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A FRACTIONAL-ORDER MODEL FOR DRUG DISTRIBUTION VIA GASTROINTESTINAL AND INTRAVENOUS ROUTES USING THE CAPUTO-FABRIZIO OPERATOR

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Abstract

This paper presents a unified mathematical framework for modeling the pharmacokinetics of the drug delivery through both oral (gastrointestinal) and intravenous pathways of Khanday et. al. [XIV] The structure is formulated using the Caputo–Fabrizio fractional derivative with a non-singular exponential kernel, offering a more realistic description of the memory and diffusion processes compared to classical integer-order and singular fractional operators. Theoretical analysis is conducted to ensure the existence and uniqueness of a solution, applying the fixed-point theorem as the core analytical tool. Laplace transform techniques are employed to obtain explicit solutions, and the dynamic behaviour of the drug concentration in the bloodstream is illustrated through numerical simulations. The results highlight the influence of the fractional-order parameters on drug absorption and distribution, offering valuable insights for biomedical and pharmaceutical applications.

Keywords : Drug Delivery Modeling; Caputo–Fabrizio Derivative; Fractional Differential Equations; Gastrointestinal Tract; Intravenous Infusion; Laplace Transform; Fixed-Point Theory.

I. Introduction

Mathematical modelling plays a crucial role in diverse fields such as finance, biology, engineering, and the social sciences because of its strong capacity to generate dependable predictions. In this study, the model introduced by Khanday et al. [XIV] is further developed by employing Caputo–Fabrizio fractional derivatives, based on the framework discussed in [IV, V, XXV]. The Caputo–Fabrizio fractional derivative, which avoids singular kernels, provides an effective alternative to classical operators such as the Riemann–Liouville and Caputo derivatives. Despite their wide range of applications, fractional operators such as the Caputo–Fabrizio derivative, which is characterized by a non-singular kernel, have received limited attention in biological modeling.

In pharmacokinetic studies, compartmental models provide a structured framework for analyzing drug distribution and activity across different physiological compartments. These models represent the body as a collection of linked compartments to simulate the distribution of drugs or chemicals through tissues, organized either in series or through simultaneous pathways. They provide a systematic method for investigating the distribution of drugs and their interactions with tissues, while capturing their kinetic dynamics within the biological system. Depending on the level of detail required to describe the transport mechanism, compartmental models may involve a single compartment or extend to two compartments representing central and peripheral regions. Initial developments in compartmental modelling can be traced back to the work of Widmark in the 1920s [XXIX], where the approach was applied to study alcohol distribution in the body.

According to Crouch et al. [VII], mathematical modelling consists of expressing real-life situations in mathematical terms, examining the model mathematically, and then relating the findings to the real-world scenario. The study of the fractional calculus, concerned with differentiation and integration of non-integer positive orders, has attracted increasing attention across disciplines including mathematics, engineering, biology, and finance [XIII, XVI, XVII, XXIII, XXVI]. The process of converting real-world systems into mathematical frameworks for analysis has made mathematical modelling a valuable approach in fluid dynamics and chemical process investigations [XV, I, II].

In biological studies, analyzing how drugs spread throughout the body is essential for understanding their physiological effects. Medications can be delivered through various pharmaceutical forms, including tablets, capsules, and injections, using approaches such as oral administration or controlled-release mechanisms [XVI, XX, XXIV, III, XXII]. Vaccination works by enhancing the body's immune defense mechanisms to prevent infections caused by harmful pathogens.

The one- and two-compartment models proposed by Koch [XVII] have provided valuable insights into the interpretation of pharmacokinetic mechanisms. In their work, Cherrauault and Sarin [VI] introduced a three-compartment model with two time lags to provide an improved representation of the process. The works of Khanday and Rafiq [XIII] and Khanday et al. [XIV] analyze drug diffusion and transdermal delivery processes, whereas Ardith and Timothy [X] expand the model by incorporating continuous infusion to study drug circulation under controlled conditions. Using experimental data, the authors in [VIII] develop models that capture the unusual transport behavior and accumulation of drugs within tissue compartments.

In this work, drug delivery within the human body is modelled using compartmental frameworks, which possess notable mathematical significance. Through the compartmental representation of the body, this technique helps in analyzing and interpreting drug kinetic processes. Depending on the context of the study, compartments may be arranged differently to describe the movement and uptake of substances.

The current research merges the first and second models developed by Khanday et al. [XIV] to provide a stronger framework for studying drug distribution in the bloodstream through oral and intravenous administration, using the Caputo–Fabrizio fractional derivative. This framework presents a refined mathematical depiction of drug concentration within the bloodstream, enabling a better understanding of pharmacokinetic processes. Our results indicate that the developed fractional model generates stable and interpretable outcomes, which may contribute to clinical research and applications.

The research at head is framed as detailed below: Section 2 deals with principles and integral fluctuations related with foundational operators, Section 3 presents the flow chart where the bloodstream flows from one compartment to another along with the parameters and demonstrates the Caputo Fabrizio fractional derivative model for drug circulation, Section 4 illustrates the existence and uniqueness of the solutions and Section 5 analyses the fractionalized models and their proposals using the Laplace transformation, Section 6 discusses the graphs with the different levels of parameter values. Conclusions and suggested directions for subsequent analysis are outlined in Section 7.

II. Theoretical Foundations

This section provides the definitions used in this work.

Definition 1. The Riemann – Liouville (R-L) fractional operator of order $\zeta > 0$, of function $h \in L^1(\mathbb{R}^+)$ is defined as

$$D^{\zeta} h(t) = \frac{1}{\Psi(\zeta)} \int_0^t (t-u)^{\zeta-1}\, h(u)du. \tag{1}$$

where $\Psi(\zeta)$ is the Euler Gamma function.

