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Analysis of Non-commensurate Model of Diclofenac Concentration in the Plasma to Enhance Drug Delivery System

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ABSTRACT

The present study explores multi-compartment FDE models with modified conditions for pharmacokinetics of anomalous drug diffusion in Caputo derivative sense. The Adomian decomposition method is implemented for analysis of non-commensurate model to depict the concentration of a single dose of enteric coated drug, in particular, Diclofenac in the blood plasma in two-compartment. Non-linear regression is used for parameter estimation. In the present text, authors validated the model showcasing the best-fit for the experimental in-vivo data from the existing literature to ensure eradication of toxicity and ineffective treatment risk. Statistical analysis is performed using Mathematica to understand significance of each estimated parameter in the regression model. Stability analysis in graphical sense is examined for decision making. The authors have justified existence and uniqueness by Picard-Lindelöf theorem.

1. INTRODUCTION

Leibniz and L'Hôspital introduced the notion of differentiation for non-integer orders in 1695. Ionescu et al. [1] found that fractional differential equation (FDE) is used for diffusion-related processes. Mainly in the compartmental study of drug diffusion, the transition rate is considered to be proportional to the contents of that compartment [2]. Instead, these conversion rates are expected to be proportional to complex functions of insertions of the compartment and time [3]. Dokoumetzidis and Macheras [4] introduced fractional calculus through one-compartment pharmacokinetics and drug dissolution applications. For the diffusion process which demonstrates characteristics of the memory effect, fractional calculus is recommended as an expedient tool for multi-compartmental modelling [5]. Researchers [6-10] analyzed two and three-compartment models with different analytic and numerical methods.

Some researchers [11-14] described the theorems based on stability, existence, and uniqueness of the solutions for commensurate and non-commensurate linear and non-linear FDE. The techniques used in the literature to solve FDE are ADM [15, 16], fractional differential transform method [17], power series method [18], variational iteration method and fractional difference method [19]. Also, some analytic methods like transforms of Laplace, Fourier, and Mellin as well as fractional Green's function have been explored for linear FDE [20]. ADM has been applied to several types of systems of differential equations in studies [21-29] successfully. The convergence of the solutions for FDE system is presented by Hosseini and Nasabzadeh [30]. The approach of ADM is an analytical continuous approximation that converges extremely quickly [31] and displays the dependencies, providing a glimpse into the nature and behavior of the solution similar to a closed-form solution. This computational technique produces analytical results and does not require linearization if the problem turns non-linear. Moreover, as discretization is not used, there are no rounding-off errors, and it does not need a lot of computer power or memory [29].

In the current study, authors have implemented two and three-compartmental models for the drug diffusion process. A two-compartmental model is explored further with the experimentation data of Diclofenac concentration in the bloodstream. The authors have analyzed the analytic solution obtained from ADM and further demonstrated efficacy and accuracy of the model through statistical and sensitivity analysis.

2. PRELIMINARY RESULTS

Podlubny [20] defined Caputo's fractional derivative as:

$$ {}_a^C D_t^\alpha \phi(t) = \frac{1}{\Gamma(\alpha - n)} \int_a^t \frac{\phi^{(n)}(\xi)}{(t-\xi)^{\alpha-n+1}} d\xi \quad (1) $$

for $n-1 < \alpha < n$, where α is an order of the fractional derivative, $n \in \mathbb{N}$ and α is the lower limit of t.

Linearity property of Caputo derivative [20] is given as:

$$ {}_a^C D_t^\alpha (p\phi(t) + q\varphi(t)) = p\,{}_a^C D_t^\alpha (\phi(t)) + q\,{}_a^C D_t^\alpha (\varphi(t)) \quad (2) $$

where, p and q are arbitrary constants, $\phi(t)$ and $\varphi(t)$ are continuous functions.

Riemann-Liouville left-sided fractional integral of order $\alpha > 0$ of a function $\phi(t)$ is given from [30] as:

$$I^{\alpha}\phi(t) = \frac{1}{\Gamma(\alpha)}\int_0^t \frac{\phi(\xi)}{(t-\xi)^{1-\alpha}}d\xi; \alpha > 0, t > 0. \tag{3}$$

$$I^{0}\phi(t) = \phi(t); \alpha = 0 \tag{4}$$

Also from literature [20, 30], we get:

$$I^{\alpha}t^{v} = \frac{\Gamma(v+1)}{\Gamma(v+\alpha+1)}t^{v+\alpha}; \alpha > 0, v > -1, t > 0 \tag{5}$$

Podlubny [20] presented that Mittag-Leffler function for one parameter is defined by:

$$E_{\alpha}(z) = \sum_{k=0}^{\infty}\frac{z^{k}}{\Gamma(\alpha k+1)}; \alpha > 0. \tag{6}$$

Mittag-Leffler function for two parameters is specified as:

$$E_{\alpha,\beta}(z) = \sum_{k=0}^{\infty}\frac{z^{k}}{\Gamma(\alpha k+\beta)}; \alpha, \beta > 0. \tag{7}$$

Assuming the whole-body immitates as uniform compartment, the point of application of the drug is considered as the central compartment as shown in Figure 1. In single-compartment model, the fractional view of first order clearance process after intravenous bolus injection described by Dokoumetzidis and Macheras [4], drug concentration y_1 of drug at time t is given by the relation:

$$D^{\alpha}y_1(t) = -k_{d1}y_1(t) \tag{8}$$

where, k_{d1} is a constant of rate elimination from first compartment with unit as $(h)^{-\alpha}$.

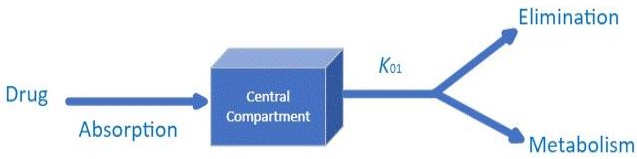


Figure 1. One-compartmental model

In Figure 2, a two-compartment biological system is deliberated in subsequence to the application of paravascular drug. The second compartment is characterized by the kinetics of the drug having movement in the body with the uniformity of plasma. Drugs can have local effects in the stomach, but the majority of them are circulated throughout the body via the bloodstream [28]. Diclofenac, an oral medication, encounters a biological barrier in the stomach's acidic environment, denaturing or depurinating the molecules delivered and significantly reducing their efficacy [29]. Gastric enzymes like pepsin and gelatinase, in addition to stomach acid, can decompose biopharmaceuticals.

Popović et al. [5] presented a system of FDE that is used to describe two-compartments as:

$$D^{\alpha}y_1(t) = -k_{21}y_1(t) \tag{9}$$

$$D^{\beta}y_2(t) = k_{21}y_1(t) - k_{02}y_2(t) \tag{10}$$

with initial conditions given by:

$$y_1(0) = l, y_2(0) = 0 \tag{11}$$

where, y_1 and y_2 are the concentration of drug at time t in first and second compartments respectively. k_{21} is normalized rate of drug transfer from compartment 1 to 2 and k_{02} is the elimination rate of drug. Writing the system (9)-(10) using Caputo derivatives is preferred for set initial conditions related to the variable as in (11) are accepted by an qFDE with Caputo derivatives, unlike R-L derivatives, which requires initial conditions on the variable's derivative which is incompatible to the existing scenerio. Caputo derivative of a constant is always zero, whereas in R-L derivatives, ${}_0D_t^{\alpha}C = \frac{Ct^{-\alpha}}{\Gamma(1-\alpha)}$ is not zero [20].

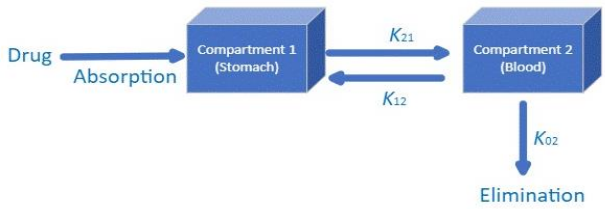


Figure 2. Bi-compartmental model

Hosseini and Nasabzadeh [30] have presented ADM on the FDE system in the form of:

$$\begin{gathered} D^{\alpha_j}y_j(t) = N_i(t, y_1, \cdots, y_n), \\ y_j^{(m)}(0) = c_m^j, \\ 0 \le m \le \lceil \alpha_j \rceil \end{gathered} \tag{12}$$

where, $1 \le j \le n, \alpha_j \in \mathbb{R}^+$

The solution for (12) is represented by the series:

$$y_j(t) = \sum_{k=0}^{\infty} y_{jk} \tag{13}$$

where, $y_{j0}(t) = \sum_{m=0}^{\lceil \alpha_j \rceil} c_m^j \frac{t^m}{m!}$ and $y_{j,k+1}(t) = I^{\alpha_j}[A_{jk}]$ for all values k=0,1,2,...

