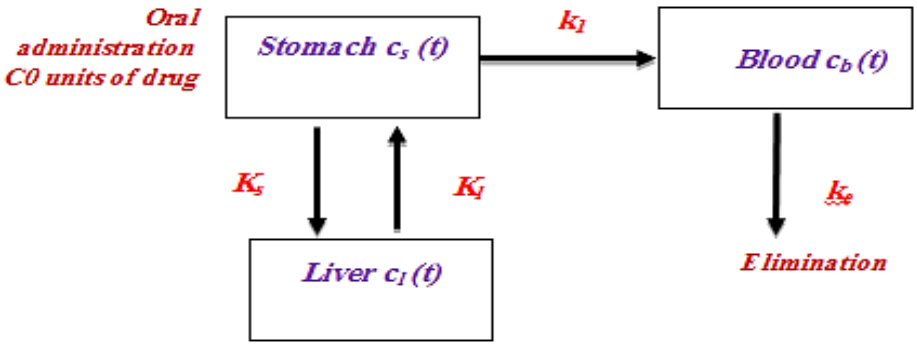

Figure 1. Simple process of drug administration through stomach and blood.

Eqs.1-3 denotes the rate of change in drug concentration followed by oral dose intake based on fractional order in individual compartments concerning time.

Definition 1:[21] *Suppose that* $f(t) \in C[a,b]$ and $c_{D_t^\alpha f(t)} \in C[a,b]$ *, for* $m-1 < \alpha \leq m$,

$$then \quad c_{D_t^\alpha f(t)} = \begin{cases} \frac{1}{\Gamma(m-\alpha)} \int_0^t \frac{f^{(m)}(\tau)}{(t-\tau)^{\alpha+1-m}} d\tau, & m-1 < \alpha < m \\ \frac{d^m}{dt^m} f(t)\,, & \alpha = m \end{cases}$$

is called the Caputo fractional derivative of order $\alpha > 0$.

Lemma 1:[21] Suppose that $f(t) \in C[a,b]$ and $c_{D_t^\alpha f(t)} \in C[a,b]$, for $0 < \alpha \leq 1$, then

$$c_{D_t^\alpha c_s(t)} = -(k_1+k_s)c_s(t) + k_l c_l(t);$$
$$c_{D_t^\alpha c_b(t)} = k_1 c_s(t) - k_e c_b(t)\,;$$
$$c_{D_t^\alpha c_l(t)} = k_s c_s(t) - k_l c_l(t)\,;$$

$f(t) = f(a) + \frac{1}{\Gamma(\alpha)} c_{D_t^\alpha f(\xi)}(t-a)^\alpha$. with $a \leq \xi \leq t, \forall\, t \in (a,b]$.

Caputo's model of drug concentration in the above three compartments is given by:

$$c_s(0) = c_0 \qquad 4$$
$$c_b(0) = 0 \qquad 5$$
$$c_l(0) = 0 \qquad 6$$

Where α represents the fractional order of the differential equation, and $0 < \alpha \leq 1$.

$$c_s(t) = c_s(a) + \frac{1}{\Gamma(\alpha)}[-(k_1+k_s)c_s(t) + k_l c_l(t)](t-a)^{\alpha} \quad 7$$

For a = 0, Eq. 7 becomes,

$$c_s(t) = c_s(0) + \frac{1}{\Gamma(\alpha)}[-(k_1+k_s)c_s(t) + k_l c_l(t)](t-0)^{\alpha} \quad 8$$

from Eqs.7 and 8,

$$c_s(t) = \frac{c_0\Gamma(\alpha) + k_l t^{\alpha} c_l(t)}{\Gamma(\alpha) + (k_1+k_s)t^{\alpha}} \quad 9$$

Now, Eq.5 becomes,

$$c_b(t) = c_b(a) + \frac{1}{\Gamma(\alpha)}[k_1 c_s(t) - k_e c_b(t)](t-a)^{\alpha} \quad 10$$

For a = 0, Eq. 10 becomes,

$$c_b(t) = c_2(0) + \frac{1}{\Gamma(\alpha)}[k_1 c_s(t) - k_e c_b(t)](t-0)^{\alpha} \quad 11$$

From Eqs. 10 and 11

$$c_b(t) = \frac{k_1 t^{\alpha} c_s(t)}{\Gamma(\alpha) + k_e t^{\alpha}} \quad 12$$

Now, Eq. 12 becomes,

$$c_l(t) = c_l(a) + \frac{1}{\Gamma(\alpha)}[k_s c_s(t) - k_l c_l(t)](t-a)^{\alpha} \quad 13$$

For a = 0, Eq.13 becomes,

$$c_l(t) = c_l(0) + \frac{1}{\Gamma(\alpha)}[k_s c_s(t) - k_l c_l(t)](t-0)^{\alpha} \quad 14$$

From Eqs. 13 and 14

$$c_l(t) = \frac{k_s t^{\alpha} c_s(t)}{\Gamma(\alpha) + k_l t^{\alpha}} \quad 15$$

From Eqs. 9 and 15

$$c_s(t) = \frac{c_0\,\Gamma(\alpha)[\Gamma(\alpha) + k_l t^{\alpha}]}{(\Gamma(\alpha) + (k_1+k_s)t^{\alpha})(\Gamma(\alpha) + k_l t^{\alpha}) - k_l k_s (t^{\alpha})^2} \quad 16$$

Mathematical Model-II:

The oral dose intake is not sufficient and potent as compared to intravenous drug delivery. As compared to intravenous infusion, oral dosage undergoes extensive first-pass metabolism, which reduces drug concentration absorption into systemic blood, further reducing drug delivery at the site of the target tissue. Besides, oral drug intake may not be suitable for patients suffering from hepatic or kidney inefficiency. The intravenous drug delivery results are giving potent and immediate drug action in case of emergencies like heart stroke or a microbial infection causing rapid drug absorption and tissue diffusion; also, I.V. is the route given to patients due to his incompatibility situation for oral dosage, i.e., comma or unconscious conditions.