Definition 2. From [IV], Let $V \in G^1(c, d), d > c, \xi \in [0,1]$ then, the definition of the arbitrary order Caputo-Fabrizio fractional derivative is given by

$${}^{CF}_{0}D_t^{\xi}\big(V(t)\big) = \frac{W(\xi)}{1-\xi} \int_0^t V'(y) exp\left[-\xi \frac{t-y}{1-\xi}\right] dy \tag{2}$$

In equation (1), $W(\xi)$ acts as a normalizing function satisfying imposed conditions $W(\xi) = W(0) = 1$

Definition 3. From [IV], assume $0 < \xi < 1$, thus fractional order integral of order ξ is denoted as

$$I_t^{\xi}\big(V(t)\big) = \frac{2(\xi-1)}{(\xi-2)W(\xi)}g(t) + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t V(\xi)d\xi, t \geq 0 \qquad (3)$$

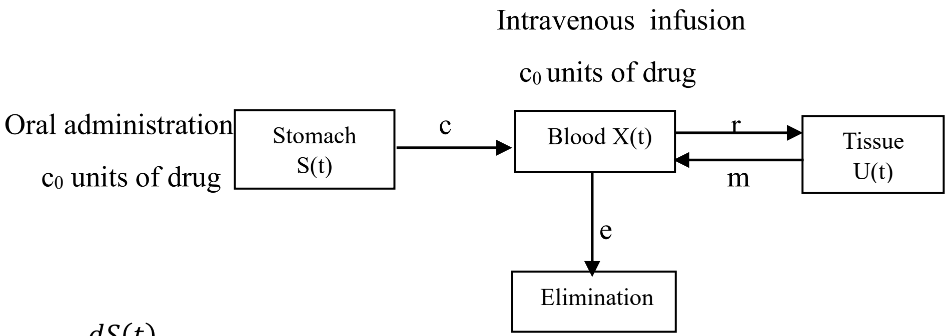
$$\frac{2}{2W(\xi) - \xi W(\xi)} = 1 \qquad (4)$$

we get $W(\xi) = \frac{2}{(2-\xi)}$, and with order $0 < \xi < 1$.

The new Caputo derivative in another form is represented by the authors [IV] as

$${}_{0}^{CF}D_t^{\xi}\big(V(t)\big) = \frac{1}{1-\xi}\int_0^t V'(y)exp\left[-\xi\frac{t-y}{1-\xi}\right]dy \qquad (5)$$

III. Drug distribution with the Combined equation of Model I and II through the Stomach, Blood and Tissue compartments



$$\frac{dS(t)}{dt} = -cS(t); \qquad S(0) = c_0$$

$$\frac{dX(t)}{dt} = cS(t) + mU(t) - (e + r)X(t); \qquad X(0) = 0$$

$$\frac{dU(t)}{dt} = r\,X(t) - m\,U(t)\,; \qquad U(0) = 0$$

where S(t), X (t) and U(t) represent the concentration of the drug in the stomach or GI tract, the blood stream compartment and tissue correspondingly. c_0 take the role of the initial concentration of the medication dose. Also, the quantities c be the rate constant from one compartment (stomach) to another compartment (bloodstream), m be the rate constant of drug diffusion from tissue again to the blood, r be the rate constant from bloodstream onto tissue and e be the clearance constant.

Over the course of this section, we implement the fractional drug delivery system of drug flow simultaneously through vein circulation to the target area and oral administration of the drug where the circulation is through the gastrointestinal tract is employed, with the unabsorbed drug either restored or released into the bloodstream and to the tissue. The model includes the drug concentration of the oral drug delivery in the stomach denoted by S(t), in the bloodstream compartment denoted by X(t) and in the tissue compartment denoted by U(t), with the rate constants c, m and r. Assumptions and parameter values from the deterministic ODE model presented in this manuscript form the basis of the differential equations model. This fractional mathematical framework for drug transport in the cardiovascular system employs compartmental modelling and utilizes the CF derivative, which is represented by:

$$ {}_{0}^{CF}D_t^{\xi} S = -cS; \qquad S(0) = c_0, $$

$$ {}_{0}^{CF}D_t^{\xi} X = cS + mU - eX - rX; \qquad X(0) = 0, $$

$$ {}_{0}^{CF}D_t^{\xi} U = rX - mU; \qquad U(0) = 0. \tag{6} $$

IV. Fractional order model with Caputo-Fabrizio Memory Effect:

We consider the system (6) governed by the Caputo-Fabrizio fractional derivative of order $\xi \epsilon (0, 1)$:

The Caputo-Fabrizio derivative of a differentiable function f(t) is defined as

$$ {}_{0}^{CF}D_t^{\xi}\big(V(t)\big) = \frac{1}{1-\xi}\int_0^t V'(y)exp\left[-\xi\frac{t-y}{1-\xi}\right]dy $$

$$ {}_{0}^{CF}D_t^{\xi}\big(V(t)\big) = \frac{1}{1-\xi}\left(V'(t) - \tau\int_0^t V(y)exp[-\tau(t-y)]dy\right) $$

where $\tau = \frac{\xi}{1-\xi} > 0.$

$$ k_{\xi}(t - y) = \frac{1}{1-\xi}e^{-\tau(t-y)} $$

is the memory kernel, capturing the contribution of the past history of the system.

Equivalent integral (memory) formulation:

The fractional differential equations (6) are equivalently expressed as the following Volterra integral equations:

$$ S(t) = S(0) - \int_0^t K_{\xi}(t-y)cS(y)\,dy, $$

$$ X(t) = x(0) - \int_0^t K_{\xi}(t-y)(cS(y) + mU(y) - (e+r)X(y))dy, $$

$$ U(t) = U(0) - \int_0^t K_{\xi}(t-y)(rX(y) - mU(y))\,dy $$

These integral equations explicitly show the memory effect such that each state depends not only on the present value but also on its entire past, weighted by the exponential kernel of the Caputo-Fabrizio operator.

Prolonged memory effect: Provided that the order of the fractional derivative or integration of the fractional order lies in (0, 0.5) as a result this system has a prolonged memory effect.

Limited memory effect: If the magnitude of the derivative of the fractional order or fractional integration falls within [0.5, 1) then the system shows a limited memory effect.

V. Analysis of the model

In this section, we prove the basic properties of the proposed model (6). We progress as follows:

Stability of the CF derivatives:

The above model (6) is linear thus the equilibrium is (0, 0, 0) since it is trivially the origin [XXI].

Theorem 1. The model (6) was locally asymptotically stable if and only if $\mathscr{R}_0 < 1$.

Proof

Write the system in matrix form as ${}_{0}^{CF}D_t^{\xi}Z(t) =$ MZ(t) with

$$Z = \begin{pmatrix} S \\ X \\ U \end{pmatrix}, M = \begin{pmatrix} -c & 0 & 0 \\ c & -(e+r) & m \\ 0 & r & -m \end{pmatrix} \text{ where c, e, r, and m} > 0. \quad (7)$$

Let us take the Jacobian matrix

$$M = \begin{pmatrix} -c & 0 & 0 \\ c & -(e+r) & m \\ 0 & r & -m \end{pmatrix} \quad (8)$$

The characteristic equation for the Jacobian matrix mentioned above is in the form:

$$\det(\lambda I - M) = (\lambda + c)(\lambda^2 + (e + r + m)\lambda + me) = 0. \quad (9)$$

Since $c > 0$, $\lambda_1 = -c < 0$,

Solving for eigen values we get

$\lambda_1 = -c,$

$\lambda_2 = roots\ of\ \lambda^2 + (e + r + m)\ \lambda + me$

which gives $\lambda_2 = \frac{-(e+r+m) + \sqrt{(e+r+m)^2 - 4me}}{2}$

Similarly, $\lambda_3 = \frac{-(e+r+m) - \sqrt{(e+r+m)^2 - 4me}}{2}$

If the parameters c, e, r, and m are non-negative then $c > 0$ and the quadratic equation has positive coefficients, hence the two roots λ_2, λ_3 have negative real parts. Thus, all the eigen values of M are in the left-half plane (i.e., $\mathscr{R}\lambda_I < 0$) on conditions that c, e, r, and m > 0.