Also

$$\begin{gathered} A_{jk} = \left[\frac{1}{k!}\frac{d^k}{d\mu^k}N_j\left(t, \sum_{k=0}^{\infty}y_{1k}\mu^k, \ldots, \sum_{k=0}^{\infty}y_{nk}\mu^k\right)\right]_{\mu=0} \\ N_i(t, y_1, \cdots, y_n) = \sum_{k=0}^{\infty}A_{jk}. \end{gathered} \tag{14}$$

where, A_{jk} are Adomian polynomials.

In the study carried by Odibat [32] stated the theorem for stability of commensurate FDE concluding the components of the solution decay towards zero.

Theorem 1 The system $D^{\alpha}y = Ay$ is asymptotically stable if and only if $|arg(eig(A))| > \frac{\alpha\pi}{2}$, where $\boldsymbol{y} = (y_1, y_2, \cdots, y_n)$ [32].

It may be noted that the eigenvalues of the matrix defined by Eberly [33] proves physical stability of the linear system. Every solution of the system $D^{\alpha}y = Ay$ is stable asymptotically, if real part of all the eigenvalues of the given matrix are negative [34]. Thus for negative real part $|arg(eig(A))| > \frac{\pi}{2}$ and for 0<α<2,$|arg(eig(A))| > \frac{\alpha\pi}{2}$.

3. MAIN RESULTS OF FDE

This section focusses on drug level modelling. The observations from experimental data [5] indicate that the concentration in delayed release drugs occur after a certain delay. The ADM method elaborated by Jafari and Daftardar-Gejji [28] is re-structured by considering new set of initial conditions.

A non-linear FDE with initial condition is represented as:

$$D^{\alpha_j}y_j(t) = N_i(t, y_1, \cdots, y_n), y_j^{(m)}(b) = c_m^j, 0 \le m \le \lceil \alpha_j \rceil \quad (15)$$

where, $1 \le j \le n, \alpha_j \in \mathbb{R}^+$.

Applying I^{α_j} on (15), we obtain:

$$y_j(t) = \sum_{m=0}^{\lceil \alpha_j \rceil} c_m^j \frac{(t-b)^m}{m!} + I^{\alpha_j} N_j(t, y_1, y_2, \cdots, y_n) \quad (16)$$

for $j = 1,2,\cdots,n$.

Let $y_j(t)$, $N_j(t, y_1, y_2, \cdots, y_n)$ as described in (13) and (14). For determining A_{jk}, (14) can be written as:

$$N_j\left(t, \sum_{k=0}^{\infty} y_{1k}(\mu-b)^k, \sum_{k=0}^{\infty} y_{2k}(\mu-b)^k, \cdots, \sum_{k=0}^{\infty} y_{nk}(\mu-b)^k\right) = \sum_{k=0}^{\infty} A_{jk}(\mu-b)^k \quad (17)$$

where, μ is the parameter.

From (17), we obtain:

$$A_{jk} = \left[\frac{1}{k!}\frac{d^k}{d\mu^k} N_j\left(t, \sum_{k=0}^{\infty} y_{1k}(\mu-b)^k, \ldots, \sum_{k=0}^{\infty} y_{nk}(\mu-b)^k\right)\right]_{\mu=b} \quad (18)$$

and representing:

$$y_{j0}(t) = \sum_{m=0}^{\lceil \alpha_j \rceil} c_m^j \frac{(t-b)^m}{m!} \quad (19)$$

$$y_{j,k+1}(t) = I^{\alpha_j}\left[\frac{1}{k!}\frac{d^k}{d\mu^k} N_j\left(t, \sum_{k=0}^{\infty} y_{1k}(\mu-b)^k, \ldots, \sum_{k=0}^{\infty} y_{nk}(\mu-b)^k\right)\right]_{\mu=b} \quad (20)$$

Thus, the solution of (15) system turns out to be a series as shown in (13).

Once drug is injected, (8) describes drug disposition in the body, distribution throughout the compartment (body) and elimination either by kidney or metabolism in liver.

After certain time lag (t_l), drug concentration increases as indicated in (21), as the process of absorption does not start right away in all the subjects. The FDE single-compartment model (8) with modified initial condition (21) is solved using ADM:

$$y_1(t_l) = l \quad (21)$$

To solve (8) and (21) using ADM, consider:

$$y_1 = \sum_{i=0}^{\infty} c_i, N_1 = -k_{d1} y_1 = \sum_{i=0}^{\infty} A_i \quad (22)$$

Adomian polynomials, using (18) are calculated as follows:

$$A_i = -k_{d1}\, c_i. \quad (23)$$

According to Eqs. (19) and (20),

$$c_0 = l \text{ and } c_{i+1} = I^{\alpha} A_i \quad (24)$$

Evaluating (24), we get:

$$c_{i+1} = (-k_{d1})^{(i+1)} \frac{l(t-t_l)^{(i+1)\alpha}}{\Gamma[1+(i+1)\alpha]}. \quad (25)$$

Considering the values of Eq. (25), we obtain the solution of Caputo FDE as:

$$y_1 = \sum_{i=0}^{\infty} (-k_{d1})^i \frac{l(t-t_l)^{i\alpha}}{\Gamma[1+i\alpha]} \quad (26)$$

The relation (26) can be represented as:

$$y_1 = lE_{\alpha}\left(-k_{d1}(t-t_l)^{\alpha}\right) \quad (27)$$

drug concentration in the human body at t.

A study on two-compartmental model is further analysed based on analytic way using ADM and used to assess the pharmacokinetics of Diclofenac in a small sample of healthy persons participating in a bioequivalence trial. The enteric coated delayed release drug, Diclofenac delays the release of the drug's active ingredients after administration. This mathematical representation with parts of human body, signified by compartments give an insight into pharmacological kinetic properties. Drug applied in first compartment (y_1), passing through interconnected organs and tissues in series of compartmental arrangement. The region in the body, where the drug kinetics is uniform like plasma, is regarded as the second compartment (y_2). Both the compartments can be expressed by the system of FDE (9)-(10) with initial conditions (28). The dose given to all subjects is same but the volume of compartment differs in every subject thus the initial concentration 'l' is treated as the parameter. Experimental data shows that the absorption/release of the

drug starts not immediately but after certain delay which is again not common in all the subjects. Thus to maintain individuality the initial time is not considered as zero but a parameter t_l.

$$y_1(t_l) = l, y_2(t_l) = 0 \tag{28}$$

Let y_1 and N_1 be as considered in (22) with $d = 2$.

$$y_2 = \sum_{i=0}^{\infty} d_i,\ N_2 = k_{21}y_1 - k_{02}y_2 = \sum_{i=0}^{\infty} B_i \tag{29}$$

Adomian polynomials are calculated as (23) for y_1. For y_2 using (18) and initial conditions (28), it is as follows:

$$B_0 = k_{21}l;\ B_i = k_{21}c_i - k_{02}d_i,\quad i \in \mathbb{N}. \tag{30}$$

Solution for y_1 is given as (27) with $d = 2$. According to (19) and (20),

$$d_0 = 0;\ d_{i+1} = I^{\beta}B_i,\quad i \in \{0\} \cup \mathbb{N}. \tag{31}$$

d_i's are evaluated as:

$$d_1 = I^{\beta}B_0 = k_{21}\frac{l(t-t_l)^{\beta}}{\Gamma(1+\beta)} \tag{32}$$

$$d_2 = I^{\beta}B_1 = -k_{21}^2\frac{l(t-t_l)^{\alpha+\beta}}{\Gamma(1+\alpha+\beta)} - k_{21}k_{02}\frac{l(t-t_l)^{2\beta}}{\Gamma(1+2\beta)} \tag{33}$$

$$d_3 = I^{\beta}B_2 = k_{21}^3\frac{l(t-t_l)^{2\alpha+\beta}}{\Gamma(1+2\alpha+\beta)} + k_{21}^2k_{02}\frac{l(t-t_l)^{\alpha+2\beta}}{\Gamma(1+\alpha+2\beta)} + k_{21}k_{02}^2\frac{l(t-t_l)^{3\beta}}{\Gamma(1+3\beta)} \tag{34}$$

and so on till d_n.

