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EXPLICIT SOLUTION OF A DRUG EMANATING CONSTANT INFUSION WITH TIME DELAY

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ABSTRACT: An archetype is evaluated to elucidate the Pharmacokinetics of Enterohepatic dissemination of a drug with time delay just as constant infusion administrated. Results for nonlinear differential equations are evolved using Laplace Transform. Matlab is inked to read the plasma degree of concentration.

I. INTRODUCTION

A two compartment model discovered by Harrison and Gibaldi [1] eminent by Chen and Gross [2] elucidate the Pharmacokinetics of drugs enduring reabsorption where compartment I represent body and compartment II constitute G.I tract. Steimer [3] projected a modification to model by appending a time lag to carry promenade of compartments. Here we discuss the analytic solution for the amount of drug in the central compartment on consecutive intervals of τ with constant infusion.

Steimer model is layout in fig1 defines the first order kinetics and elimination transpires in the both compartments with K_{10} & K_{20} coefficients respectively. K_{12} & K_{21} are the rate constants for biliary excretion and reabsorption, The time-lag might be due to deferred transformation, a storage in the glad bladder or a transportation in the bile from the situates of excretion to absorption.

A dose D of Drug is administrated intravenously at time t=0 as a bolus in compartment I as predominantly both were empty. The drug leaves the central compartment at time t reaches at time $(t+\tau)$ where it is liable to be reabsorbed on account of delay.

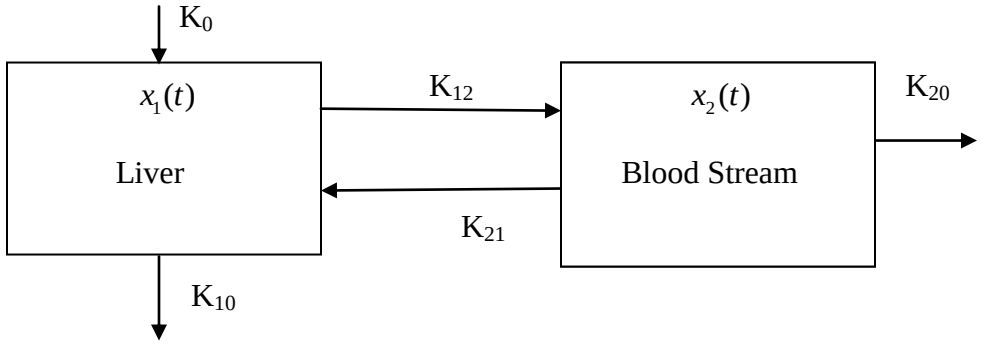
Let $x_i(t) =$ amount of drug at time t in central compartment

$\partial(t) =$ Dirac delta function

$K_0 =$ Constant rate of infusion

Let U be the Heaviside's unit step function

$$u(t-\tau)=\begin{cases}0 \text{ if } & 0 \le t<\tau \\ 1 \text{ if } & t>\tau\end{cases}$$



(Figure1)

The mathematical fabrication of two compartment model with a time-lag τ is inclined by the set of differential equations.

Say compartment I reap an infusion at constant rate of K_0, then $x_1(t)$ is the convolution of K_0 and the function $\frac{1}{D}x_1^{i.v}(t)$ where

$x_1^{i.v}(t) =$ Volume of drug after intravenous injection of Dose D

$$\begin{cases}\frac{dx_1(t)}{dt} = -(K_{10}+K_{12})x_1(t)+K_{21}x_2(t)+D\partial(t) \\ \frac{dx_2(t)}{dt} = -(K_{20}+K_{21})x_2(t)+K_{12}u(t-\tau)x_1(t-\tau)\end{cases} \quad -(1)$$

$$x_1(t) = x_2(t) = 0 \quad -(2)$$

Let $a=K_{20}+K_{21}, b=K_{10}+K_{12}$

$$\left.\begin{aligned}\frac{dx_1(t)}{dt} &= -bx_1(t) + K_{21}x_2(t) + K_0\partial(t)\\ \frac{dx_2(t)}{dt} &= -ax_2(t) + K_{12}u(t-\tau)x_1(t-\tau)\end{aligned}\right\} \text{-(3)}$$