For $\mathscr{R}_0 < 1$ the equation (8) has all positive coefficients and by the criteria of Routh-Hurwitz for the second order polynomial $a_i > 0$ for i = 0,1,2. Therefore the model (6) is locally asymptotically stable for $\mathscr{R}_0 < 1$.

Remark:

Since the parameters c, e, r, and m are positive. By equating the equations to zero, the equilibrium is only (0, 0, 0), so there is no endemic equilibrium to check for unstable conditions if $\mathscr{R}_0 > 1$.

Positivity and Boundedness:

In this segment, we illustrate the positivity and boundedness [XXI] for the solution of system (6).

Theorem 2. Let $0 < \xi < 1, c > 0$.

If the initial value satisfies $c_0 \geq 0$, then the solution S(t) remains nonnegative $\forall\, t \geq 0$. Moreover, if $c_0 > 0$, then S(t) > 0 for every $t > 0$

${}_{0}^{CF}D_t^{\xi} S(t) = -cS(t)$ satisfies $S(t) \geq 0$

Proof. Consider the fractional differential equation

$$ {}_{0}^{CF}D_t^{\xi} S(t) = -cS(t), \qquad S(0) = c_0, $$

Where ${}_{0}^{CF}D_t^{\xi}$ denotes the Caputo-Fabrizio fractional derivative.

By the definition (5),

$$ \left({}_{0}^{CF}D_t^{\xi} S \right)(t) = \frac{1}{1-\xi} \int_0^t S'(y) exp\left[-\xi \frac{(t-y)}{1-\xi} \right] dy $$

Using the inverse property of the associated convolution operator, the differential equation can be written equivalently as

$$ S(t) = c_0 - c \int_0^t \frac{1}{1-\xi} exp\left[-\xi \frac{(t-y)}{1-\xi} \right] S(y) dy $$

Define the kernel,

$$ K(t-y) = \frac{1}{1-\xi} exp\left[-\xi \frac{(t-y)}{1-\xi} \right] $$

For $0 < \xi < 1$, we clearly have

$K(t-y) > 0$ for all $0 \leq y \leq t$,

Assume $c_0 \geq 0$,

Suppose, contrary to the claim, that the solution becomes negative at some time.

Let $t^* > 0$ be the first instant such that $S(t^*) = 0$ and $S(t) \geq 0$ for $0 \leq t \leq t^*$.

Evaluating the integral equation at t^*,

$$ S(t^*) = c_0 - c \int_0^t K(t^* - y) S(y) dy \tag{10} $$

Implies that $c_0 \geq 0$, $K(t^* - y) > 0, S(y) \geq 0$ for $y \leq t^*$, the integral term is nonnegative.

Hence, $S(t^*) \geq c_0 - c$ (nonnegative quantity).

But since t^* is the first zero crossing, the integral cannot exceed c_0/c. Thus, the right hand side cannot be negative.

This contradicts the assumption that the solution becomes negative.

Therefore, $S(t) \geq 0$ for all $t \geq 0$

If $c_0 > 0$, the integral term is strictly positive for $t > 0$, so $S(t) > 0$ for all $t > 0$. The solution preserves positivity.

Theorem 3. Let $0 < \xi < 1$, $c > 0$ and consider ${}_{0}^{CF}D_t^{\xi} S = -cS$; $S(0) = c_0$, from (6) where ${}_{0}^{CF}D_t^{\xi}$ denotes the Caputo-Fabrizio fractional derivative. Then the solution S(t) is uniformly bounded on $[0, \infty)$.

Moreover, $|S(t)| \leq |c_0| \exp(C_\xi)$, $\forall\, t \geq 0$, for some constant $C_\xi > 0$.

Proof. Using the CF fractional integral operator, the equation is equivalent to

$$S(t) = S(0) - cI_t^{CF,\xi}\, S(t).$$

Taking absolute values,

$$|S(t)| \leq |c_0| + c\left|I_t^{CF,\xi}\, S(t)\right|$$

From the definition of the CF integral,

$$\left|I_t^{CF,\xi}\, S(t)\right| \leq \frac{1-\xi}{W(\xi)} \int_0^t e^{-\alpha(t-s)}\, |S(t)|\, ds,$$

Where $\alpha = \frac{\xi}{1-\xi}$.

Hence,

$$|S(t)| \leq |c_0| + C_\xi \int_0^t e^{-\alpha(t-s)}\, |S(t)|\, ds$$

Where $C_\xi = \frac{c\,(1-\xi)}{W(\xi)}$

Now applying the Fractional Gronwall inequality,

Let $x(t) = |S(t)|$

Then

$$x(t) \leq |c_0| + C_\xi \int_0^t e^{-\alpha(t-s)}\, x(s)\, ds$$

Thus,

$$x(t) \leq |c_0| \exp\left(\int_0^t C_\xi\, e^{-\alpha s}\, ds\right)$$

But

$$\int_0^t C_\xi\, e^{-\alpha s}\, ds = \frac{C_\xi}{\alpha}\,(1 - e^{-\alpha s}) \leq \frac{C_\xi}{\alpha}$$

Therefore,

$$|S(t)| \leq |c_0| \exp\left(\frac{C_\xi}{\alpha}\right), \qquad \forall\, t \geq 0. \tag{11}$$

Since the right-hand side is a finite constant independent of t,

$$|S(t)| \leq C \quad \forall\, t \geq 0.$$

Hence the solution of the CF fractional differential equation is globally bounded.

Similarly, boundedness can be proved for the other two equations of (6).