Combining (32)-(34) in particular for $\alpha = \beta$, the solution is shown in (35),

$$y_2 = \frac{k_{21}l}{k_{21}-k_{02}}\left(-1 + \frac{k_{21}(t-t_l)^{\alpha}}{\Gamma(1+\alpha)} - \frac{k_{21}^2(t-t_l)^{2\alpha}}{\Gamma(1+2\alpha)} + \frac{k_{21}^3(t-t_l)^{3\alpha}}{\Gamma(1+3\alpha)} - \cdots + 1 - \frac{k_{02}(t-t_l)^{\alpha}}{\Gamma(1+\alpha)} + \frac{k_{02}^2(t-t_l)^{2\alpha}}{\Gamma(1+2\alpha)} - \frac{k_{02}^3(t-t_l)^{3\alpha}}{\Gamma(1+3\alpha)} + \cdots\right) \tag{35}$$

The closed form of the solution is obtained as

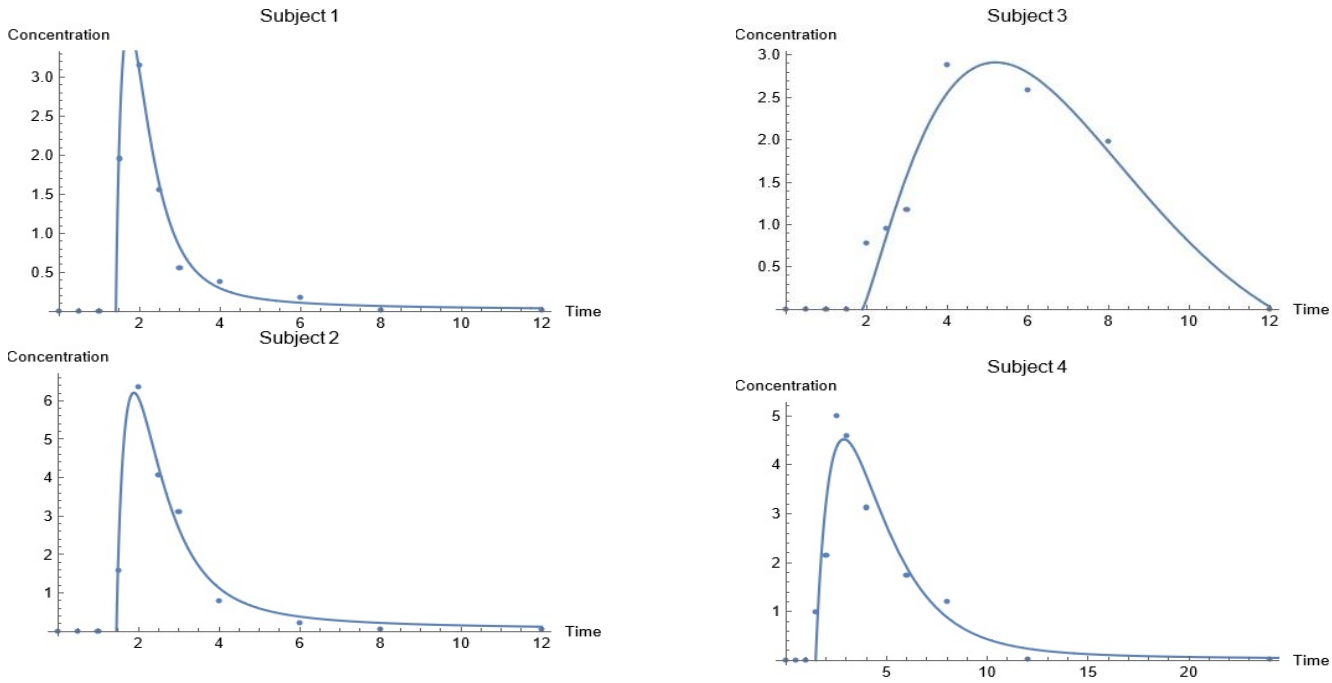
$$y_2 = \frac{k_{21}l}{k_{21}-k_{02}}[E_{\alpha}(-k_{02}(t-t_l)^{\alpha}) - E_{\alpha}(-k_{21}(t-t_l)^{\alpha})] \tag{36}$$

provides the instantaneous estimate of Diclofenac concentration in second compartment (y_2) through solution of the compartmental model. Solution of two-compartmental model (36) is investigated further for the parameters such as integer order of the differential, rate of transfer, rate of elimination and time delay using software Mathematica 13.0. The essential factors such as loading capacity and release rate can be analysed using Table 1 parameters.

In Figure 3, the smooth curve shows the Diclofenac concentration-time profile as a result of (36) and dots shows the experimental data points from Popović's research [5].

Table 1. Parameters estimation for (36)

Sub	α	k_{21}	k_{02}	l(mg/ltr)	t_l (h)	MSE
1	0.95 (0.0147)	2.83 (6.5115)	2.59 (5.905)	9.79 (0.302)	1.42 (0.00645)	0.11049
2	0.936 (0.0197)	2.14 (4.726)	1.88 (3.986)	17.15 (0.545)	1.46 (0.00659)	0.04823
3	1.17 (0.0497)	0.31 (1.79)	0.28 (1.635)	6.64 (0.536)	1.9 (0.134)	0.1649
4	0.97 (0.059)	0.779 (2.569)	0.63 (2.022)	11.04 (0.8288)	1.42 (0.06265)	0.29198
5	1 (0.0001)	0.36 (1.657)	0.325 (1.502)	7.48 (0.389)	2.17 (0.07198)	0.05823
6	0.95 (0.0438)	1.037 (1.188)	0.676 (0.726)	7.94 (0.409)	0.99 (0.033)	0.11
Mean±SD	0.996±0.088	1.24±1.02	1.06±0.948	10.0067±3.85	1.56±0.415	



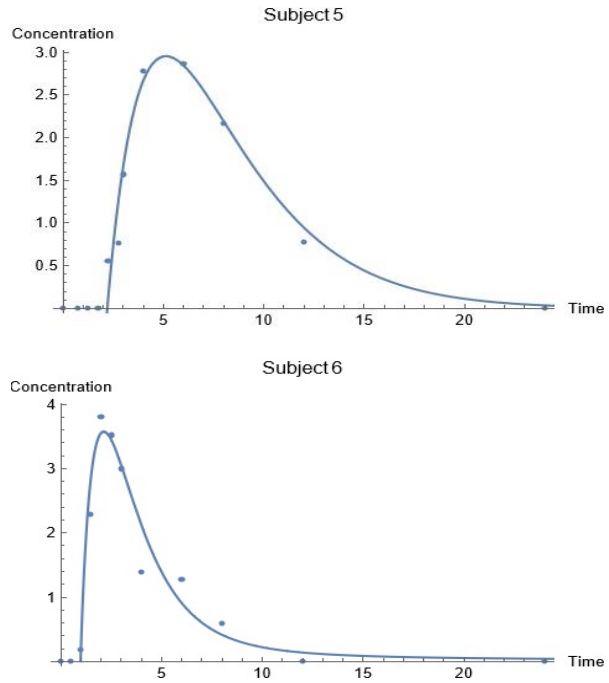


Figure 3. Plots of Diclofenac concentration verses time (hours) for subjects 1-6

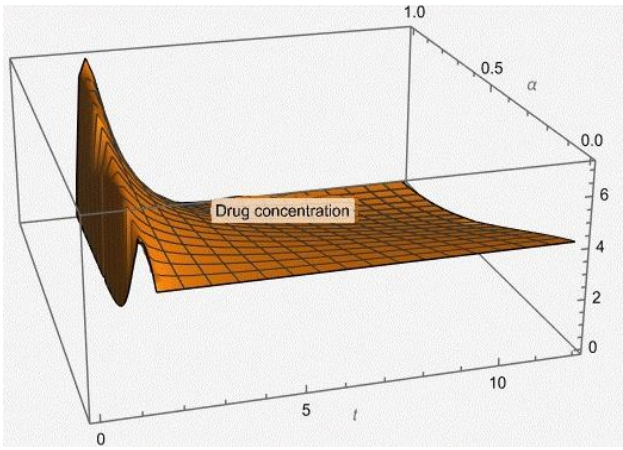


Figure 4. Concentration level over time for varying α-values

Assuming parameters estimated from the data-fit as constant, in Figure 4, it is observed that the drop in concentration increases gradually with the fractional order value approaching the first order, for varying values of α ranging from 0 to 1.