The intravenous drug delivery system explained in Model II, considers reversible and irreversible drug flow kinetics. Since the systemic blood itself is divided into oxygenated and deoxygenated forms, the blood flows through arterial and venous systems considered in designing compartments of Model II. The intravenous administered drug enters into the venous system through capillary blood vessels representing drug absorption in arterial blood reservoir (compartment I), further diffuses into tissue (compartment II), and the drug gets eliminated through deoxygenated venous blood (compartment IV). A very small amount of drug diffusion is considered through the liver, so to avoid manual error liver is also represented as a different compartment (i.e., compartment III). To formulate mathematical

equations for Model II, parameter values include k_a, k_b, k_t, k_l, and k_e as a rate constant of the drug through arterial blood, tissue compartment, liver, venous blood, and excretion rate from venous blood, respectively. Concerning time duration, the drug concentration increases rapidly in venous blood and gradually falls to approximately 50 units (remaining drug molecules are considered to eliminate slowly from the liver to venous blood) as shown in Fig. 5a. When excretory organs like renal and hepatic systems metabolize and eliminate drugs from the body tissue compartments, denoted by k_e and k_l as a clearance rate. Similarly, assuming $c_{ab}(t)$, $c_t(t)$, $c_l(t)$, *and* $c_{vb}(t)$ as drug concentration in the arterial blood compartment, tissue compartment, liver compartment, and venous blood compartment respectively, where c_0 is considered as initial drug dose.

The differential equations from Fig. 2 are formulated as follows:

$$\frac{dc_{ab}(t)}{dt} = -(k_b + k_a)c_{ab}(t)\,; \qquad c_{ab}(0) = c_0 \tag{17}$$

$$\frac{dc_t(t)}{dt} = k_b c_{ab}(t) - k_t c_t(t)\,; \qquad c_t(0) = 0 \tag{18}$$

$$\frac{dc_l(t)}{dt} = k_a c_{ab}(t) - k_l c_l(t)\,; \qquad c_l(0) = 0 \tag{19}$$

$$\frac{dc_{vb}(t)}{dt} = k_t c_t(t) - k_e c_{vb}(t)\,; \qquad c_{vb}(0) = 0 \tag{20}$$

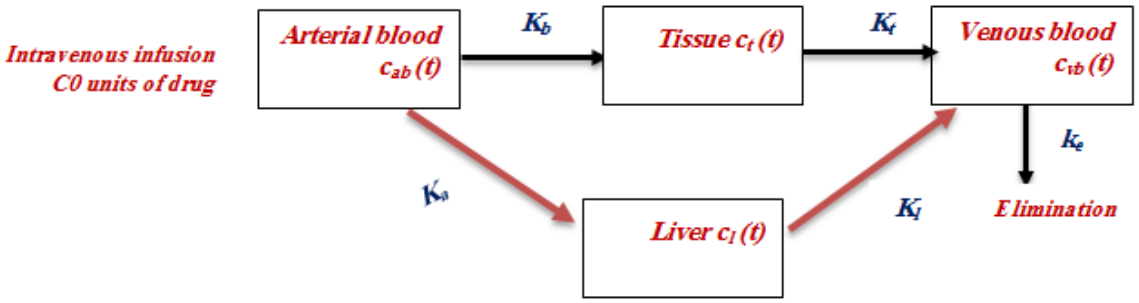

Figure 2. Drug administration through arterial blood and tissue and venous blood with initial drug dose c_0.

Caputo's model of drug concentration in the above four compartments is given by:

$$c_{D_t^\alpha c_{ab}(t)} = -(k_b + k_a)c_{ab}(t)\,; \qquad c_{ab}(0) = c_0 \tag{21}$$

$$c_{D_t^\alpha c_t(t)} = k_b c_{ab}(t) - k_t c_t(t)\,; \qquad c_t(0) = 0 \tag{22}$$

$$c_{D_t^\alpha c_l(t)} = k_a c_{ab}(t) - k_l c_l(t)\,; \qquad c_l(0) = 0 \tag{23}$$

$$c_{D_t^\alpha c_{vb}(t)} = k_t c_t(t) - k_e c_{vb}(t) + k_l c_l(t); \qquad c_{vb}(0) = 0 \tag{24}$$

where α represents the fractional order and $0 < \alpha \leq 1$.

Now, Eq. 21 becomes,

$$c_{ab}(t) = c_{ab}(a) + \frac{1}{\Gamma(\alpha)}[-(k_b + k_a)c_{ab}(t)](t-a)^\alpha \tag{25}$$

For a = 0, Eq. 25 becomes,

$$c_{ab}(t) = c_{ab}(0) + \frac{1}{\Gamma(\alpha)}[-(k_b + k_a)c_{ab}(t)](t-0)^\alpha \tag{26}$$

From Eqs. 25 and 26

$$c_{ab}(t) = \frac{c_0\Gamma(\alpha)}{\Gamma(\alpha) + (k_b + k_a)t^\alpha} \tag{27}$$

Now, Eq. 22 gives,

$$c_t(t) = c_t(a) + \frac{1}{\Gamma(\alpha)}[k_b c_{ab}(t) - k_t c_t(t)](t-a)^\alpha \tag{28}$$

For a = 0, Eq. 28 becomes,

$$c_t(t) = c_t(0) + \frac{1}{\Gamma(\alpha)}[k_b c_{ab}(t) - k_t c_t(t)](t-0)^\alpha \tag{29}$$

From Eq. 28 and 29

$$c_t(t) = \frac{k_b c_{ab}(t)t^\alpha}{\Gamma(\alpha) + k_t t^\alpha} \tag{30}$$

Now, Eq.23 gives,

$$c_l(t) = c_l(a) + \frac{1}{\Gamma(\alpha)}[k_a c_{ab}(t) - k_l c_l(t)](t-a)^{\alpha} \quad 31$$