Applying Laplace Transform on both sides

$$\left.\begin{aligned}sL\{x_1(t)\} + bL\{x_1(t)\} - K_{21}L\{x_2(t)\} &= \frac{K_0}{s}\\ sL\{x_2(t)\} + aL\{x_2(t)\} - K_{12}\exp(-s\tau)L\{x_1(t)\} &= 0\end{aligned}\right\} \text{-(4)}$$

Since $L\{\partial(t) = 1\}$

i.e.

$$\left.\begin{aligned}(s+b)L\{x_1(t)\} - K_{21}L\{x_2(t)\} &= \frac{K_0}{s}\\ (s+a)L\{x_2(t)\} - K_{12}\exp(-s\tau)L\{x_1(t)\} &= 0\end{aligned}\right\} \text{- (5)}$$

Solving for $L\{x_1(t)\}$

$$= \frac{|K_0(s+a)|}{|s(s+a)(s+b)-ce^{-s\tau}|} \text{ where } c = K_{21}K_{12} \text{ - (6)}$$

$$Let\ Z_1(s) = \frac{|K_0(s+a)|}{|s(s+a)(s+b)-ce^{-s\tau}|} \qquad \text{- (7)}$$

Using First class theorem $\lim_{t\to\infty} x_1(t) = \lim_{s\to 0} s.Z_1(s)$ - (8)

$$\lim_{t\to\infty} x_1(t) = \lim_{s\to 0} s.\frac{|K_0(s+a)|}{|s(s+a)(s+b)-ce^{-s\tau}|}$$

$$\frac{K_0.a}{ab-c} \text{ - (9)}$$

(9) is independent of time delay

Solving for $L\{x_2(t)\}$

$$= \frac{\left|K_0 K_{12} \exp(-s\tau)\right|}{\left|s(s+a)(s+b) - ce^{-s\tau}\right|} \quad \text{- (10)}$$

Let $z_2(s) = \frac{\left|K_0 K_{12} \exp(-s\tau)\right|}{\left|s(s+a)(s+b) - ce^{-s\tau}\right|}$ - (11)

Using First class theorem $\lim_{t\to\infty} x_2(t) = \lim_{s\to 0} s.Z_2(s)$ - (12)

$$\lim_{t\to\infty} x_2(t) = \lim_{s\to 0} s. \frac{\left|K_0 K_{12} \exp(-s\tau)\right|}{\left|s(s+a)(s+b) - ce^{-s\tau}\right|} \quad \text{- (13)}$$

$$\frac{K_0.K_{12}}{ab-c} \quad \text{- (14)}$$

(14) is independent of delay

Case-1

Initial condition $x_1(0)=A$;$x_2(0)=0$

When the dose D is intravenously injected in compartment I, which is not empty i.e. $x_1(0) = A$

The system (1) with non zero initial condition gives

$$Z_3(s) = \frac{(D+A)(s+a)}{(s+a)(s+b) - ce^{-s\tau}} \quad \text{- (15)}$$

Thus $L^{-1}\{Z_3(s)\} = L^{-1}\left\{\frac{(D+A)(s+a)}{(s+a)(s+b) - ce^{-s\tau}}\right\}$

(D+A)(s+a) $L^{-1}\left\{\frac{1}{(s+a)(s+b) - ce^{-s\tau}}\right\}$

$$= \frac{(D+A)}{(s+b)} L^{-1}\left\{c^j e^{-s\tau} h(s)\right\} = u(t-\tau)H_j(t-\tau)$$

Therefore $K(t) = L^{-1}\{H(s)\} = \frac{(D+A)}{(s+b)} \sum_0^K c^j u(t-j\tau)H_j(t-j\tau)$

Where K is an integer such that $K\tau \le t \le (K+1)\tau$ and

$$H_J(t) = L^{-1}\{h(s)\} \text{ with } h(s) = \frac{1}{(s+a)^j (s+b)^{j+1}}$$

If j=0 then

$$H_0(t) = (D+A)L^{-1}\left\{\frac{1}{(s+b)}\right\}$$

$$= e^{-bt}(D+A)$$

For j≥ 1 we get

$$(D+A)\left[\frac{(-1)^J (J)^{2J-1} e^{-bt}}{(b-a)^{2j}} + \frac{1}{(j!)^2}\sum_{n=0}^{j-1}\frac{(j_n)(j+n-1)!t^{j-1-n}}{(b-a)^{j+n-1}}(-1)^n (j^2-n^2)e^{-at} - (-1)^j jt(a-b)e^{-bt}\right]$$

$$Z_4(s) = \frac{(D+A)K_{12}.e^{-s\tau}}{(s+a)(s+b)-ce^{-s\tau}} \quad \text{- (16)}$$