In three-compartment model, plasma (g_1) is considered to be first compartment, highly (g_2) and scarcely (g_3) perfused organs and tissues are considered to be the peripheral compartments.

$$\left.\begin{aligned} D^{\alpha} g_1 &= -k_{21} g_1 \\ D^{\beta} g_2 &= k_{21} g_1 - k_{32} g_2 \\ D^{\gamma} g_3 &= k_{32} g_2 - k_{03} g_3 \end{aligned}\right\} \tag{37}$$

with initial conditions

$$g_1(0) = l, \quad g_2(0) = 0, g_3(0) = 0 \tag{38}$$

Let g_1, g_2 be as considered in (22) and (29) respectively:

$g_3 = \sum_{i=0}^{\infty} e_i$,
$N_1 = -k_{21} g_1 = \sum_{i=0}^{\infty} A_i$, $N_2 = k_{21} g_1 - k_{32} g_2 = \sum_{i=0}^{\infty} B_i$,
$N_3 = k_{32} g_2 - k_{03} g_3 = \sum_{i=0}^{\infty} C_i$.

Adomian polynomials are calculated as (23) for y_1 and (30) for y_2. For y_3 using (18) and initial condition (38), it is as follows:

$$\left.\begin{aligned} C_0 &= 0. \\ C_i &= k_{32} d_i - k_{03} e_i, i \in \mathbb{N}. \end{aligned}\right\} \tag{39}$$

Solution for y_1 is given as (27) with $d = 2$ whereas solution for y_2 is given as (36) with change as $k_{02} = k_{32}$.

According to (19) and (20), $e_0 = 0$ and $e_{i+1} = I^{\gamma} C_i$, $i \in \{0\} \cup \mathbb{N}$. e_i's are evaluated as:

$$\begin{aligned} e_1 &= I^{\gamma} C_0 = 0; \\ e_2 &= I^{\gamma} C_1 = k_{21} k_{32} \frac{l t^{\beta+\gamma}}{\Gamma(1+\beta+\gamma)}. \\ e_3 &= I^{\gamma} C_2 = -k_{21}^2 k_{32} \frac{l t^{\alpha+\beta+\gamma}}{\Gamma(1+\alpha+\beta+\gamma)} \\ &\quad - k_{21} k_{32}^2 \frac{l t^{2\beta+\gamma}}{\Gamma(1+2\beta+\gamma)} \\ &\quad - k_{21} k_{32} k_{03} \frac{l t^{\beta+2\gamma}}{\Gamma(1+\beta+2\gamma)} \\ e_4 &= I^{\gamma} C_3 = k_{21}^3 k_{32} l \frac{t^{2\alpha+\beta+\gamma}}{\Gamma(1+2\alpha+\beta+\gamma)} \\ &\quad + k_{21}^2 k_{32}^2 l \frac{t^{\alpha+2\beta+\gamma}}{\Gamma(1+\alpha+2\beta+\gamma)} \\ &\quad + k_{21} k_{32}^3 l \frac{t^{3\beta+\gamma}}{\Gamma(1+3\beta+\gamma)} \\ &\quad + k_{21}^2 k_{32} k_{03} l \frac{t^{\alpha+\beta+2\gamma}}{\Gamma(1+\alpha+\beta+2\gamma)} \\ &\quad + k_{21} k_{32}^2 k_{03} l \frac{t^{2\beta+2\gamma}}{\Gamma(1+2\beta+2\gamma)} \\ &\quad + k_{21} k_{32} k_{03}^2 l \frac{t^{\beta+3\gamma}}{\Gamma(1+\beta+3\gamma)} \end{aligned}$$

and so on till e_n, which are combined to get the solution for $\alpha = \beta$,

$$g_3 = k_{21} k_{32} l \left(\begin{aligned} &\frac{t^{2\alpha}}{\Gamma(1+2\alpha)} - \frac{k_{21} t^{3\alpha}}{\Gamma(1+3\alpha)} - \frac{k_{32} t^{3\alpha}}{\Gamma(1+3\alpha)} - \frac{k_{03} t^{3\alpha}}{\Gamma(1+3\alpha)} \\ &+ \frac{k_{21}^2 t^{4\alpha}}{\Gamma(1+4\alpha)} + \frac{k_{21} k_{32} t^{4\alpha}}{\Gamma(1+4\alpha)} + \frac{k_{32}^2 t^{4\alpha}}{\Gamma(1+4\alpha)} + \frac{k_{21} k_{03} t^{4\alpha}}{\Gamma(1+4\alpha)} \\ &+ \frac{k_{32} k_{03} t^{4\alpha}}{\Gamma(1+4\alpha)} + \frac{k_{03}^2 t^{4\alpha}}{\Gamma(1+4\alpha)} + \cdots \end{aligned} \right) \tag{40}$$

The closed form of (40) can be written as:

$$g_3 = k_{21} k_{32} l \left(\begin{aligned} &\frac{1}{k_{32} - k_{21}} E_{\alpha}(-k_{21} t^{\alpha}) + \frac{1}{(k_{32} - k_{21})(k_{32} - k_{03})} E_{\alpha}(-k_{32} t^{\alpha}) \\ &+ \frac{1}{(k_{03} - k_{21})(k_{03} - k_{32})} E_{\alpha}(-k_{03} t^{\alpha}) \end{aligned} \right) \tag{41}$$

The drug concentration in the third compartment is given by (41).

Using ADM technique in this context, provides a convergent series solution to the FDE system (8), (9), (10) and (37) with the initial conditions (21), (28) and (38) respectively. The solution is a convergent series with readily quantifiable constituents, which is further written in the closed form (exact solution) analogous to (27), (36) and (41).

4. STATISTICAL ANALYSIS

In this section, regression analysis is performed using Mathematica to understand significance of each parameter in the regression model. Tables 2-7 suggest that the parameters α, l and $\boldsymbol{t}_l$ are significant predictors in the model, as they have high *t*-statistic and low *p*-value for all the six subjects. The lower values of MSE in Table 1, shows the approximations of predicted values to that of the actual values. It may be observed through the Tables 2-7, R^2 (R-squared) value tending to 1, displays higher percentage of the variance in the dependent variable which may be predictable from the independent variables considered in the model.

Further the model is validated through the *t*-test on the residuals considering null-hypothesis as the mean of the residuals which is zero. The mod of *t*-value is compared with the *t*-table for the value at 95% LOS and '*n* minus parameters' degree of freedom. Thus, the combination of these tests verifies the goodness-of-fit for the considered model with the experimental data.

Table 2. Regression analysis for Subject 1

Sub 1	*t*-Stats	*p*-Value	Confidence Interval	R^2	*t*-Test on Residual
α	64.7502	$5.50597*10^{-11}$	{0.91715, 0.98667}	0.991593	0.161552
k_{21}	0.434075	0.682326	{-13.9121, 19.5651}		
k_{02}	0.438997	0.678986	{-12.5883, 17.7734}		
l	32.42	$6.87249*10^{-9}$	{9.07788, 10.5063}		
t_l	221.01	$1.02493*10^{-14}$	{1.41089, 1.44141}		

Table 3. Regression analysis for Subject 2

Sub 2	*t*-Stats	*p*-Value	Confidence Interval	R^2	*t*-Test on Residual
α	47.4197	$4.8514*10^{-10}$	{0.889826, 0.983227}		
k_{21}	0.453952	0.668888	{-10.0041, 14.2952}		
k_{02}	0.471766	0.656963	{-8.36727, 12.1288}	0.989459	-0.542947
l	31.4566	$8.47752*10^{-9}$	{15.862, 18.4406}		
t_l	222.411	$9.80598*10^{-15}$	{1.45031, 1.48148}		

Table 4. Regression analysis for Subject 3

Sub 3	*t*-Stats	*p*-Value	Confidence Interval	R^2	*t*-Test on Residual
α	23.5564	$3.84049*10^{-7}$	{1.04918, 1.29242}		
k_{21}	0.176775	0.868275	{-1.9157, 2.5487}		
k_{02}	0.177034	0.868085	{-1.59249, 2.12138}	0.877688	0.318133
l	12.3879	0.000016888	{5.32904, 7.95246}		
t_l	13.4589	0.0000104252	{1.47856, 2.13565}		

Table 5. Regression analysis for Subject 4

Sub 4	*t*-Stats	*p*-Value	Confidence Interval	R^2	*t*-Test on Residual
α	16.3862	$1.93856*10^{-7}$	{0.835407, 1.10905}		
k_{21}	0.303402	0.771829	{-5.50843, 7.06781}		
k_{02}	0.313406	0.764581	{-4.31482, 5.58249}	0.902456	-0.257336
l	13.3227	$9.62803*10^{-7}$	{9.13112, 12.9538}		
t_l	22.7836	$1.45992*10^{-8}$	{1.28304, 1.57201}		