VI. Existence of a solution for the combined model of drug administration in the human body on the blood flow level FODEs mathematical model

In this part, the fixed point theorem is applied to the solution that exists for the Fractional Ordinary Differential Equation model. Using the Caputo-Fabrizio fractional integral operator in equation (6) we compute,

$$\begin{aligned} S(t) - S(0) &= {}^{CF}_{0}D^{\xi}_{t}\{-cS\}; \\ X(t) - X(0) &= {}^{CF}_{0}D^{\xi}_{t}\{cS + mU - eX - rX\}; \\ U(t) - U(0) &= {}^{CF}_{0}D^{\xi}_{t}\{rX - mU\} \end{aligned} \tag{12}$$

The definition of CF integral [IV, V] is formulated as

$${}^{CF}_{0}D^{\xi}_{t}(G(t)) = \frac{2(1-\xi)}{(2-\xi)W(\xi)}G(t) + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t G(t)\,dy$$

We make use of this definition on equation (12) by choosing the kernels K_i, for i = 1, 2, 3. Then we will get

$$S(t) - S(0) = \frac{2(1-\xi)}{(2-\xi)W(\xi)}[K_1(t,S)] + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t K_1(y,S)\,dy\,;$$

$$X(t) - X(0) = \frac{2(1-\xi)}{(2-\xi)W(\xi)}[K_2(t,X)] + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t K_2(y,X)\,dy\,;$$

$$U(t) - U(0) = \frac{2(1-\xi)}{(2-\xi)W(\xi)}[K_3(t,U)] + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t K_3(y,U)\,dy \tag{13}$$

Now we will assume that the non-negative bounded functions are S, X and U such that

$\|S(t)\| \leq \mu_1$, $\|X(t)\| \leq \mu_2$ and $\|U(t)\| \leq \mu_3$ where μ_1, μ_2 and μ_3 represent the positive constants. At this time to prove the existence and uniqueness theorems. First theorem we aim to establish that the kernels fulfil the Lipschitz and contraction mapping.

Theorem 1. The kernels satisfy the Lipschitz conditions and contraction mapping,

$0 \leq M$ = maximum value of $\{\zeta_1, \zeta_2, \zeta_3\} < 1$ if the following inequality holds.

Proof. We consider the first kernel K_1. Assume that any two functions S and S_1. Upon plugging those into the first kernel K_1 and taking the norm, we get

$$\|K_1(t,S)-K_1(t,S_1)\| = \left\|\lambda_1\big(S(t)-S_1(t)\big)+\lambda_2 X+\lambda_3 U+\lambda_4\right\|$$

Next, we make use of the triangular inequality,

$$\|K_1(t,S)-K_1(t,S_1)\| \le \left\|\lambda_1\big(S(t)-S_1(t)\big)\right\| + \|\lambda_2 X\| + \|\lambda_3 U\| + \|\lambda_4\|$$
$$\|K_1(t,S)-K_1(t,S_1)\| \le \lambda_1\left\|\big(S(t)-S_1(t)\big)\right\| + \lambda_2\mu_2 + \lambda_3\mu_3 + \lambda_4$$
$$\|K_1(t,S)-K_1(t,S_1)\| \le \lambda_1\left\|\big(S(t)-S_1(t)\big)\right\|$$

Now $\lambda_1 = \zeta_1$ in which $0 \le \zeta_1 < 1$ follows the Lipschitz conditions and contraction mapping for the kernel K_1. Following the same approach, we can also justify the other two kernels. The equation under consideration is (13) and locating the S(0), X (0) and U(0) on the equation's right-side yields

$$S(t) = S(0) + \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_1(t,S)\} + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_1(y,S)\}dy\,;$$

$$X(t) = X(0) + \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_2(t,X)\} + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_2(y,X)\}dy\,;$$

$$U(t) = U(0) + \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_3(t,U)\} + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_3(y,U)\}dy \quad (14)$$

Utilizing this equation (14) it is possible to apply the recursive formula to the n^{th} term and considering the initial values $S(0) = S_0(t)$, $X(0) = X_0(t)$ and $U(0) = U_0(t)$ we get

$$S_n(t) = \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_1(t,S_{n-1})\} + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_1(y,S_{n-1})\}dy\,;$$

$$X_n(t) = \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_2(t,X_{n-1})\} + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_2(y,X_{n-1})\}dy\,;$$

$$U_n(t) = \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_3(t,U_{n-1})\} + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_3(y,U_{n-1})\}dy \quad (15)$$

The successive term difference for the above system is

$$\vartheta_n(t) = \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_1(t,S_{n-1}) - K_1(t,S_{n-2})\} + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_1(y,S_{n-1}) - K_1(y,S_{n-2})\}dy\,;$$

$$\Omega_n(t) = \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_2(t,X_{n-1}) - K_2(t,X_{n-2})\} + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_2(y,X_{n-1}) - K_2(y,X_{n-2})\}dy\,;$$

$$\tau_n(t) = \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_3(t,U_{n-1}) - K_3(t,U_{n-2})\} + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_3(y,U_{n-1}) - K_3(y,U_{n-2})\}dy \quad (16)$$

Now the summation of all the differences is expressed in the form

$$S_n(t) = \sum_{i=1}^{n} \vartheta_i(t);$$
$$X_n(t) = \sum_{i=1}^{n} \Omega_i(t);$$
$$U_n(t) = \sum_{i=1}^{n} \tau_i(t) \quad (17)$$

Now the norm $\|\vartheta_n(t)\| = \|S_n(t) - S_{n-1}(t)\|$

From equation (16)

$$\|\vartheta_n(t)\| = \left\| \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_1(t,S_{n-1}) - K_1(t,S_{n-2})\} + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_1(y,S_{n-1}) - K_1(y,S_{n-2})\}dy \right\| \quad (18)$$

Now using the above two equations we can get

$$\|S_n(t) - S_{n-1}(t)\| = \left\| \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_1(t,S_{n-1}) - K_1(t,S_{n-2})\} + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_1(y,S_{n-1}) - K_1(y,S_{n-2})\}dy \right\| \quad (19)$$

Now Appling triangular inequality

$$\|S_n(t) - S_{n-1}(t)\| \leq \left\| \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_1(t,S_{n-1}) - K_1(t,S_{n-2})\} \right\| + \left\| \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_1(y,S_{n-1}) - K_1(y,S_{n-2})\}dy \right\| \quad (20)$$

$$\|S_n(t) - S_{n-1}(t)\| \leq \frac{2(1-\xi)}{(2-\xi)W(\xi)}\|\{K_1(t, S_{n-1}) - K_1(t, S_{n-2})\}\| + \frac{2\xi}{(2-\xi)W(\xi)}\|\{K_1(y, S_{n-1}) - K_1(y, S_{n-2})\}\|\, dy \qquad (21)$$

Knowing the kernel K_1 satisfy the Lipschitz conditions and contraction for ζ_1 we get

$$\|S_n(t) - S_{n-1}(t)\| \leq \frac{2(1-\xi)}{(2-\xi)W(\xi)}\zeta_1\|\{S(t) - S_{n-2}(t)\}\| + \frac{2\xi}{(2-\xi)W(\xi)}\zeta_1\int_0^t \|\{S_{n-1}(y) - S_{n-2}(y)\}\|\, dy \qquad (22)$$

Thus, we obtain

$$\|\vartheta_n(t)\| \leq \frac{2(1-\xi)}{(2-\xi)W(\xi)}\zeta_1\|\{\vartheta_{n-1}(t)\}\| + \frac{2\xi}{(2-\xi)W(\xi)}\zeta_1\int_0^t \|\{\vartheta_{n-1}(y)\}\|\, dy \qquad (23)$$

Similarly, the other parts can be proved. This result will now be used in the next theorem.