For a = 0, Eq. 31 becomes

$$c_l(t) = c_l(0) + \frac{1}{\Gamma(\alpha)}[k_a c_{ab}(t) - k_l c_l(t)](t-0)^{\alpha} \quad 32$$

From Eqs. 31and 32

$$c_l(t) = \frac{k_a t^{\alpha} c_{ab}(t)}{\Gamma(\alpha) + k_l t^{\alpha}} \quad 33$$

Now, Eq.24 gives,

$$c_{vb}(t) = c_{vb}(a) + \frac{1}{\Gamma(\alpha)}[k_t c_t(t) - k_e c_{vb}(t) + k_l c_l(t)](t-a)^{\alpha} \quad 34$$

For a = 0, Eq. 35 becomes

$$c_{vb}(t) = c_{vb}(0) + \frac{1}{\Gamma(\alpha)}[k_t c_t(t) - k_e c_{vb}(t) + k_l c_l(t)](t-0)^{\alpha} \quad 35$$

From Eq. 34 and 35

$$c_{vb}(t) = \frac{[k_t c_t(t) + k_l c_l(t)]t^{\alpha}}{\Gamma(\alpha) + k_e t^{\alpha}} \quad 36$$

Results:

The mathematical analysis explains different models that divided the human body into a possible number of compartments followed by drug administration either by oral route or by intravenous route. The model development and its mathematical analysis were executed using Fick's law of perfusion, first-order kinetics, fractional-order kinetics-Caputo model, and conservation law of mass. The model graphical results were plotted using the mathematical simulation software MATLAB (version R2019b). The fractional-order derivative (Caputo model) by using one of the Lemmas 1, significantly helps to find drug concentration at any fractional order of derivative $(0 < \alpha \leq 1)$. All model parameter values considered from physiological studies as per the literature review[5,8,22].

The model I simulated in two different patterns, first where the entire body is assumed as a single compartment and a second pattern of modeling the human body into three individual compartments: stomach, liver, and blood.

The absorption and distribution of drug concentration throughout the body as one compartment concerning time against the varying rate of drug flow with an initial drug administration of 500 units, as depicted in Fig. 3. The graph indicates based upon the decrease rate constant of the drug during the period, its concentration also slowly and sustainably decreases, only if $\alpha=0.5$. Notations of the rate of drug diffusion are k_l i.e., from the stomach to blood, k_s i.e., from the stomach to the liver, and k_l i.e., from the liver to stomach. As per Fig. 3 curves in the graph explained in four cases, where k_l, k_s, and k_l in case 1 are considered as *0.9776/hr*, *0.1998/hr*, and *0.0848/hr* show faster drug flow rate with low sustainability, quick drug absorption and its faster elimination from body as compared to decrease drug flow rate as in case 2 representing k_l*=0.7448/hr*, k_s*=0.1767/hr*, and k_l*=0.625/hr;* in case 3 k_l*=0.3293/hr*, k_s*=0.1446*, and k_l*=0.0428/hr;* lastly case 4 considers k_l*=0.2213/hr*, k_s*=0.1282/hr*, and k_l*=0.0265/hr;* these cases shows consecutive slow and sustain drug absorption, distribution, and excretion. Throughout the model condition, α *is* assumed to be *0.5* which indicates to show continued drug action in the human body for a more extended period. Such a situation α*=0.5* and decreasing rate of drug diffusion helps to avoid frequent intake of drugs.

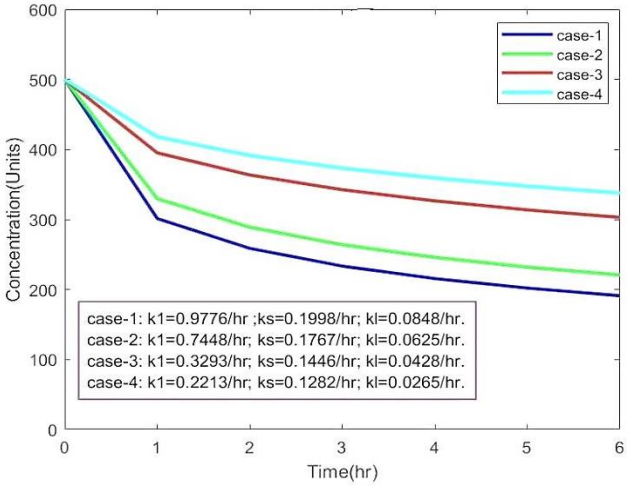

Figure 3. Drug concentration at a varying rate of drug constants concerning the time when $\alpha = 0.5$.

Mathematical Model I (single compartment), shows the consecutive increase in sustained drug concentration throughout the body considering decreasing drug diffusion constants as per cases explained in Fig. 4.

Here considering the plot of an individual case of drug diffusion constant while α*=0.6, 0.7, 0.8, 0.9*, and *1.0* are shown in Figs. 4 - 7. With these conditions, each graphical plot found that as α increases the drug concentration and its

sustainability gradually decrease in the body. Among all the graphical results from 4- 7, found that when the drug diffusion constant assumed as in case 4, it showed better and sustained drug concentration in the body followed by a sequential decrease when diffusion constants are shown as in cases 3, 2, and 1 respectively.

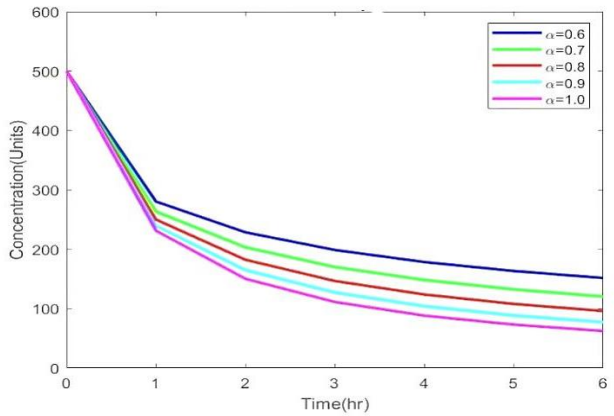

Figure 4. Drug concentration at a fixed rate of constant k_1=0.9776/hr, k_s=0.1998/hr, and k_l=0.0848/hr concerning time, when $\alpha = 0.6, 0.7, 0.8, 0.9$ and 1.0.