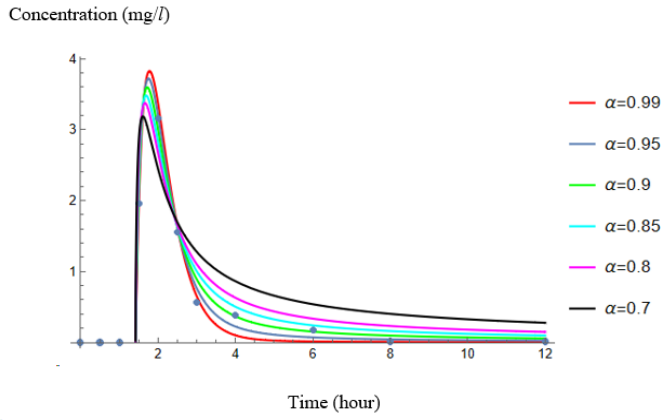
Table 6. Regression analysis for Subject 5

Sub 5	*t*-Stats	*p*-Value	Confidence Interval	R^2	*t*-Test on Residual
α	9.56027*10^8	$3.61813*10^{-61}$	{1., 1.}		
k_{21}	0.216063	0.837477	{-3.9026, 4.61884}		
k_{02}	0.215559	0.837849	{-3.53893, 4.18678}	0.944988	-0.242391
l	19.2113	$2.57919*10^{-7}$	{6.56332, 8.4058}		
t_l	30.2153	$1.12166*10^{-8}$	{2.00496, 2.34542}		

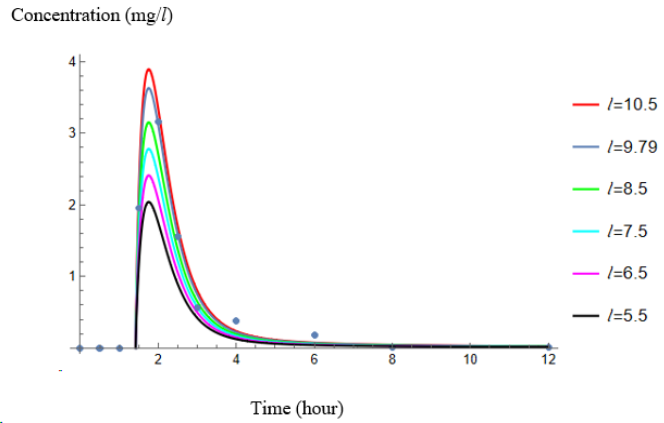
Table 7. Regression analysis for Subject 6

Sub 6	*t*-Stats	*p*-Value	Confidence Interval	R^2	*t*-Test on Residual
α	21.7497	$4.32822*10^{-9}$	{0.854387, 1.05275}		
k_{21}	0.87268	0.41177	{-1.77269, 3.84648}		
k_{02}	0.930133	0.383258	{-1.04251, 2.39444}	0.945409	0.0420123
l	19.3927	$1.19152*10^{-8}$	{7.01581, 8.86874}		
t_l	30.0038	$2.48087*10^{-10}$	{0.916361, 1.06581}		

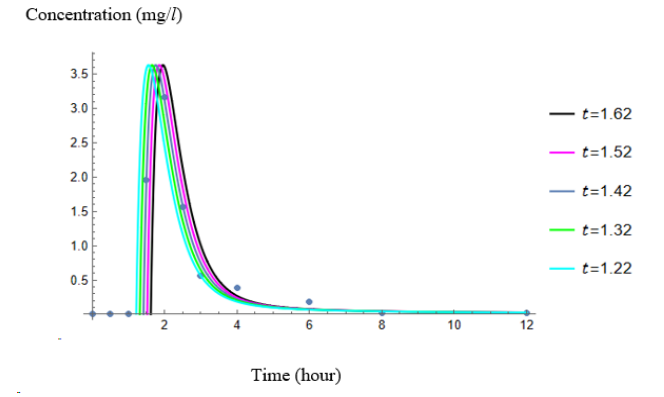
As the parameters α, l and t_l display to be significant predictors of the model, authors have included a sensitivity analysis on these parameters to understand their impact on the drug concentration profile.



(a)



(b)



(c)

Figure 5. The impact of α,l and t_l on the drug concentration for Subject 1

The concentration in the second compartment rises quickly for all values of α as observed in Figure 5 (a), but it falls down slowly as the α value decreases, while keeping all other parameters fixed. As initial amount of drug in the first compartment at time t_l decreases, the AUC of drug profile in the second compartment reduces. Understanding how drugs disseminate throughout the body and how dosage adjustments/ initial doses may influence the drug's concentration in various tissues over time are dependent as seen in Figure 5 (b). With the varying value of t_l, the AUC remains unchanged and only the time-concentration curve translates along the time-axis, Figure 5 (c). Similar analysis is illustrated for the remaining subjects as mentioned in the 'Annexure' at the concluding text. The present situation demonstrates the significance of comprehending the interactions between pharmacokinetic factors in order to preserve the intended level of drug exposure in the context of variations in individual parameters. Modifications in dosage may account for variations in distribution, clearance, or elimination to attain the expected therapeutic result.

The analysis on stability, existence and uniqueness is explored in the next sections.

5. STABILITY

In this study, a fractional differential system (9)-(10) and (28) for prediction of concentration of Diclofenac in body is investigated. To examine the sensitivity of FDE, stability analysis proves to be a useful tool in improving the performance prediction ensuring an appropriate application of model [35]. A stable model (36) of differential equation in physical problem, supports decision making in drug manufacturing. The methodology for assessment of stability for commensurate and non-commensurate FDE is discussed by Odibat [32]. Using values in Table 1 for subjects 1-6 with respective initial conditions, solution components of the system (9)-(10) and (28) with $\alpha = \beta$ for different subjects are analysed considering c_1 and c_2 as arbitrary constants and $\boldsymbol{y}(t) = (y_1(t), y_2(t))$.

Subject 1:

$$\boldsymbol{y}(t) = c_1 \begin{pmatrix} 0.0845023 \\ -0.996423 \end{pmatrix} E_\alpha(-2.83t^\alpha) + c_2 \begin{pmatrix} 0 \\ 1 \end{pmatrix} E_\alpha(-2.59t^\alpha) \quad \text{with } c_1 = 118.577, c_2 = 118.153 \tag{42}$$

Subject 2:

$$\boldsymbol{y}(t) = c_1 \begin{pmatrix} 0.120608 \\ -0.9927 \end{pmatrix} E_\alpha(-2.14t^\alpha) + c_2 \begin{pmatrix} 0 \\ 1 \end{pmatrix} E_\alpha(-1.88t^\alpha) \quad \text{with } c_1 = 139.866, c_2 = 138.845 \tag{43}$$

Subject 3:

$$\boldsymbol{y}(t) = c_1 \begin{pmatrix} 0.0963242 \\ -0.99535 \end{pmatrix} E_\alpha(-0.31t^\alpha) + c_2 \begin{pmatrix} 0 \\ 1 \end{pmatrix} E_\alpha(-0.28t^\alpha) \quad \text{with } c_1 = 77.0173, c_2 = 76.6592 \tag{44}$$

Subject 4:

$$\boldsymbol{y}(t) = c_1 \begin{pmatrix} 0.187865 \\ -0.982195 \end{pmatrix} E_\alpha(-0.779t^\alpha) + c_2 \begin{pmatrix} 0 \\ 1 \end{pmatrix} E_\alpha(-0.63t^\alpha) \quad \text{with } c_1 = 60.0697, c_2 = 59 \tag{45}$$

Subject 5:

$$\boldsymbol{y}(t) = c_1 \begin{pmatrix} 0.096766 \\ -0.995307 \end{pmatrix} E_\alpha(-0.36t^\alpha) + c_2 \begin{pmatrix} 0 \\ 1 \end{pmatrix} E_\alpha(-0.325t^\alpha) \quad \text{with } c_1 = 77.1655, c_2 = 76.8034 \tag{46}$$

Subject 6:

$$\boldsymbol{y}(t) = c_1 \begin{pmatrix} 0.328768 \\ -0.944411 \end{pmatrix} E_\alpha(-1.037t^\alpha) + c_2 \begin{pmatrix} 0 \\ 1 \end{pmatrix} E_\alpha(-0.676t^\alpha) \quad \text{with } c_1 = 24.1508, c_2 = 22.8083 \tag{47}$$