Theorem 2. If for $t_0 > 0$ and the inequalities below holds

$$\frac{2(1-\xi)}{(2-\xi)W(\xi)}\zeta_1 + \frac{2\xi}{(2-\xi)W(\xi)}\zeta_1,\ t_0 < 1$$

then a solution exists.

Proof: Taking into account the bounded functions serve as S, X, and U and the Lipschitz conditions satisfies the kernel which demonstrates the existence and smoothness of the function. We shall prove the convergence for completing the proof of $S_n(t)$, $X_n(t)$, $U_n(t)$ where it gives the outcome of the Caputo – Fabrizio model. Suppose $R_n(t)$, $N_n(t)$, $M_n(t)$ as $S(t) - S(0) = S_n(t) - R_n(t)$ similarly for other too.

$$\|R_n(t)\| = \left\| \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_1(t, S) - K_1(t, S_{n-1})\} + \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_1(y, S) - K_1(y, S_{n-1})\}dy \right\| \qquad (24)$$

Using the triangular inequality, we derive

$$\|R_n(t)\| \leq \left\| \frac{2(1-\xi)}{(2-\xi)W(\xi)}\{K_1(t, S) - K_1(t, S_{n-1})\} \right\| + \left\| \frac{2\xi}{(2-\xi)W(\xi)}\int_0^t \{K_1(y, S) - K_1(y, S_{n-1})\}dy \right\| \qquad (25)$$

The process is repetitively applied then we get

$$\|\mathrm{R_n(t)}\| \leq \left[\frac{2(1-\xi)}{(2-\xi)W(\xi)}\zeta_1 + \frac{2\xi}{(2-\xi)W(\xi)}\zeta_1 t\right]^{n+1} \tag{26}$$

At $\mathrm{t} = \mathrm{t_0}$

$$\|R_n(t)\| \leq \left[\frac{2(1-\xi)}{(2-\xi)W(\xi)}\zeta_1 + \frac{2\xi}{(2-\xi)W(\xi)}\zeta_1 t_0\right]^{n+1} \tag{27}$$

Applying the limits as $n \to \infty$, we get,

$$\|\mathrm{R_n(t)}\| \to 0 \tag{28}$$

In a similar manner, the rest of the model equations X and U can be derived.

Theorem 3. The Caputo-Fractional Model has a unique solution if

$$\left[1 - \left(\frac{2(1-\xi)}{(2-\xi)W(\xi)}\zeta_1 + \frac{2\xi}{(2-\xi)W(\xi)}\zeta_1 t\right)\right] > 0$$

Proof : Let $\mathrm{S_1(t)}$ be another solution of the CF model, then

$$\|S(t) - S_1(t)\| \left[1 - \left(\frac{2(1-\xi)}{(2-\xi)W(\xi)}\zeta_1 + \frac{2\xi}{(2-\xi)W(\xi)}\zeta_1 t\right)\right] \leq 0 \tag{29}$$

Hence,

$$\mathrm{S(t)} = \mathrm{S_1(t)}$$

Similarly,

$$\mathrm{X(t)} = \mathrm{X_1(t)}$$

$$\mathrm{U(t)} = \mathrm{U_1(t)}$$

VII. Caputo Fractional Model and Solutions

Considering the first Caputo derivative of (6) and solving

$${}^{\mathrm{CF}}_{0}\mathrm{D}^{\xi}_{t}\mathrm{S(t)} = -\mathrm{cS(t)} \quad ; \quad \mathrm{S(0)} = c_0 \tag{30}$$

where S(t) is a predefined function.

By making use of a CF derivative,

$$\frac{N(\xi)}{(1-\xi)}\int_0^t \frac{dS}{dv}(v)exp\left[\frac{-\xi(t-v)}{1-\xi}\right]dv = -cS(t) \tag{31}$$

Using the Laplace transform on both sides and solving we find,

$$\tilde{S}(s)\left[\frac{N(\xi)}{1-\xi}\,\frac{s}{s+\frac{\xi}{1-\xi}} + c\right] = \frac{N(\xi)}{1-\xi}\,\frac{S(0)}{s+\frac{\xi}{1-\xi}} \tag{32}$$

On rearranging we obtain,

$$\tilde{S}(s) = \frac{N(\xi)}{1-\xi}\left(\frac{S(0)}{s\left[\frac{N(\xi)}{1-\xi}+c\right]-\frac{c\xi}{1-\xi}}\right) \tag{33}$$

By performing the inverse Laplace transform, we obtain

$$S(t) = L\left[\tilde{S}(s)\right] = \frac{N(\xi)}{1-\xi}\ \frac{S(0)}{\frac{N(\xi)}{1-\xi}+c}\ L\left[\frac{1}{s+\frac{c\xi}{N(\xi)+c-c\xi}}\right]$$

$$S(t) = \left(\frac{N(\xi)}{N(\xi)+c-c\xi}\right) S(0)L\left[\frac{1}{s+\frac{c\xi}{N(\xi)+c-c\xi}}\right] \tag{34}$$

$$S(t) = \left(\frac{c_0 N(\xi)}{N(\xi)+c-c\xi}\right) exp\left[\frac{-c\xi t}{N(\xi)+c-c\xi}\right] \tag{35}$$

Considering the second Caputo derivative of (6) and solving

$${}_{0}^{CF}D_{t}^{\xi}X(t) = cS(t) + mU(t) - eX(t) - rX(t)\ ; \quad X(0) = 0 \tag{36}$$

where B(t), U(t) are predefined function.

By making use of a CF derivative,

$$\frac{N(\xi)}{1-\xi}\int_0^t \frac{dX}{dv}(v)\, exp\left[\frac{-\xi(t-v)}{1-\xi}\right] dv = cS(t) + mU(t) - eX(t) - rX(t) \tag{37}$$

Using the Laplace transform on both sides and solving we find,

$$\tilde{X}(s)\left[\frac{N(\xi)}{(1-\xi)}\ \frac{s}{s+\frac{\xi}{1-\xi}} + e + r\right] = \frac{N(\xi)}{(1-\xi)}\ \frac{X(0)}{s+\frac{\xi}{1-\xi}}\ \left[c\tilde{S}(s) + m\tilde{U}(s)\right] \tag{38}$$

On rearranging we obtain,

$$\tilde{X}(s) = \left[c\tilde{S}(s) + m\tilde{U}(s)\right]\left[\frac{s+\frac{\xi}{1-\xi}}{s\left[\frac{N(\xi)}{1-\xi}+e+r\right]-\frac{\xi}{1-\xi}}\right] \tag{39}$$

The computed inverse Laplace transform is

$$X(t) = L[\tilde{X}(s)] = \frac{c}{\frac{N(\xi)}{1-\xi} + e + r}\left[\frac{s\tilde{S}(s)}{s + \frac{\frac{\xi}{1-\xi}}{\frac{N(\xi)}{1-\xi} + e + r}}\right] + \left[\frac{\tilde{S}(s)\frac{\xi}{1-\xi}}{s + \frac{\frac{\xi}{1-\xi}}{\frac{N(\xi)}{1-\xi} + e + r}}\right]$$

$$+ \frac{m}{\frac{N(\xi)}{1-\xi} + e + r}\left[\frac{s\tilde{U}(s)}{s + \frac{\frac{\xi}{1-\xi}}{\frac{N(\xi)}{1-\xi} + e + r}}\right] + \left[\frac{\tilde{U}(s)\frac{\xi}{1-\xi}}{s + \frac{\frac{\xi}{1-\xi}}{\frac{N(\xi)}{1-\xi} + e + r}}\right]$$

$$X(t) = \frac{c(1-\xi)}{N(\xi) + e + r - \xi(e+r)}\left[\tilde{S}(s) + \frac{\tilde{S}(s)\left(\frac{\xi}{1-\xi} - \frac{1}{N(\xi) + e + r - \xi(e+r)}\right)}{s + \frac{1}{N(\xi) + e + r - \xi(e+r)}}\right]$$

$$\left[s + \frac{\xi}{N(\xi) + e + r - \xi(e+r)}\right]\left[\frac{\xi}{1-\xi} - \frac{1}{N(\xi) + e + r - \xi(e+r)}\right]$$

$$+\frac{m(1-\xi)}{N(\xi) + e + r - \xi(e+r)}\left[\tilde{U}(s) + \frac{\tilde{U}(s)\left(\frac{\xi}{1-\xi} - \frac{1}{N(\xi) + e + r - \xi(e+r)}\right)}{s + \frac{1}{N(\xi) + e + r - \xi(e+r)}}\right]$$

$$\left[s + \frac{\xi}{N(\xi) + e + r - \xi(e+r)}\right]\left[\frac{\xi}{1-\xi} - \frac{1}{N(\xi) + e + r - \xi(e+r)}\right]$$

$$X(t) = \left[\frac{c(1-\xi)}{N(\xi) + e + r - \xi(e+r)}\right] S(t) + \left[\frac{c(1-\xi)}{N(\xi) + e + r - \xi(e+r)}\right]$$

$$\left[\frac{\xi}{1-\xi} - \frac{1}{N(\xi) + e + r - \xi(e+r)}\right]\int_0^t S(v)\, exp\left[\frac{\xi(t-v)}{N(\xi) + e + r - \xi(e+r)}\right] dv$$

$$+\left[\frac{m(1-\xi)}{N(\xi) + e + r - \xi(e+r)}\right] U(t) + \left[\frac{m(1-\xi)}{N(\xi) + e + r - \xi(e+r)}\right]$$

$$\left[\frac{\xi}{1-\xi} - \frac{1}{N(\xi) + e + r - \xi(e+r)}\right]\int_0^t U(v)\, exp\left[\frac{\xi(t-v)}{N(\xi) + e + r - \xi(e+r)}\right] dv \quad (40)$$

Considering the third Caputo derivative of (6) and solving

$$ {}_{0}^{CF}D_t^{\xi}U(t) = rX(t) - mU(t) \quad ; \quad U(0) = 0 \qquad (41)$$

where B(t) is a predetermined function.

Computing the derivative of a CF,

$$\frac{N(\xi)}{(1-\xi)}\int_0^t \frac{dU}{dv}(v) exp\left[\frac{-\xi(t-v)}{1-\xi}\right] dv = rX(t) - mU(t) \qquad (42)$$

By performing the Laplace transform on both sides and solving, we find

$$\tilde{U}(s)\left[\frac{N(\xi)}{1-\xi}\,\frac{s}{s+\frac{\xi}{1-\xi}}+m\right]=\frac{N(\xi)}{1-\xi}\,\frac{U(0)}{s+\frac{\xi}{1-\xi}}+r\,\tilde{\mathrm{X}}(\mathrm{s}) \tag{43}$$

On rearranging we obtain,

$$\tilde{U}(s)=\left[\frac{r\,\tilde{\mathrm{X}}(\mathrm{s})\left(s+\frac{\xi}{1-\xi}\right)}{s\left[\frac{N(\xi)}{1-\xi}+m\right]-\frac{\xi}{1-\xi}}\right] \tag{44}$$

The computed inverse Laplace transform is

$$U(t)=L\left[\tilde{U}(s)\right]=\frac{r}{\frac{N(\xi)}{1-\xi}+m}\left[\frac{s\tilde{\mathrm{X}}(\mathrm{s})}{s+\frac{\frac{\xi}{1-\xi}}{\frac{N(\xi)}{1-\xi}+m}}+\frac{\tilde{\mathrm{X}}(\mathrm{s})\frac{\xi}{1-\xi}}{s+\frac{\frac{\xi}{1-\xi}}{\frac{N(\xi)}{1-\xi}+m}}\right]$$

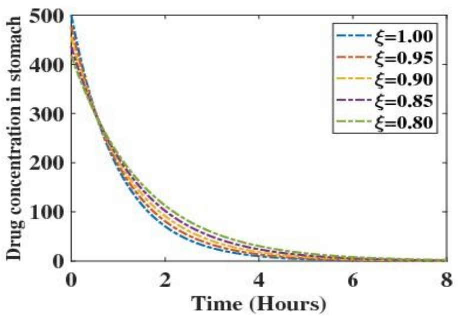
$$U(t)=\frac{r}{\frac{N(\xi)}{1-\xi}+m}\left[\frac{\tilde{\mathrm{X}}(\mathrm{s})\left(\frac{\xi}{1-\xi}-\frac{1}{N(\xi)+m-m\xi}\right)}{s+\frac{1}{N(\xi)+m-m\xi}}\right]$$