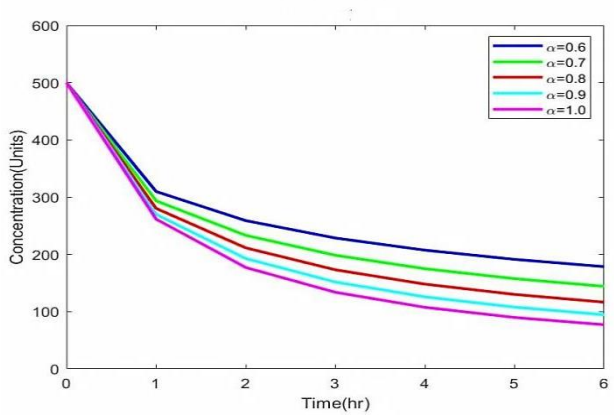

Figure 5. Drug concentration at a fixed rate of constant k_1=0.7448/hr, k_s=0.1767/hr, and k_l=0.625/hr concerning the time, when $\alpha = 0.6$, 0.7, $0.8, 0.9$, and 1.0.

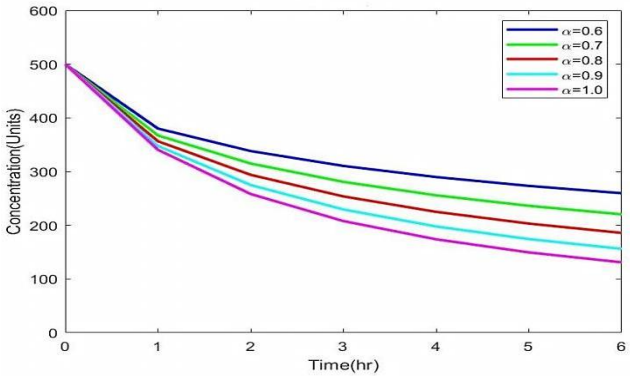

Figure 6. Drug concentration at a fixed rate of constant k_1=0.3293/hr, k_s=0.1446 and k_l=0.0428/hr concerning the time, when $\alpha = 0.6$, 0.7, 0.8, 0.9, and 1.0.

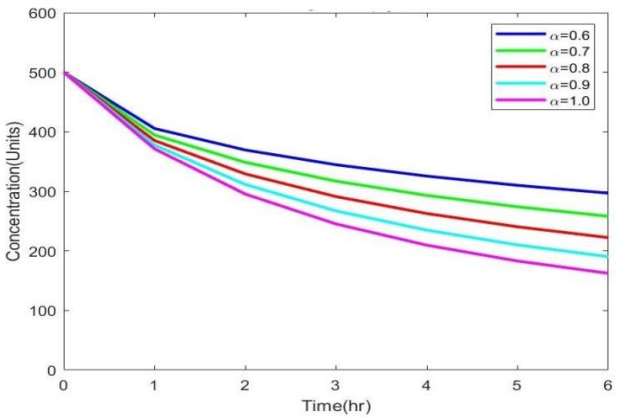

Figure 7. Drug concentration at a fixed rate of constant k_1=0.2213/hr, k_s=0.1282/hr, and k_l=0.0265/hr concerning the time, when $\alpha = 0.6, 0.7, 0.8, 0.9$ and 1.0.

Fig.8. of Model I, result explains the drug concentration and its efficacy in the body when initial drug concentrations c_0=*600, 400, 200,* and *100* units were taken considering a fixed rate of constant as in case 1 where k_1=*0.9776/hr*, k_s=*0.1998/hr*, and k_l=*0.0848/hr* concerning the time; and α *is 0.5.* Different initial drug concentrations are found and prescribed depending on the age and health condition of the patient. High initial drug concentration, i.e., 600 units remain in the body for a more extended period with good therapeutic effect followed by initial drug concentration of 400, 200, and 100 units, respectively, where the former shows better and sustained drug concentration in the body. When a patient is prescribed with low initial drug concentration, the frequent dose intake increases, and maintaining the therapeutic index becomes difficult.

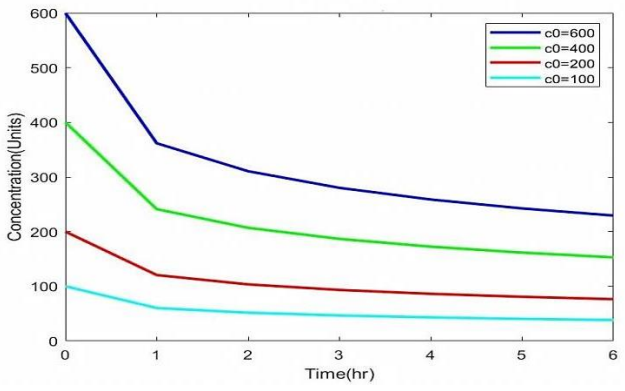

Figure 8. Varying drug concentration at a fixed rate of constant k_1=0.9776/hr, k_s=0.1998/hr, and k_l=0.0848/hr concerning the time, when $\alpha = 0.5$.

The behavior of different initial doses of drugs in Figs. 9-12. depicted considering fixed rate

constants as depicted in cases 1, 2, 3, and 4 concerning time, where *α=0.6. 0.7, 0.8, 0.9,* and *1.0.* When the initial drug concentration is 600 units, and the α value ranges from 0.6 to 1.0 with a fixed rate constant as k_1*=0.9776/hr*, k_s*=0.1998/hr*, and k_l*=0.0848/hr*, the drug concentration in the body significantly decreases with an increase in α as shown in Fig.9. the impact of α is effectively more potent and viable only when initial drug concentration is high. While indicating the study of low initial dose intake, results show minimal differences in the sink of drug concentration in the body when α ranges from 0.6 to 1.0.