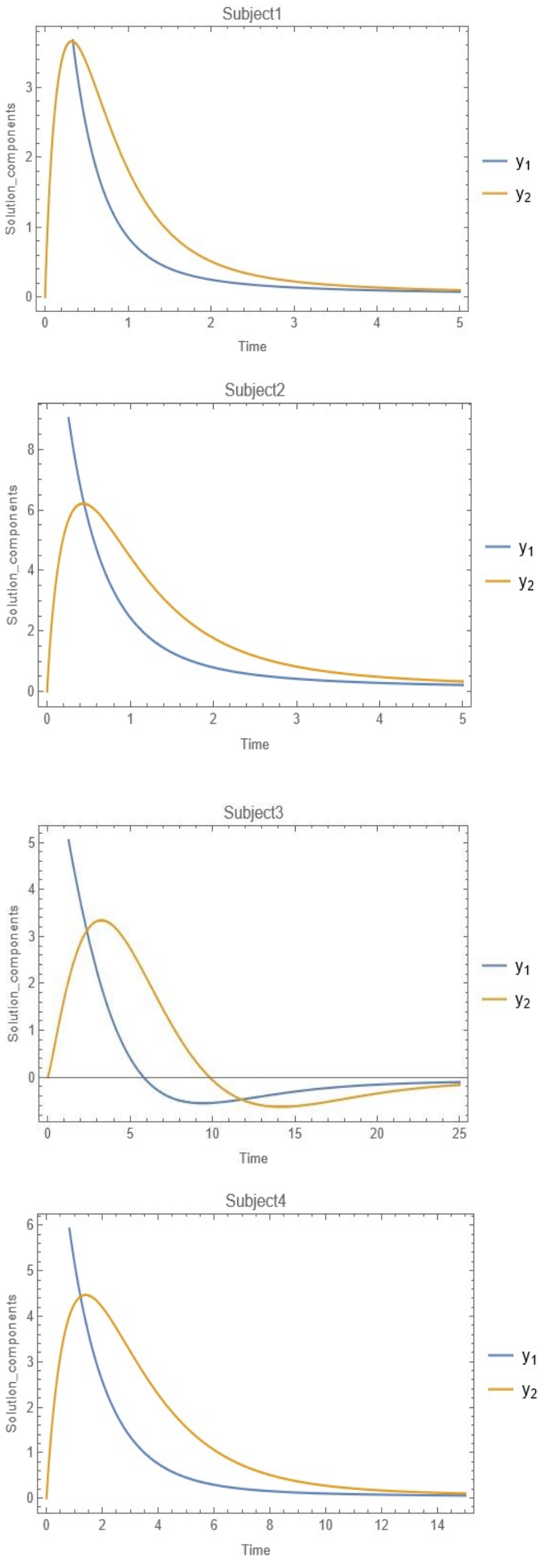


Figure 6. Component-wise solution verses time (hours) for Subjects 1-6

Values of c_1 and c_2 for (42)-(47) are evaluated and presented using Mathematica 13.0. For the initial value FDE (9)-(10) with initial conditions (28), Figure 6 shows the solution components $(y_1(t), y_2(t))$ approaches to zero as t increases. Moreover, the condition $|arg(eig(A))| > \frac{\alpha\pi}{2}$ satisfies for all the subjects. Thus, the system (9)-(10) with initial conditions (28) is stable. One observes that the material is transferred from one-compartment to another over a period of time, the model remains stable.

6. EXISTENCE AND UNIQUENESS

As seen in this study, two-compartmental FDE (9)-(10) with initial condition (28) have been solved using ADM and results for the stability are analysed. Further, the uniqueness and existence of the solution is explored using Picard-Lindelöf theorem [11, 36]. The model is said to be the best if it predicts a single solution providing useful inference [37]. Having a unique solution in the context of the current work is essential to eliminate the possibility of obtaining multiple drug concentration values for the same time t.

Theorem 2. Let $\phi(t, \boldsymbol{y}): V \to \mathbb{R}^2$ be bounded function, where,

$$V = \left[t_l, \tau^*\right] \times \left[y_1(t_l) - r_1, y_1(t_l) + r_1\right] \times \left[y_2(t_l) - r_2, y_2(t_l) + r_2\right],$$
$$\tau^* > t_l > 0, r_1, r_2 > 0.$$

If $\phi(t,\mathbf{y})$ satisfies Lipschitz condition with respect to $\mathbf{y} = (y_1, y_2)$ i.e.,

$$\|\phi(t,\mathbf{y}) - \phi(t,\mathbf{z})\| \le L\|\mathbf{y} - \mathbf{z}\| \tag{48}$$

for all $(t,\mathbf{y})$ and $(t,\mathbf{z})$ in V and for some $L \ge 0$ then the initial value problem $D^{\alpha}\mathbf{y} = \phi(t,\mathbf{y}), \mathbf{y}(t_l) = \mathbf{y}_0$, $0 < \alpha < 1$ has an unique solution $\mathbf{y}(t): [t_l, \tau] \to \mathbb{R}^2$ where $\tau - t_l = min\left[\tau^* - t_l, \left(\frac{r\Gamma(\alpha+1)}{\|\phi\|}\right)^{1/\alpha}\right]$, $r = min\{r_1, r_2\}$.

Proof. FDE given by systems (9)-(10) can be expressed for $\alpha = \beta$ as:

$$\begin{pmatrix} D^{\alpha} y_1 \\ D^{\alpha} y_2 \end{pmatrix} = \begin{pmatrix} -k_{21} & 0 \\ k_{21} & -k_{02} \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \end{pmatrix} \tag{49}$$

with initial conditions as (28).

$$D^{\alpha} y = Ay = \left(-k_{12}y_1 + 0y_2, k_{12}y_1 - k_{02}y_2\right) = \phi(t,\mathbf{y}). \tag{50}$$

Using the norm defined as $\|\phi\| = \sup|\phi_i|$, thus,

$$\|\mathbf{y} - \mathbf{z}\| = \sup\left\{|y_1 - z_1|, |y_2 - z_2|\right\} \tag{51}$$

We observe the value of L can be evaluated in two cases as follows:

Case 1: Suppose $\|\mathbf{y} - \mathbf{z}\| = |y_1 - z_1|$ from Eq. (51), we get:

$$\begin{aligned} &\|\boldsymbol{\phi}(t,\mathbf{y}) - \boldsymbol{\phi}(t,\mathbf{z})\| \\ &= \left\|-k_{21}(y_1 - z_1), k_{21}(y_1 - z_1) - k_{02}(y_2 - z_2)\right\| \\ &\le \sup\left\{|k_{21}||y_1 - z_1|, |k_{21}||y_1 - z_1| + |k_{02}||y_2 - z_2|\right\} \\ &= |k_{21}||y_1 - z_1| = L\|\mathbf{y} - \mathbf{z}\|; \end{aligned}$$

where, $L = |k_{21}|$.

One of the possibilities and the conclusion of case-1 may be:

$$\|\boldsymbol{\phi}(t,\mathbf{y}) - \boldsymbol{\phi}(t,\mathbf{z})\| = |k_{21}||y_1 - z_1| \tag{52}$$

The second possibility and the conclusion of case-1 may be:

$$\begin{aligned} \|\boldsymbol{\phi}(t,\mathbf{y}) - \boldsymbol{\phi}(t,\mathbf{z})\| &= |k_{21}||y_1 - z_1| + |k_{02}||y_2 - z_2| \\ &\le |k_{21}||y_1 - z_1| + |k_{02}||y_1 - z_1| \\ &= \left\{|k_{21}| + |k_{02}|\right\}|y_1 - z_1| = L\|\mathbf{y} - \mathbf{z}\| \end{aligned} \tag{53}$$

where, $L = |k_{21}| + |k_{02}|$.

Case 2: Suppose $\|\mathbf{y} - \mathbf{z}\| = |y_2 - z_2|$ from Eq. (51), we get:

$$\begin{aligned} &\|\boldsymbol{\phi}(t,\mathbf{y}) - \boldsymbol{\phi}(t,\mathbf{z})\| \\ &\le \sup\left\{|k_{21}||y_1 - z_1|, |k_{21}||y_1 - z_1| + |k_{02}||y_2 - z_2|\right\} \\ &= |k_{21}||y_1 - z_1| \le |k_{21}||y_2 - z_2| = L\|\mathbf{y} - \mathbf{z}\|; \end{aligned}$$

where $L = |k_{21}|$.