Thus $L^{-1}\{Z_4(s)\} = (D+A)K_{12}L^{-1}\left\{\frac{e^{-s\tau}}{(s+a)(s+b)-ce^{-s\tau}}\right\}$

$$= \frac{(D+A)K_{12}}{(s+a)(s+b)} L^{-1}\left\{\sum_{j=0}^{k} c^j u(t-s\tau).M_J(t-\tau j)\right\}$$

Where K is an integer such that $K\tau \le t \le (K+1)\tau$ and

$$M_j(t) = L^{-1}\{h(s)\}$$

With M(s) = $\frac{1}{(s+a)^{j+1}(s+b)^{j+1}}$

If j=0

$$M_0 = \frac{(D+A).K_{12}}{(b-a)}\{e^{-at} - e^{-bt}\}$$

For j≥ 1 we get

$$(D+A)K_{12}\left[\frac{(-1)^{2j} j^{2j-1}(e^{-at}-e^{-bt})}{(b-a)^{j+1}} + \frac{1}{(j!)^2}\sum_{n=0}^{j-1}\frac{(j_n)(j+n-1)!(2(e^{-at}-e^{-bt}) + t^j(-1)^j(e^{-at}-e^{-bt})}{(b-a)^{2j+n-1}}\right]$$

Figure 1.1

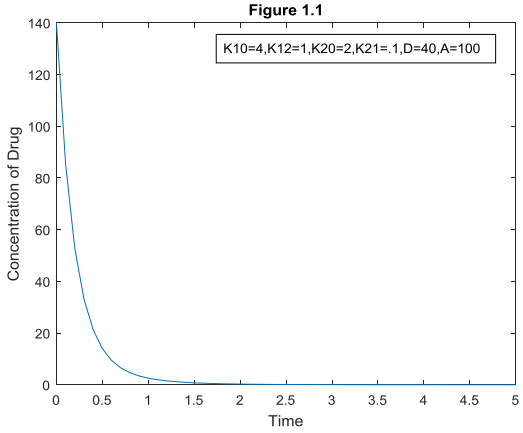


Figure 1.2

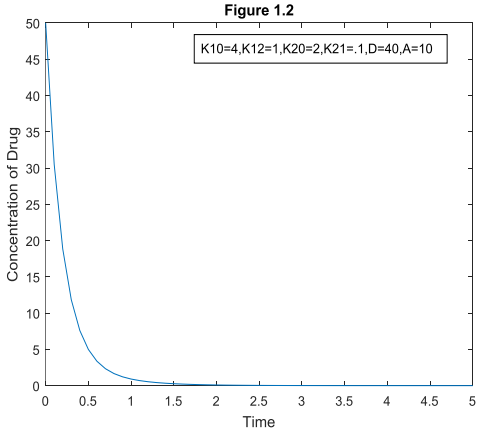