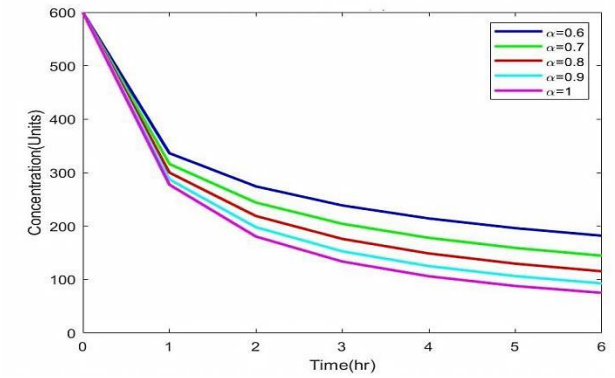

Figure 9. Fixed drug concentration c_0=600 units at a fixed rate of constant k_1=0.9776/hr, k_s=0.1998/hr, and k_l=0.0848/hr concerning the time when $\alpha = 0.6, 0.7, 0.8, 0.9$ and 1.0.

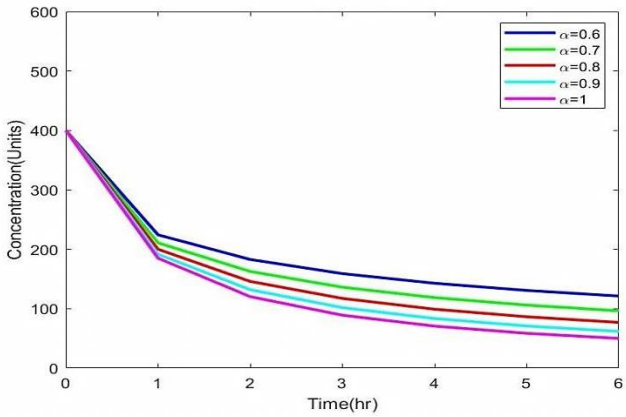

Figure 10. Fixed drug concentration c_0=400 units at a fixed rate of constant k_1=0.9776/hr, k_s=0.1998/hr, and k_l=0.0848/hr concerning the time when $\alpha = 0.6, 0.7, 0.8, 0.9$ and 1.0.

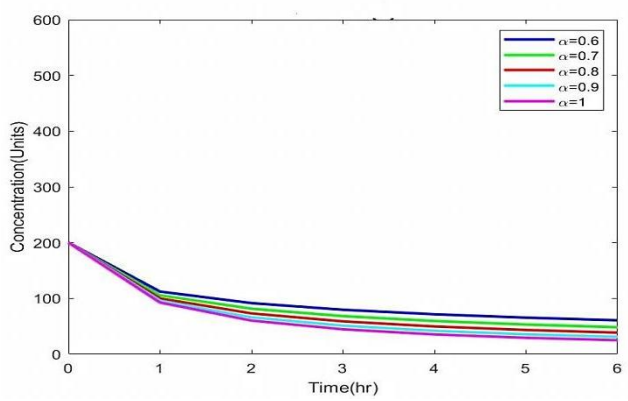

Figure 11. Fixed drug concentration c_0=200 units at a fixed rate of constant k_1=0.9776/hr, k_s=0.1998/hr, and k_l=0.0848/hr concerning the time when $\alpha = 0.6, 0.7, 0.8, 0.9$ and 1.0.

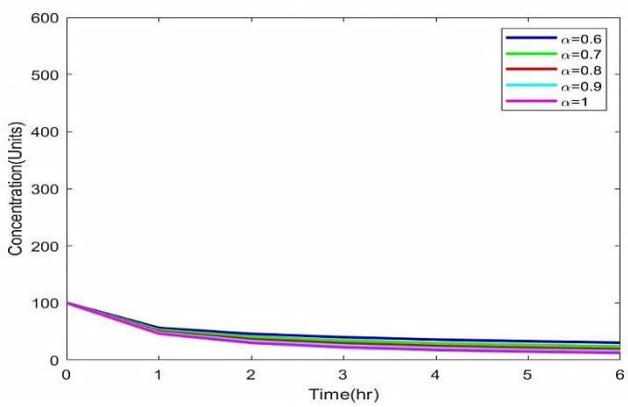

Figure 12. Fixed drug concentration c_0=100 units at a fixed rate of constant k_1=0.9776/hr, k_s=0.1998/hr, and k_l=0.0848/hr concerning the time when $\alpha = 0.6, 0.7, 0.8, 0.9$ and 1.0.

Considering three compartments of model I (stomach, blood, and liver), assumptions are made in Fig.13. includes, the initial dose taken as 500 units enter into the first compartment (stomach) at a constant rate k_1*=0.9776/hr*, k_s*=0.1998/hr*, and k_l*=0.0848/hr*, when *α is 0.5,* showed a persistent decrease in drug concentration in the stomach concerning time (indicated as the blue curve in the graph). The drug concentration gradually increases in the second compartment (blood). Considering the first past metabolism of drugs in the liver (compartment III) and the availability of drug concentration in the blood will vary based on rate constants. The graph shows that the drug concentration initially increases from zero irrespective of rate constants. Then decreases accordingly, if k_e increases the gradient from *0.2213/hr, 0.3293/hr, 0.5228/hr to 0.7748hr*, throughout the condition *α is 0.5.* The overall results of Fig. 13. estimate that as the elimination rate constant decreases, the drug concentration in the blood remains for a longer time, and drug sustainability can be obtained.

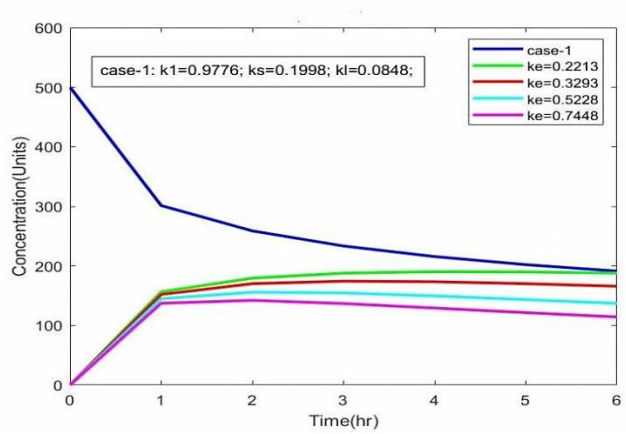

Figure 13. Fixed drug concentrations c_0=500 units concerning time, at varying elimination rates of constants when $\alpha = 0.5$.

Evidence of Figs. 14 -17 of Model I (three-compartment), where the initial dose of 500 units enters into the stomach at a rate k_1=*0.9776/hr*, k_s=*0.1998/hr*, and k_l=*0.0848/hr* and further get absorbed into blood followed by its excretion from blood at different elimination rate constants k_e=*0.2213/hr, 0.3293/hr, 0.5228/hr,* and *0.7448/hr* respectively, concerning time. The drug concentration in blood initially increases rapidly following the quick drop in its concentration if the α value is considered high as 1.0. So, if the α value gradually decreases i.e., 0.9, 0.8, 0.7, and 0.6 then the drug concentration in blood sustains for a longer time concerning α, and the elimination of drugs becomes slow.

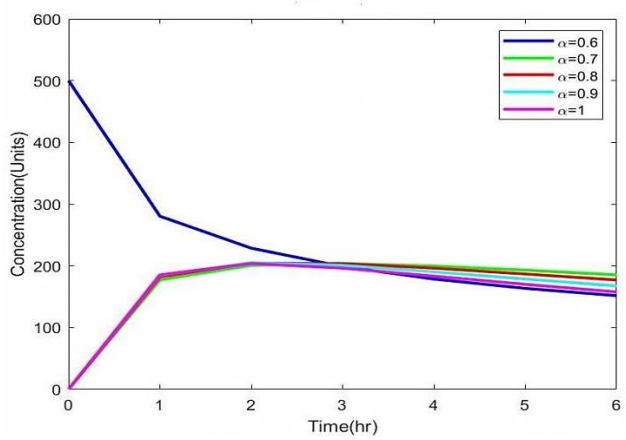

Figure 14. Fixed drug concentrations c0=500 units with respect to the time, at a fixed rate of constants k1=0.9776/hr, ks=0.1998/hr and kl=0.0848/hr and ke=0.2213/hr, when $\alpha = 0.6, 0.7, 0.8, 0.9$ and 1.0.

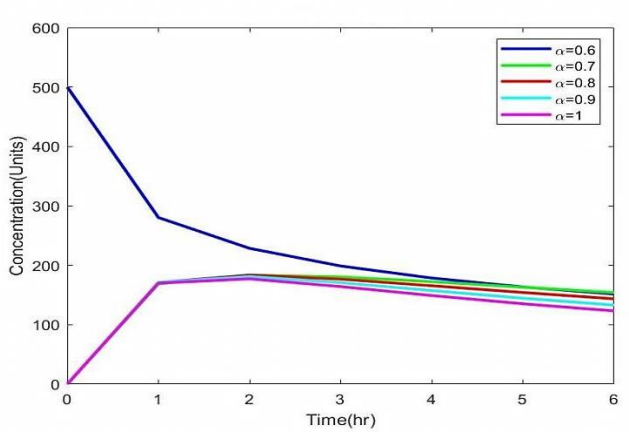

Figure 15. Fixed drug concentrations c0=500 units with respect to the time, at a fixed rate of constants k1=0.9776/hr, ks=0.1998/hr and kl=0.0848/hr and ke=0.3293/hr, when $\alpha = 0.6, 0.7, 0.8, 0.9$ and 1.0.

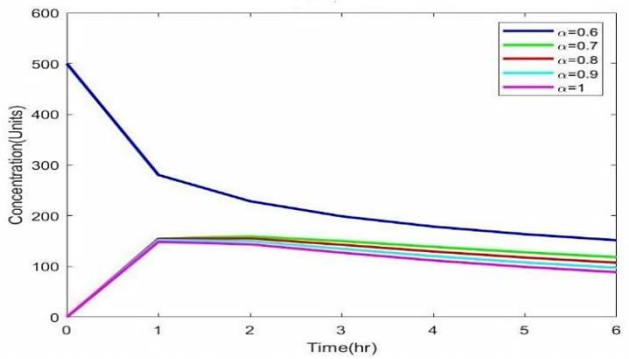

Figure 16. Fixed drug concentrations c0=500 units concerning the time, at a fixed rate of constants k1=0.9776/hr, ks=0.1998/hr, and kl=0.0848/hr and ke=0.5228/hr when $\alpha = 0.6, 0.7, 0.8, 0.9$ and 1.0.

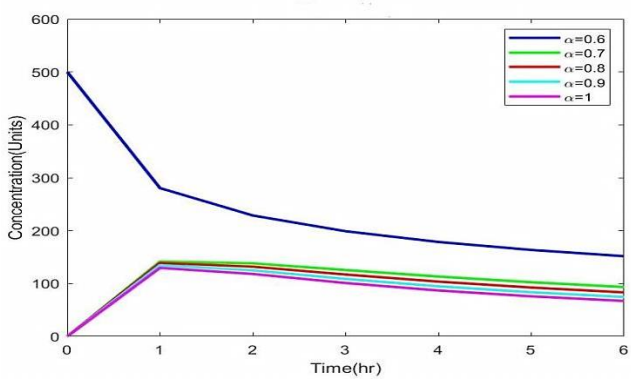

Figure 17. Fixed drug concentrations c0=500 units with respect to the time, at a fixed rate of constants k1=0.9776/hr, ks=0.1998/hr and kl=0.0848/hr and ke=0.7448/hr, when $\alpha = 0.6, 0.7, 0.8, 0.9$ and 1.0.

Mathematical Model II analysis is illustrated in Figs.18, 19. The initial intravenous dose is considered as 500 units; here, the change in drug concentration in arterial blood, tissue, liver,

and venous blood compartments is estimated at variable rate constants (Fig. 18.) and fractional order (Fig. 19 and 20) concerning time.

The results of Fig.18 delineate changes in drug concentration in four different compartments (arterial blood, tissue, liver, and venous blood) and understand the impact of variable flow rate over drug concentration explained in two instances. In the first condition, rate constants k_b arterial blood to tissue, k_t tissue compartment to venous blood, k_a arterial blood to the liver, k_l liver to venous blood, and k_e from venous blood, assumed to be *0.9776/hr, 0.3293/hr, 0.76/hr, 0.0848/hr, and 0.2213/hr* respectively. Whereas in the second condition, k_b*=0.5/hr,* k_t*=0.25/hr,* k_a*=0.15/hr,* k_l*=0.0265/hr, and* k_e*=0.05/hr,* were considered, throughout both cases, α remains 0.5. From the graph, it is clear that only when *α is 0.5* and the drug diffusion constant in the arterial blood compartment decreases then the increased drug concentration prolongs to stay for a more extended period. Whereas, in tissue and venous blood compartments as the rate constant increases, the drug absorption increases.

By applying different α values in increasing order, drug concentration in arterial and venous blood decreases rapidly but grows spontaneously in the tissue compartment and sustains at target sites.

The fractional derivative order application plays a vital role in maintaining drug concentration in the respective compartments.

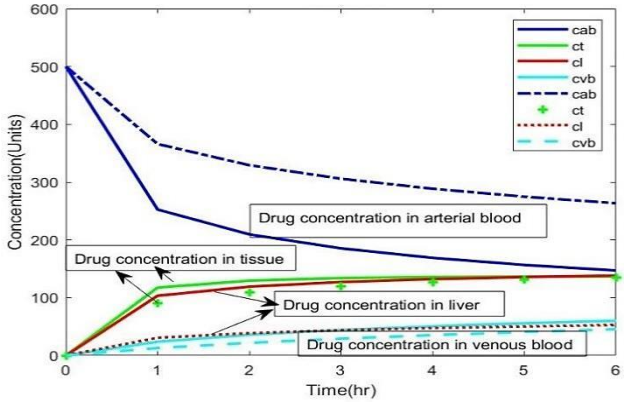

Figure 18. Initial intravenous dose of 500 units estimates drug concentration in four individual compartments against different rate constants assumed in two variable cases.
i.e., Case-1: k_b=0.9776/hr, k_e=0.2213, k_t=0.3293/hr, k_a = 0.76/hr and k_l = 0.0848/hr.
Case-2: k_b=0.5/hr, k_e=0.05/hr, k_t=0.25/hr, k_a = 0.15/hr and k_l = 0.0265/hr, when $\alpha = 0.5$.

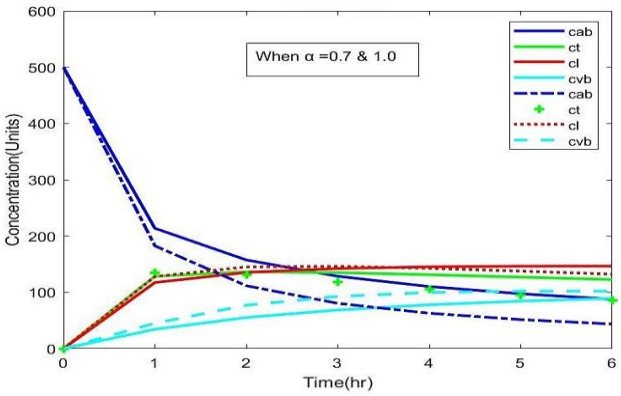

Figure 19. Initial intravenous dose 500 units estimates drug concentration in four individual compartments against different rate constants assumed in a single case, when $\alpha = 0.7, \text{and } 1.0$.

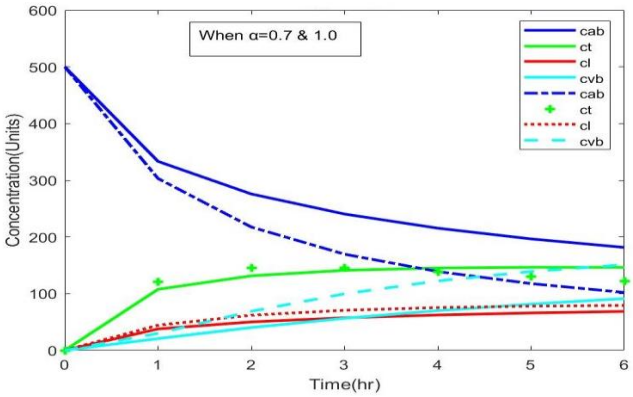

Figure 20. Initial intravenous dose 500 units estimates drug concentration in four individual compartments against different rate constants assumed in a single case, when $\alpha = 0.7, \text{and } 1.0$.

Discussion:

In this study, depending upon the general physiological process, the drug diffusion kinetics are explained in two different patterns denoted as Mathematical Model I, and II based upon its route of administration. The mathematical analysis was done using the Caputo model. Various model parameter values are considered with all possible approximates to understand the change in drug concentration in any compartment of the body with fixed or changed rate constants in fractional order. Due to a novel mathematical approach to the analysis of model compartments, the pattern of drug transport is well understood. Its concentration in compartments sustains for a more extended period only when considering a fractional order ($0 < \alpha \leq 1$). Simulation with the Caputo model gives a brief application in designing drug formulation with therapeutic dose adjustments and in deciding the route of administration. The model results suggest

developing drugs with a sustained release pattern of the drug in target tissue compartments.

As the literature review data reports, the mathematical simulation using the fractional derivative Caputo model is used to understand the epidemiology of infectious disease outbreaks in society[14].

Evidence of such mathematical simulation used in epidemiology research includes scientific results reported by Qureshi proposed epidemiological findings to trace the measles epidemic in society via the Caputo fractional-order operator using fixed point theory[23]. Besides, another research published by Ullah et al. represents the study of the dynamic of tuberculosis by using the same mathematical method as the nonlinear fractional-order derivative Caputo model[24,25]. Almeida et al. explained in their research data regarding the fractional MSEIR model, the numerical simplification done by applying the Caputo model[26]. Likewise, many scientific types of research involving dynamic findings include epidemic and pandemic outbreaks of various infectious diseases such as Hepatitis B[27], Nipah virus[28]and related respiratory infectious virus[29], Rubella virus[30], chickenpox[23], SARS-CoV-2[31]and many more contagious infections.

Naisani et al. in their research used mathematical expression to explain the reversible and diffusion mechanism of solute in Liquid membrane systems by developing a kinetic model which helped to correlate our study drug diffusion through body membrane system[32]. Angstmann et al.explained the application of fractional order derivatives in a wide range of pharmacological areas, including the dynamic of infectious spread in society, the pharmaceutical nature of the drug, and the tracing of drug pharmacokinetics in compartment models[14]. Several compelling studies using the fractional derivative Caputo model have already been reported, but its specific application in trafficking drug kinetics is nowhere developed and evaluated yet. Here arises the novelty of our research work by applying the fractional derivative Caputo model to analyze drug diffusion patterns in compartment models of the human body.

Conclusion:

Conclude that by using the Caputo model understanding the availability of the drug concentration concerning the time in any compartment of the human body. Caputo model helps to estimate the sustainability of the drug before it is formulated. And corresponding results motivate that due to the Caputo model, the drug remains in the body for a more extended period depending upon rate constants. Such conclusions will help in designing and formulating sustained and controlled-release drug formulae in pharmaceutical research. Many research findings using this mathematical method were applied only for pharmacodynamic studies, where our research findings enabled an understanding of the pharmacokinetics of the drug and its absorption in different body compartments based on its administration route.

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Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures in the manuscript are ours. Besides, the Figures and images, which are not ours, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in Raju Institute of Technology.

Authors' contributions:

RK formulated and interpreted the Mathematical model and was a major contributor to the manuscript. RJ analyzed the mathematical part of the manuscript. SK interpreted pharmacy-related terms and depicted physiological diagrams of the manuscript also helped in getting results. SRB used MATLAB software to draw and analysed the conclusion. All authors read and approved the final manuscript.

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مراعاة الحركية الدوائية لصياغة الأدوية ذات الإطلاق المستمر :فهم انتشار الدواء الخاضع للرقابة من خلال مقصورة الجسم للدورة الدموية الجهازية ووسط الأنسجة -نموذج كابوتو

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[3]قسم علم الأدوية ، معهد فيشنو للتعليم والبحوث الصيدلانية، نارسابور، حي ميداك .تيلانجانا - 502313، الهند.

الخلاصة:

الهدف من هذه الدراسة هو تقديم لمحة عامة عن النماذج المختلفة لدراسة انتشار الدواء لفترة طويلة في جسم الإنسان وداخله. تم التأكيد على نماذج المقصورة الرياضية باستخدام نهج المشتقة الجزئية (نموذج كابوتو) للتحقيق في التغير في تركيز الدواء المستدام في أجزاء مختلفة من نظام جسم الإنسان من خلال الطريق الفموي أو الطريق الوريدي. و تم استخدام قانون العمل الجماعي ، وحركية الدرجة الأولى ، ومبدأ الإرواء لفيك لتطوير نماذج المقصورة الرياضية التي تمثل انتشارا مستداما للأدوية في جميع أنحاء جسم الإنسان .للتنبؤ بشكل كافٍ بانتشار الدواء المستمر في أجزاء مختلفة من جسم الإنسان، وضعنا في الاعتبار(نموذج كابوتو) للتحقيق في معدل تغير التركيز اعتمادًا على التغيير في ترتيب التمايز الجزئي في جميع الأجزاء الممكنة من الجسم، أي الدوران الجهازي وحجرات الأنسجة. أيضا ، تم تعيين قيمة معلمة عددية لمعدل تدفق الدواء في مقصورات مختلفة لتقدير تركيز الدواء. تم حساب النتائج وتصوير الأرقام باستخدام برنامج MATLAB (الإصدار R2020a). التأثيرات الرسومية الموضحة للتغير في معدل التركيز بافتراض قيم وسيطة مختلفة وفقا للمشتقة الكسرية (نموذج كابوتو). التأثيرات الرسومية الموضحة للتغير في معدل التركيز بافتراض قيم وسيطة مختلفة وفقا للمشتقة الكسرية (نموذج كابوتو). يخلص التمثيل البياني الناتج إلى أنه بالنظر إلى ترتيب قيم المعادلات التفاضلية ، يختلف تركيز الدواء اعتمادا على معدل الثوابت في المقصورات المتعلقة بالوقت . النظر في الحالة الأولية للتقدير التقريبي حيث يشير الجسم كحجرة كاملة، بعد تقسيم الجسم إلى مقصورتين نموذجيتين .في حين أن النموذج الأول يمثل المعدة والكبد والدم الجهازي ؛ والنموذج الثاني يأخذ في الاعتبار الدم الشرياني وأنسجة الكبد والدم الوريدي.

الكلمات المفتاحية: نموذج كابوتو، نموذج المقصورة، انتشار الدواء، مشتق الترتيب الجزئي، النمذجة الرياضية.