One of the possibilities and the conclusion of case-2 is observed in Eq. (52).

The second possibility and the conclusion of case-2 is obtained from (53).

$$\begin{aligned} &\|\boldsymbol{\phi}(t,\mathbf{y}) - \boldsymbol{\phi}(t,\mathbf{z})\| \\ &= |k_{21}||y_1 - z_1| + |k_{02}||y_2 - z_2| \\ &\le |k_{21}||y_2 - z_2| + |k_{02}||y_2 - z_2| \\ &= \left\{|k_{21}| + |k_{02}|\right\}|y_2 - z_2| = L\|\mathbf{y} - \mathbf{z}\|; \end{aligned}$$

where $L = |k_{21}| + |k_{02}|$.

Finally, we observe inequality (48) holds true for the mentioned L.

Hence the function $\phi(t,\mathbf{y})$ is Lipschitz continuous. As $\phi_i(t,\mathbf{y})$ is continuous where $i = 1,2$; for $\epsilon > 0, \exists\ \delta > 0$ such that:

$$|\phi_i(t,\mathbf{y}) - \phi_i(t,\mathbf{z})| < \frac{\epsilon\Gamma(\alpha+1)}{(\tau - t_l)^{\alpha}} \tag{54}$$

whenever $\|\mathbf{y} - \mathbf{z}\| < \delta$.

Picard-Lindelöf operator is defined as $F: Y \to Y$, where $Y = \{\mathbf{y}(t) = (y_1(t), y_2(t)), y_i \in C[t_l, \tau]: |y_i(t) - y_i(t_l)| \le r\}$, as presented by Sene and Abdelmalek [38].

Clearly, Y is non-empty closed subset of a Banach space $C([t_l, \tau] \times [t_l, \tau])$.

Denote

$$F(\mathbf{y}) = \left(F_1(\mathbf{y}), F_2(\mathbf{y})\right) \tag{55}$$

where,

$$F_i(\mathbf{y}(t)) = y_i(t_l) + \frac{1}{\Gamma(\alpha)}\int_{t_l}^{t} (t-a)^{(\alpha-1)}\,\phi_i(a, \mathbf{y}(a))da.$$

The following relation is obtained as:

$$\begin{aligned} &\|F\mathbf{y}(t) - \mathbf{y}(t_l)\| \\ &= \left\|\mathbf{y}(t_l) + \frac{1}{\Gamma(\alpha)}\int_{t_l}^{t}(t-a)^{(\alpha-1)}\phi(a,\mathbf{y}(a))da - \mathbf{y}(t_l)\right\| \\ &= \frac{1}{\Gamma(\alpha)}\sup\left|\int_{t_l}^{t}(t-a)^{(\alpha-1)}\phi_i(a,\mathbf{y}(a))da\right| \\ &\le \frac{1}{\Gamma(\alpha)}\int_{t_l}^{\tau}(\tau-a)^{(\alpha-1)}\sup|\phi_i(t,\mathbf{y}(t))|da \\ &\le \frac{\|\phi(t,\mathbf{y})\|}{\Gamma(\alpha+1)}(\tau - t_l)^{\alpha} = \frac{\|\phi(t,\mathbf{y})\|}{\Gamma(\alpha+1)}\frac{r\Gamma(\alpha+1)}{\|\phi(t,\mathbf{y})\|} = r. \end{aligned}$$

Hence

$$\|F\mathbf{y}(t) - \mathbf{y}(t_l)\| \le r \tag{56}$$

Thus inequality (56) concludes that Picard's operator maps Y into itself.

$$
\begin{aligned}
&\| F\mathbf{y}(t) - F\mathbf{z}(t)\| \\
&= \frac{1}{\Gamma(\alpha)} \left\| \int_{t_l}^{t} (t-a)^{(\alpha-1)} [\phi(a,\mathbf{y}(a)) - \phi(a,\mathbf{z}(a))] da \right\| \\
&= \sup \frac{1}{\Gamma(\alpha)} \left| \int_{t_l}^{t} (t-a)^{(\alpha-1)} \left[\phi_i(a,\mathbf{y}(a)) - \phi_i(a,\mathbf{z}(a)) \right] da \right| \\
&\le \frac{1}{\Gamma(\alpha)} \int_{t_l}^{\tau} (\tau-a)^{(\alpha-1)} \sup \left| \phi_i(t,\mathbf{y}(t)) - \phi_i(t,\mathbf{z}(t)) \right| da \\
&\le \frac{\epsilon \Gamma(\alpha+1)}{(\tau-t_l)^{\alpha}} \frac{1}{\Gamma(\alpha+1)} (\tau-t_l)^{\alpha} = \epsilon.
\end{aligned}
$$

Thus

$$
\| F\mathbf{y}(t) - F\mathbf{z}(t)\| \le \epsilon \tag{57}
$$

shows that the Picard's operator is continuous.

Further to prove that Picard's operator is Lipschitz continuous, the following relation is considered from inequality (57).

$$
\begin{aligned}
&\| F\mathbf{y}(t) - F\mathbf{z}(t)\| \\
&\le \frac{1}{\Gamma(\alpha)} \int_{t_l}^{\tau} (\tau-a)^{(\alpha-1)} \sup \left| \phi_i(t,\mathbf{y}(t)) - \phi_i(t,\mathbf{z}(t)) \right| da \\
&\le \frac{1}{\Gamma(\alpha)} \int_{t_1}^{\tau} (\tau-a)^{(\alpha-1)} \| \phi(t,\mathbf{y}) - \phi(t,\mathbf{z})\| \, da \\
&\le \frac{1}{\Gamma(\alpha+1)} (\tau-t_l)^{\alpha} \| \phi(t,\mathbf{y}) - \phi(t,\mathbf{z})\|
\end{aligned}
$$

Hence

$$
\begin{aligned}
&\| F\mathbf{y}(t) - F\mathbf{z}(t)\| \\
&\le \frac{1}{\Gamma(\alpha+1)} (\tau-t_l)^{\alpha} \| \phi(t,\mathbf{y}) - \phi(t,\mathbf{z})\|
\end{aligned} \tag{58}
$$

Thus inequality (58) shows that Picard's operator is Lipschitz continuous. By Banach fixed point theorem, the solution (36) of FDE (9)-(10) with initial conditions (28) exists and is unique.

7. DISCUSSION

In the present study authors have demonstrated analytic solution of drug diffusion non-commensurate model for Diclofenac (9)-(10) with initial conditions (28) using ADM. As claimed, the results of the current study incorporate all α, greater than, less than or equal to 1. The linear two-compartmental FDE results (estimated parameters) suits best (gives less Mean square error and high R^2 value) to the experimental dataset of Diclofenac.

The loss of standard error while estimating the five parameters was faced while using Mathematica 13.0 which has been overcome by fixing two parameters considering the least MSE, and the remaining parameters were estimated. While finding standard error for the fixed parameters, other estimated parameters were used in the same build-in symbol, keeping previously assigned fixed parameters unknowns.

Significant fluctuations in drug concentration can lead to harmful issues like toxicity or inefficient treatment. Control rate as in Table 1, enhances accurate dosing, adequacy and health stability while regulating desired drug concentration. The transition rates are complex functions of time and the contents of various compartment levels. Solutions (36) and (41) of compartment models (8), (9), (10) with initial conditions (28) and (37) are the combination of Mittag-Leffler functions of t whose special case is exponential function. The appropriate fits in pharmacokinetics can also be dealt with non-linear FDE. In further studies, non-linear compartmental FDE can be discussed to represent the ADME process.

8. CONCLUSIONS

Multi-compartmental fractional models for drug absorption and disposition in PK/PD are solved using ADM. Using analytic method ADM, a closed solution to non-commensurate FDE models are obtained in the study. Non-linear regression is used for parameter estimation. Stability, existence and uniqueness for two-compartment model is exploited in the present study. The regression model is further validated statistically so that the mathematical model for drug diffusion in this context, forms a tool to comprehend the elements of bio-transport processes. Also ADM demonstrates its effectiveness in solving FDE, both linear and non-linear, with reasonable computation and accuracy. In the concluding section, the authors illustration through analytic model is robust than the previous studies as mentioned by convolution form, assuring enhancement of drug delivery system.