Figure 1.3

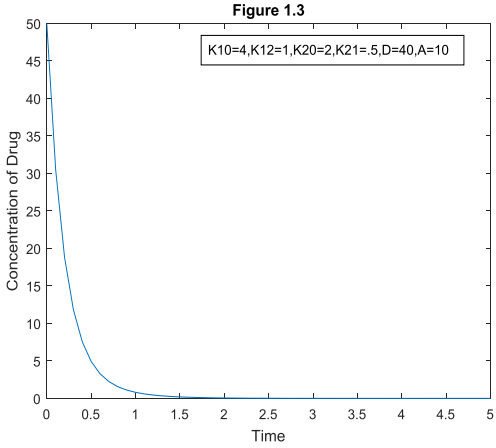


Figure 1.4

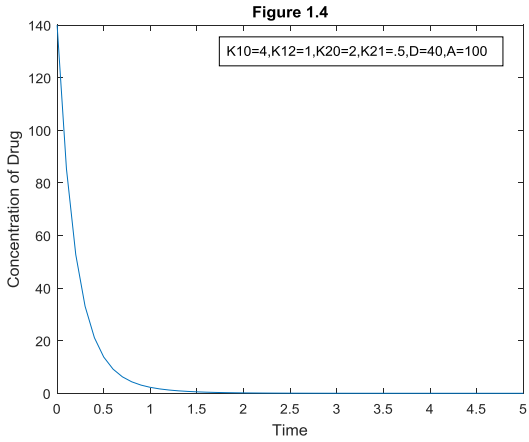


Figure 1.5

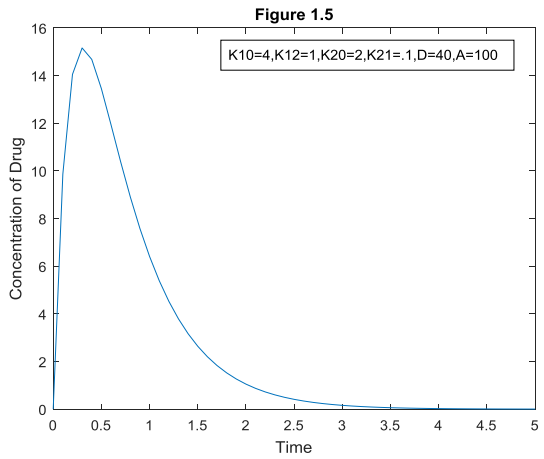
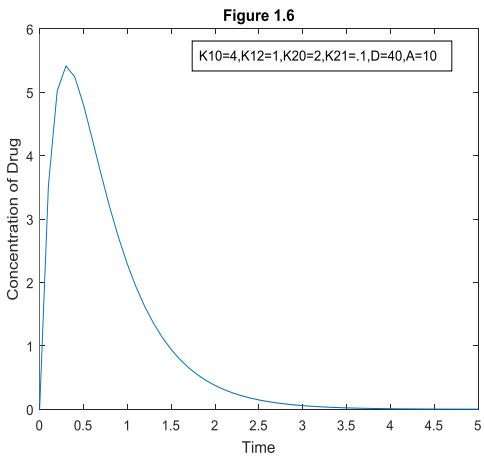
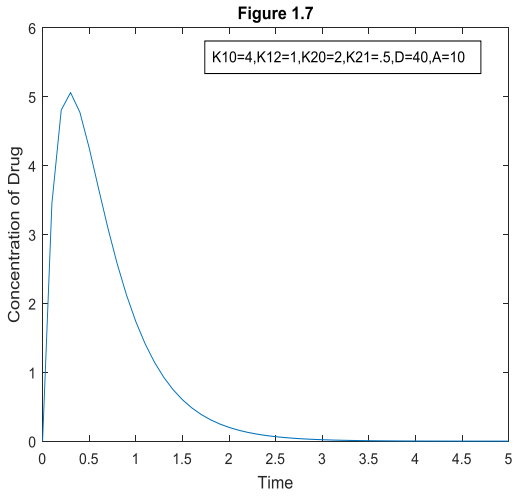
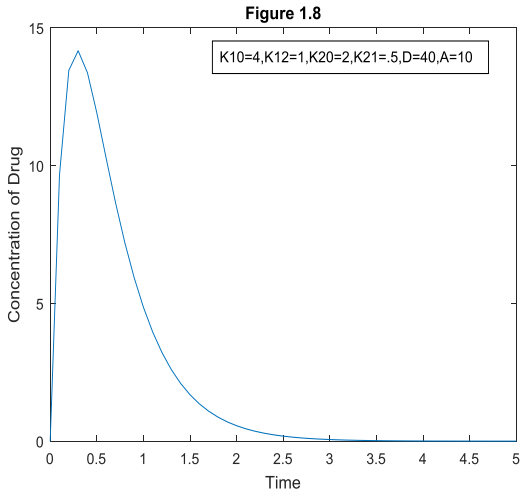


Figure 1.6







In this analytical study we considered the parameters K_{10}, K_{12}, D as constants such that $K_{10}=4, K_{12}=1, D=40$ and A varies from 10 to 100 from 1.1 -1.8 and we investigated the demeanour of the drug concentration in two compartments Central $x_1(t)$ and tissue $x_2(t)$ respectively for different values of K_{21} individually. We observe that the concentration of drug takes 6 hours to reach steady state and it varies from 0 to 5.

Case-2

Initial condition $x_1(0)=A\ ; x_2(0)=B$

When the dose D is intravenously injected in compartment I which is not empty i.e

$x_1(0)=A\ ; x_2(0)=B$

The system (1) with non zero initial condition gives

$$\left\{\begin{array}{l}(s+b)L\{x_1(t)\}-K_{21}L\{x_2(t)\}=D+A\\(s+a)L\{x_2(t)\}-K_{12}\exp(-s\tau)L\{x_1(t)\}=B\end{array}\right\} \text{ - (17)}$$

$$Z_5(s)=\left\{\frac{(D+A)(s+a)}{(s+a)(s+b)-ce^{-s\tau}}\right\}+\left\{\frac{K_{21}B}{(s+a)(s+b)-ce^{-s\tau}}\right\} \text{ -(18)}$$

Applying Inverse Laplace transform

$$L^{-1}\{Z_5(s)\} = \left\{\left\{\frac{(D+A)(s+a)}{(s+a)(s+b)-ce^{-s\tau}}\right\} + \left\{\frac{K_{21}B}{(s+a)(s+b)-ce^{-s\tau}}\right\}\right\} \text{ - (19)}$$

$$= (D+A)(s+a)L^{-1}\left\{\left\{\frac{1}{(s+a)(s+b)-ce^{-s\tau}}\right\}\right\} + K_{21}BL^{-1}\left\{\frac{1}{(s+a)(s+b)-ce^{-s\tau}}\right\} \text{ - (20)}$$

$$\frac{(D+A)}{(s+b)}\sum_{j=0}^{K} c^j u(t-j\tau)I_j(t-j\tau) + K_{21}B\sum_{J=0}^{K} c^j u(t-j\tau)P_j(t-j\tau)$$

Where K is a integer such that $K\tau \le t \le (K+1)\tau$ and

$$I_j(t) = L^{-1}\{I(s)\} \text{ with } i(S) = \frac{1}{(s+a)^j (s+b)^{j+1}}$$

$$P_j(t) = L^{-1}\{p(s)\} \text{ with } p(s) = \frac{1}{(s+a)^{j+1}(s+b)^{j+1}}$$

For j=0

$$I_0(t) = (D+A)L^{-1}\left\{\frac{1}{s+b}\right\}$$

$$= e^{-bt}(D+A)$$

$$P_0(t) = \frac{1}{b-a}(e^{-at} - e^{-bt})$$

For j≥1

$$(D+A)\left[\frac{(-1)^j (j)^{2j-1} e^{-bt}}{(b-a)^{2j}} + \frac{1}{(j!)^2}\sum_{n=0}^{j-1}\frac{(j_n)(j+n-1)!t^{j-1-n}}{(b-a)^{j+n-1}}(-1)^n (j^2-n^2)e^{-at} - (-1)^j jt(a-b)e^{-bt}\right] +$$

$$K_{21}B\left[\frac{(-1)^J (J)^{2J-1}(e^{-at}-e^{-bt})}{(b-a)} + \frac{1}{(j!)^2}\sum_{n=0}^{j-1}\frac{(j_n)(j+n-1)!t^{j-1-n}}{(a-b)^{j+n+1}}(-1)^{j+n}(e^{-at}-e^{-bt}) + (-1)^{n+j}t(a-b)(e^{-at}+e^{-bt})\right]$$

$$Z_6(s) = \left\{\frac{(D+A)K_{12}.e^{-s\tau}}{(s+a)(s+b)-ce^{-s\tau}} + \frac{B(s+b)}{(s+a)(s+b)-ce^{-s\tau}}\right\} \text{ - (21)}$$

Applying Inverse Laplace transform

$$(D+A)K_{12}L^{-1}\left\{\frac{e^{-s\tau}}{(s+a)(s+b)-ce^{-s\tau}}\right\} + B(s+b)L^{-1}\left\{\frac{1}{(s+a)(s+b)-ce^{-s\tau}}\right\}$$

$$\frac{(D+A)K_{12}}{(s+a)(s+b)}L^{-1}\left\{\sum_{j=0}^{K}c^{j}u(t-\tau j)Q(t-\tau j)\right\}+B(s+b)L^{-1}\left\{\sum_{j=0}^{K}c^{j}u(t-\tau j)R(t-\tau j)\right\}$$

Where K is a integer such that $K\tau \le t \le (K+1)\tau$ and

$$Q_j(t)=L^{-1}\{q(s)\}\ withq(s)=\frac{1}{(s+a)^{j+1}(s+b)^{j+1}}\ and$$

$$R_j(t)=L^{-1}\{r(s)\}\ withr(s)=\frac{1}{(s+a)^{j+1}(s+b)^{j}}$$

If j=0

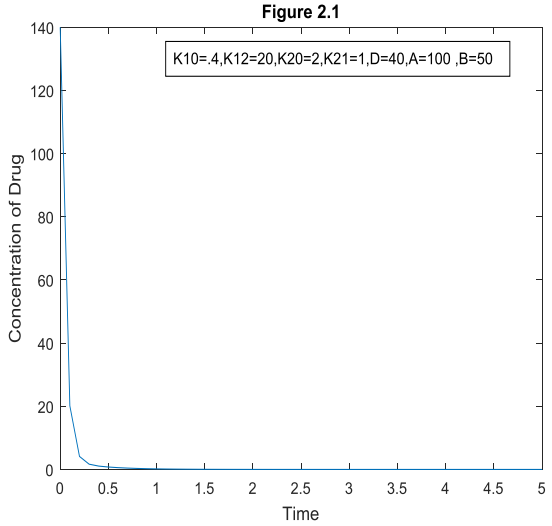
$$Q_0=\frac{(D+A)K_{12}}{(b-a)}\left\{e^{-at}-e^{-bt}\right\}$$

$$R_0=Be^{-bt}$$

$$Therefore\ \frac{(D+A)K_{12}}{(b-a)}\left\{e^{-at}-e^{-bt}\right\}+Be^{-at}$$

For j≥1

$$(D+A)K_{12}\left\{\frac{2}{(a-b)^{j+2}}\left\{(e^{-at}-e^{-bt})+(a-b)t^{j}(e^{-at}-e^{-bt})\right\}\right\}+B\left\{\frac{1}{(a-b)^{j+1}}\left(e^{-bt}-e^{-at}\right)+\frac{1}{(b-a)^{j}}t^{j}e^{-at}\right\}$$



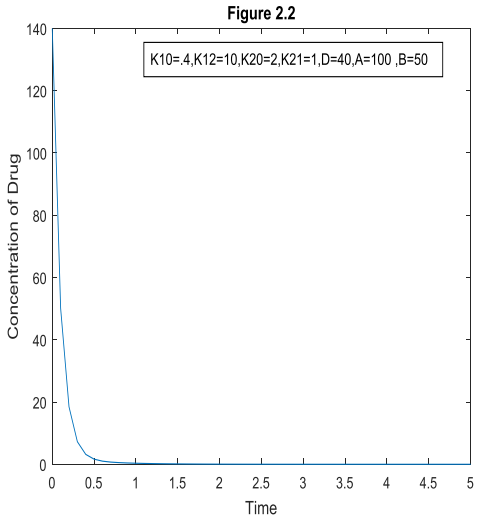
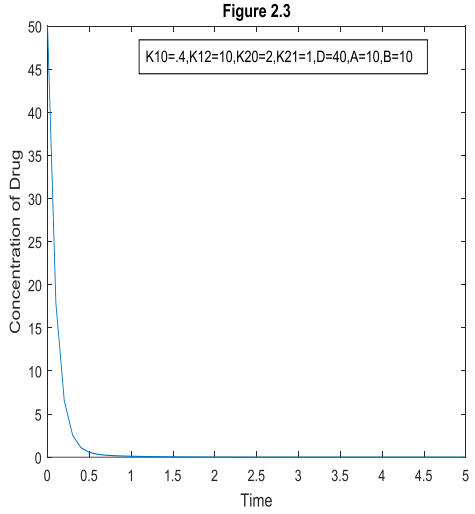


Figure 2.3



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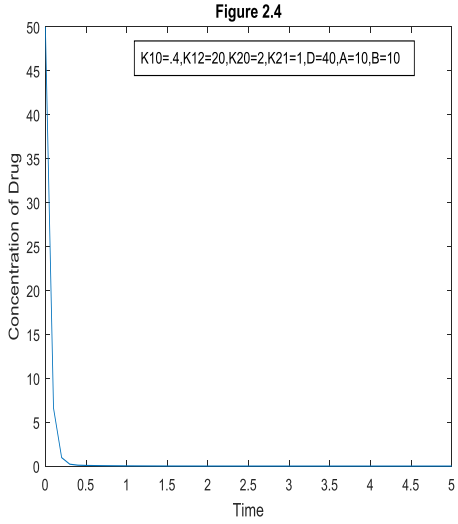


Figure 2.5

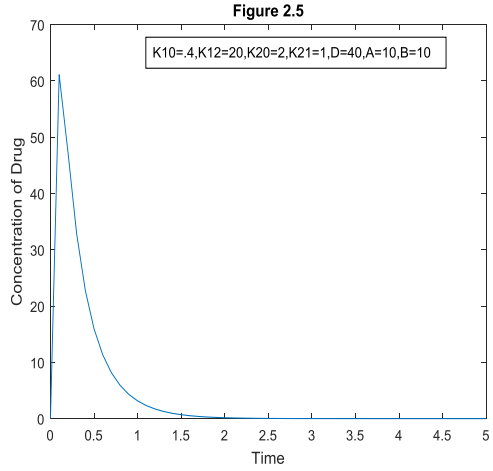
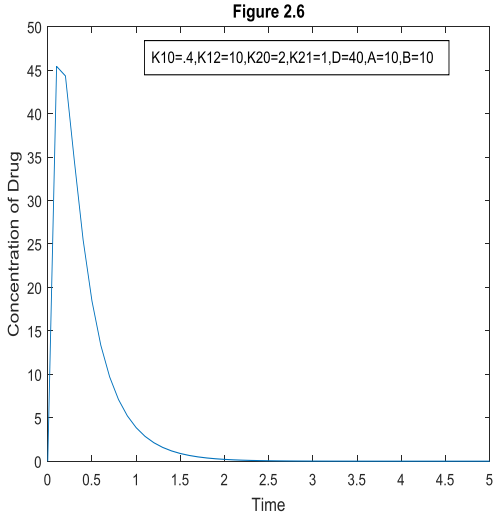


Figure 2.6



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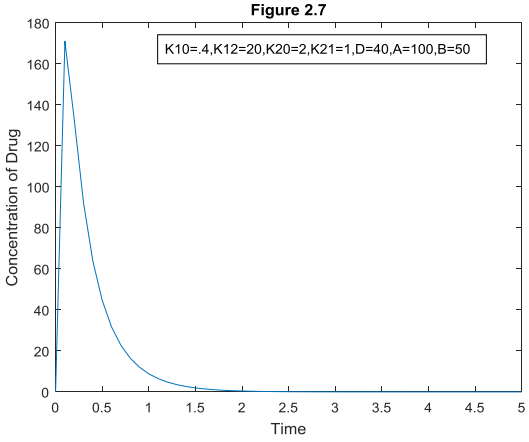
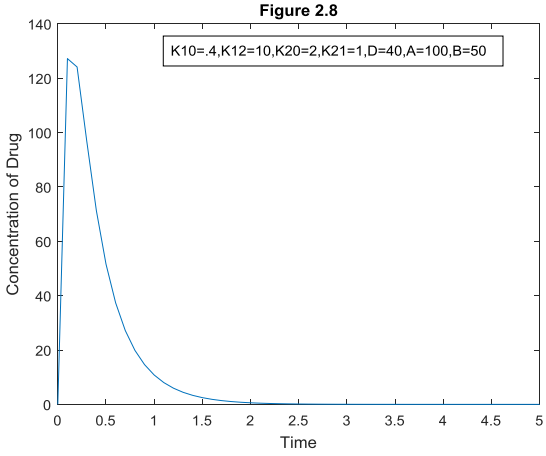


Figure 2.8



In this analytical study we considered the parameters $K_{10}, K_{21}, K_{20,} D$ as constants such that $K_{10} = 0.4, K_{21} = 1, D = 40, K_{20} = 2$ and A varies from 10 to 100 and the other value B differs we investigated the behavior of the drug concentration in two central compartment $x_1(t)$ and tissue compartment $x_2(t)$ respectively for different values of K_{12} exclusively. We perceive that the concentration of drug in central compartment and tissue compartment individually as the parameter K_{12} contrasts concentration of drug takes 5 hours to reach steady state as the drug concentration varies.

II. CONCLUSION:

A two compartment model was contemplate for the explanation of pharmacokinetics of drug with constant infusion being focused on Enterohepatic circulation associated with time-lag .Analytical solutions were formulated by Laplace transform, and it is detected that the time-lag could be due to transformation delay, gall bladder storage or due to transportation in bile due to excretion to the site of reabsorption. The plasma level profiles are by the computer simulations preeminent to rebound and secondary peaks.

III. REFERENCE:

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