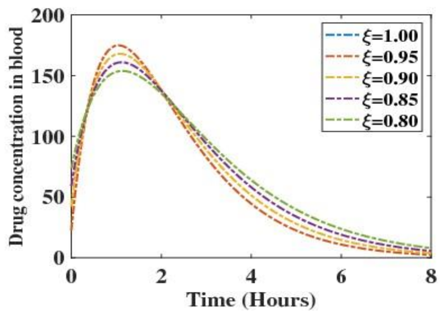
$$\left[s+\frac{\xi}{N(\xi)+m-m\xi}\right]\;\left[\frac{\xi}{1-\xi}-\frac{1}{N(\xi)+m-m\xi}\right]$$

$$U(t)=\left[\frac{r(1-\xi)}{N(\xi)+m-m\xi}\right]X(t)+\left[\frac{r(1-\xi)}{N(\xi)+m-m\xi}\right]$$

$$\left[\frac{\xi}{1-\xi}-\frac{1}{N(\xi)+m-m\xi}\right]\int_0^t X(\upsilon)exp\left[\frac{\xi(t-v)}{N(\xi)+m-m\xi}\right]dv \tag{45}$$

VIII. Graphical Discussion





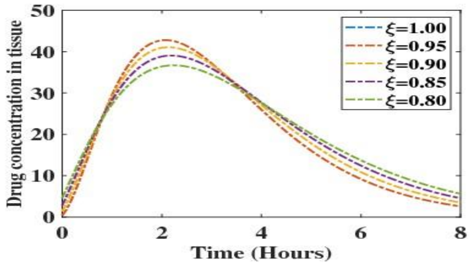


Fig.1. Drug delivery pattern in the stomach, blood and tissue taking initial dosage as 500 units for fractional level $\xi = 1$, $\xi = 0.95$, $\xi = 0.90$, $\xi = 0.85$ and $\xi = 0.80$.

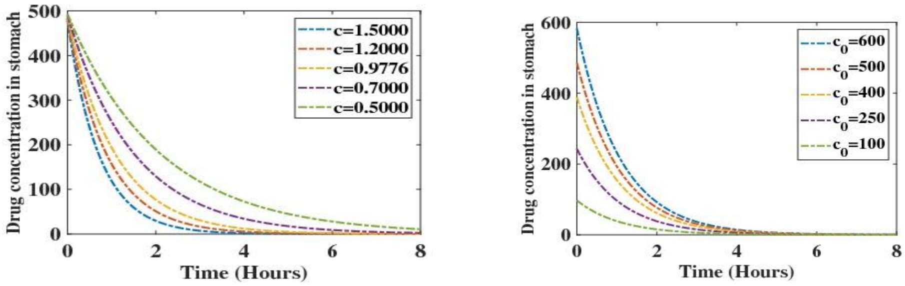
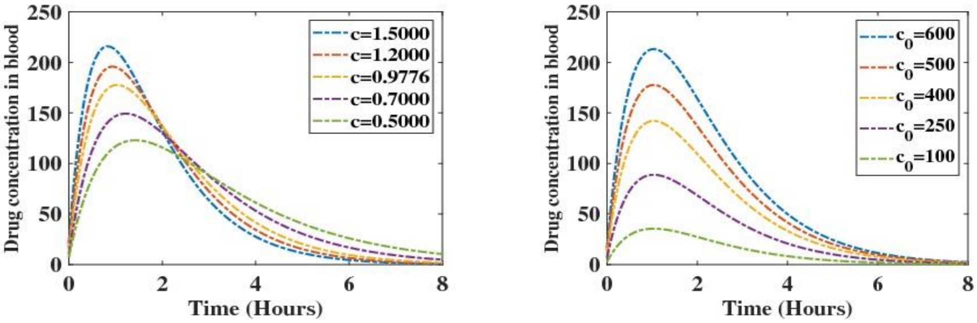


Fig.2. It shows the drug distribution of stomach with different c and c_0 values.



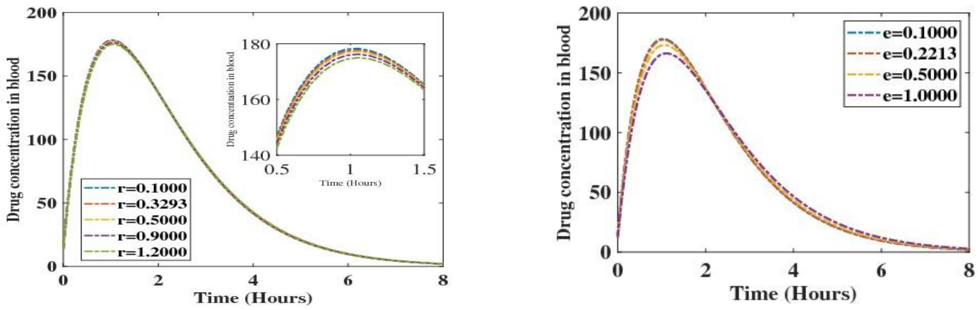


Fig.3. It shows the drug distribution of blood with different c, c_0, r and e values.

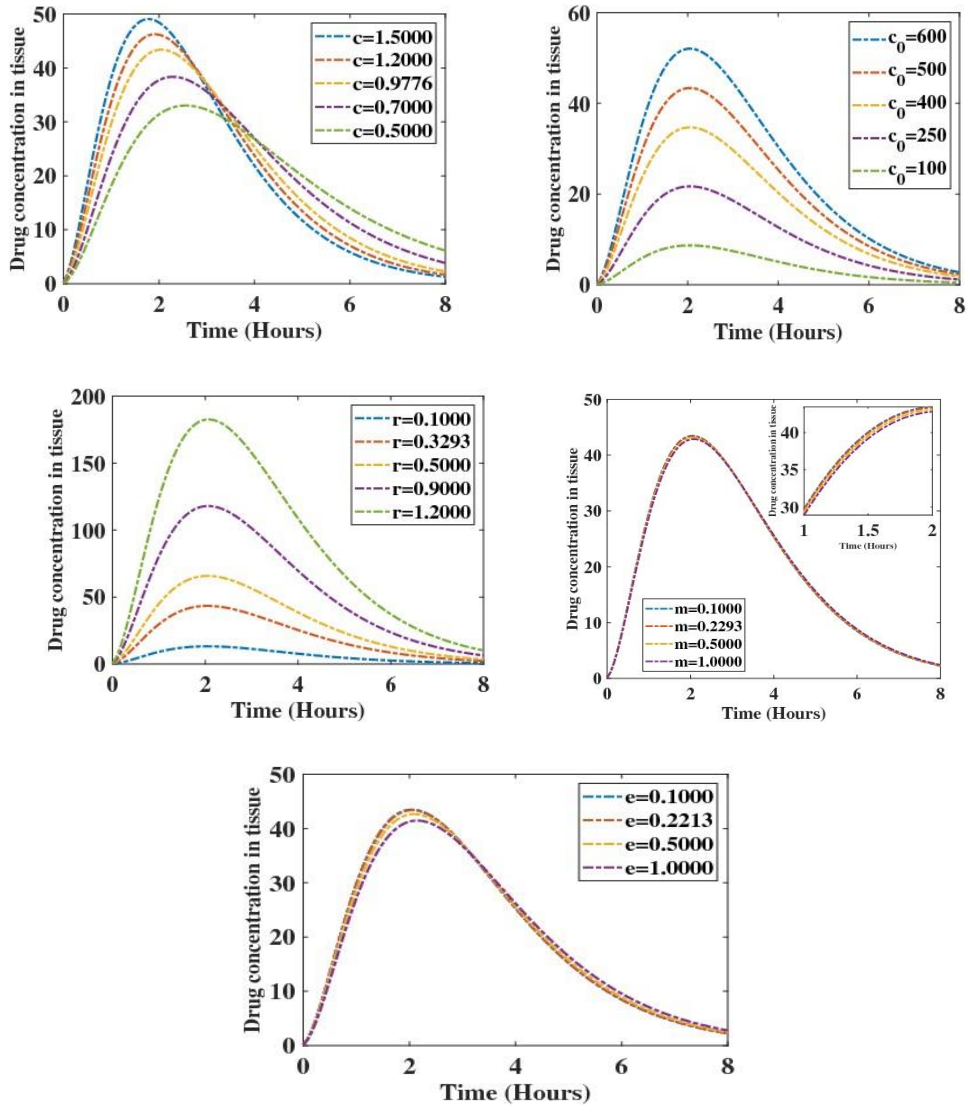


Fig.4. It shows the drug distribution in blood and tissue with different c, c_0, r, m and e values

This section extends the graphical discussion concerning the Caputo-Fabrizio fractional derivative models that have been addressed utilize the Laplace transformation approach, and the corresponding graphs were mapped using MATLAB software.

Fig.1 shows the fractional order behaviour $\xi=1$, $\xi=0.95$, $\xi=0.90$, $\xi=0.85$ and $\xi=0.80$ with an initial dosage in the stomach, blood and tissue of 500 units. On comparing all the figures, we observe that the dosage concentration decreases in the stomach gradually and enters the bloodstream where it initially increases and then decreases. Also, a residual amount of the drug remains in the body when the rate constants are poor which may lead to complications.

Fig.2(a) demonstrates the rate of drug delivery in the stomach. The elimination rate is higher at $c = 1.5$ compared to $c = 0.5$, revealing that the drug disintegrates more quickly in the stomach when the elimination rate is elevated. As c increases, the drug concentration in the stomach also increases. Fig.2(b) reflects the variation in drug concentration.

Fig.3(a) shows the elimination rate of the drug dissolution pattern in the blood. Here, the drug dissolves faster at $c = 1.5$ compared to $c = 0.5$. In Fig.3(b) the drug concentration with an initial dose of $c_0 = 600$ shows a higher entering rate compared to $c_0 = 100$. Fig.3(c) demonstrates that the drug dissolves more slowly when $r = 0.1$ compared to $r = 1.2$ due to its entry into the tissue compartment. Fig.3(d) demonstrates that the drug eliminates slower when $e = 0.1$ compared to $e = 1$ from the body.

Similarly, Fig.4(a) shows the drug concentration rate c as the drug enters from the blood to the tissue compartment. The rate of the drug delivery from the tissue compartment to other parts of the body is higher at $c = 1.5$ than at $c = 0.5$. Fig.4(b) demonstrates the entering rate of drug from the tissue with an initial dosage of $c_0 = 600$ units which decreases after two hours. Fig.4(c) demonstrates that the drug dissolves more slowly when $r = 0.1$ compared to $r = 1.2$ due to its entry into the tissue compartment. Fig.4(d) demonstrates the entering rate of the drug from the tissue again to the blood which decreases after two hours. Fig.4(e) demonstrates that the drug is eliminated more slowly when $e = 0.1$ compared to $e = 1$ from the body. After absorption, the pharmaceutical compound shifts from the circulation to the tissue and returns to the vein, yielding optimal results. The effects of vascular flow are crucial in this study.

IX. Comparison with the integer-order model:

Compared to the integer-order model of [XIV], the CF fractional model generates a similar descriptive compartmental transfer of the drug dosage combining the Gastrointestinal tract and the Bloodstream Models but with extended relaxation for $\xi < 1$. In the practical way, the fractional model forecast prolonged residence and enhanced residual concentration under equivalent rate constants, pointing out the significance of memory effects if therapeutic observed level distributions reveal long tails. We propose that forthcoming work employ these models to match investigational pharmacokinetic records, as a result determining the most effective ξ value and analyzing the medical contribution of the history-dependent effect.

X. Conclusion

The mathematical modeling of the drug distribution is crucial in the biomedical and pharmaceutical sciences, particularly in optimizing therapeutic efficacy and safety. This study presents a unified framework to analyse drug dispersion following oral and intravenous administration by employing the Caputo–Fabrizio fractional derivative, which features a non-singular kernel. Unlike classical fractional approaches, this derivative offers enhanced modeling flexibility and aligns better with physiological processes.

The well-posedness of the model is established through a rigorous analysis based on the fixed-point theorem, ensuring both the existence and uniqueness of the solution. Analytical solutions are obtained using the Laplace transform method, and the dynamics of the drug concentration across compartments are examined graphically for varying fractional orders.

The model captures the drug's passage into the bloodstream and subsequent absorption in tissues, revealing key insights into pharmacokinetics influenced by administration route. The graphical analysis demonstrates how different fractional orders impact drug retention and release profiles. These findings may aid in tailoring dosage regimens based on individual patient characteristics such as age, weight, blood pressure, metabolic rate, and gastrointestinal function.

This modeling approach opens new avenues in personalized medicine by enabling more accurate predictions of the drug behaviour within the body. It also lays the groundwork for extending such models to account for other delivery mechanisms and physiological parameters, potentially leading to reduced healthcare costs and improved patient outcomes in clinical pharmacology. Future research may compare this fractional framework to traditional integer-order models to evaluate their respective performance in diverse therapeutic scenarios.

Conflict of Interest:

There was no relevant conflict of interest regarding this paper.

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