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NOMENCLATURE

t	time in h
$\phi^{(n)}$	n^{th} order derivative of the function
$\mathbb{N}$	set of natural numbers
$E_\alpha(z)$	Mittag-Leffler function of z with order α
k_{ij}	transfer rate of drug from j^{th} compartment to j^{th} compartment
k_{0j}	elimination Rate of drug from j^{th} compartment
[]	greatest integer not greater than
!	factorial
$eig(A)$	eigenvalues of matrix A
$\boldsymbol{t_l}$	time lag
MSE	mean square error
$\mathbb{R}^2$	set of order pairs with real elements
$\|\|\ \|\|$	norm of the function in a normed space
Sup	supremum

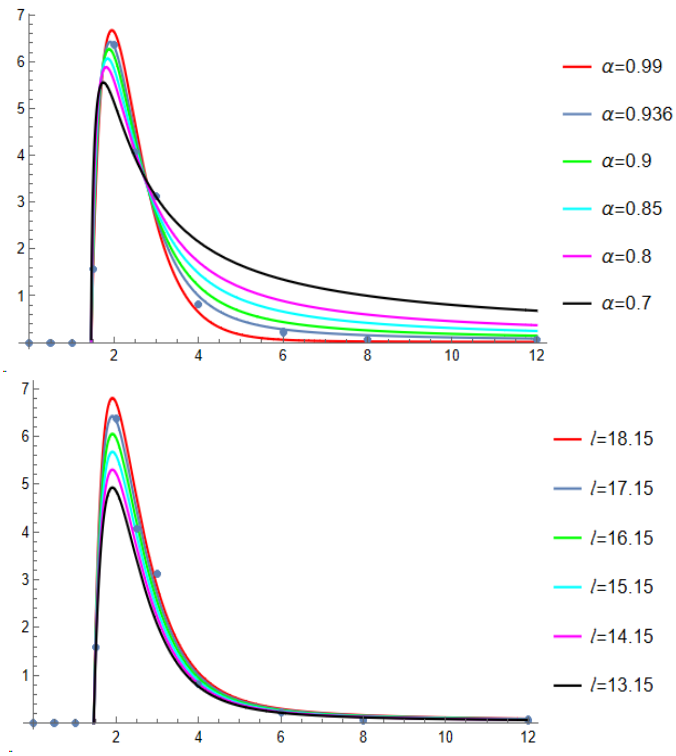
Greek symbols

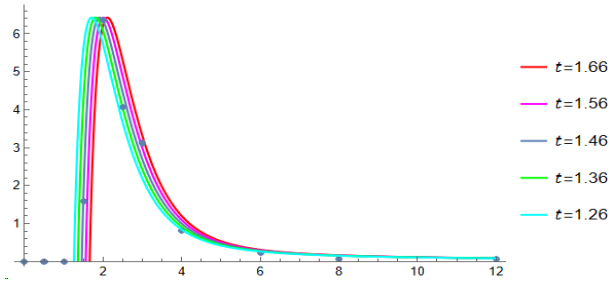
α, β	non-integer order
Γ	Gamma function
$\sum$	summation

APPENDIX

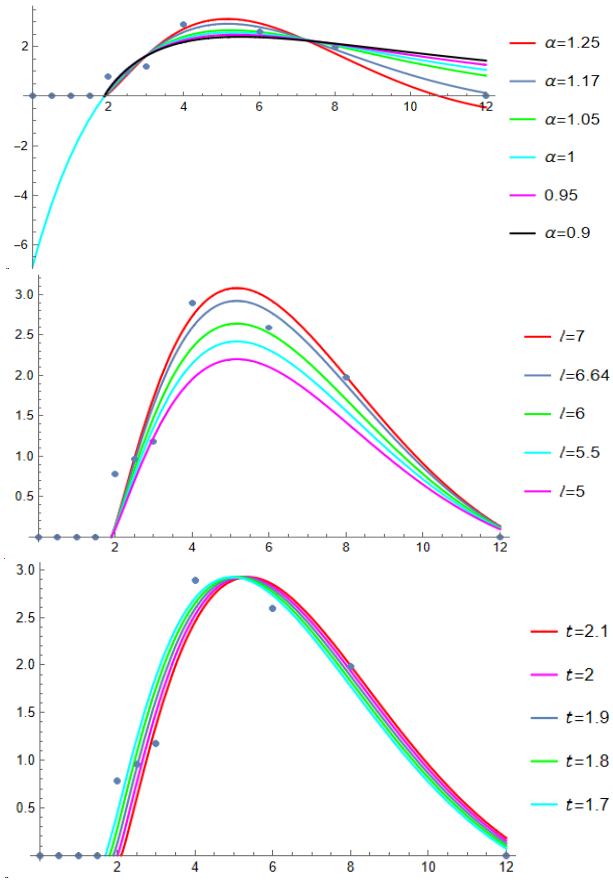
The continuation of statistical analysis of the subjects 2-6 with parameters α, l and t_l based on sensitivity analysis for the drug concentration profile is presented:

Subject 2





Subject 3



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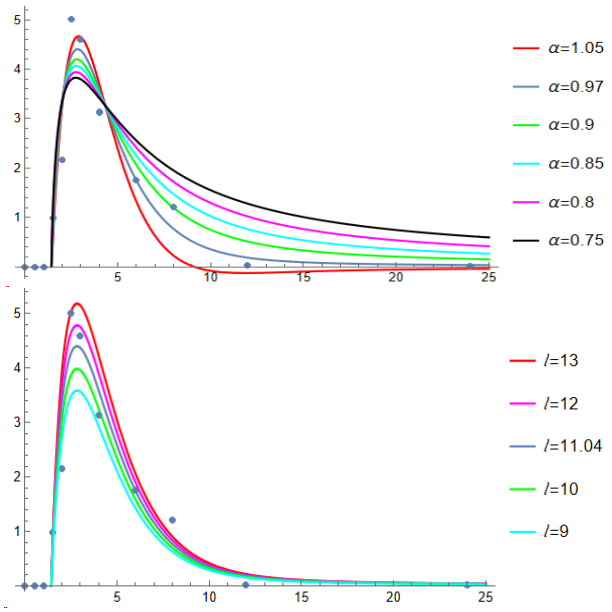
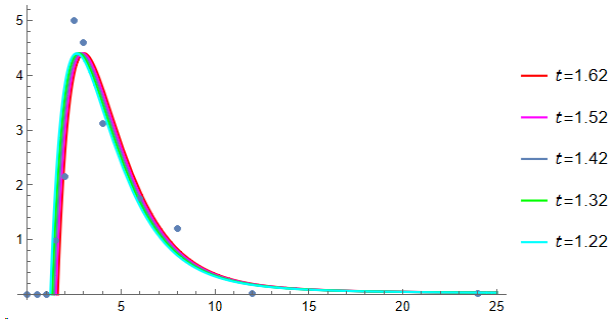
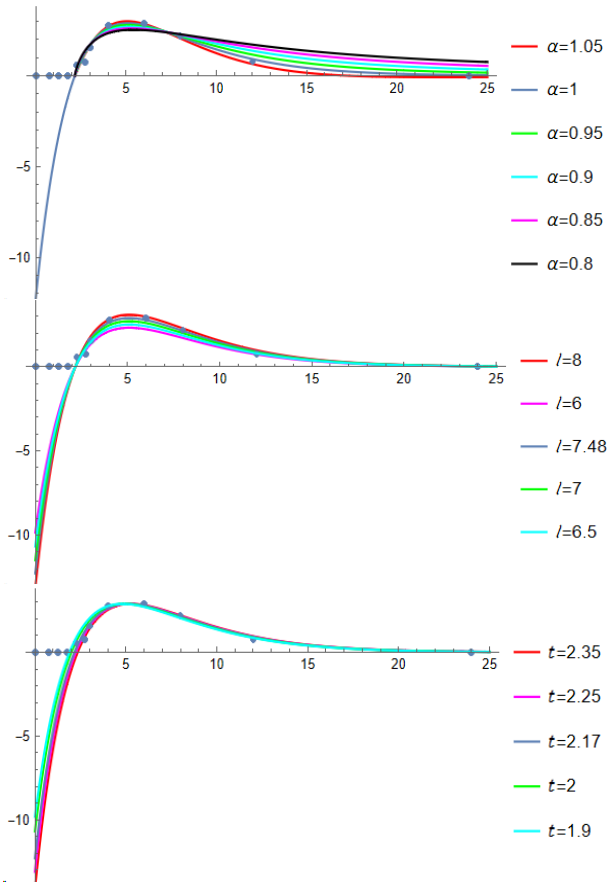




Subject 5:



Subject 6: