



RESEARCH ARTICLE



The concentration of digoxin after intravenous and oral administration studied by a two-compartment model

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ABSTRACT

The present paper is designed to compare the distribution of digoxin administered through an Intravenous (i.v.) and Oral (p.o.) in central and peripheral compartments. The model under consideration is denoted by a system of three non-linear ordinary differential equations. The Eigenvalue and the Laplace transform methods were used to solve the system of equations. In this model, digoxin was administered to three subjects through i.v. and three subjects through p.o. then, the serum concentrations were measured over a period of 6 h. The transfer coefficients were obtained from digoxin concentrations using the method of residuals and the variation of digoxin concentration–time curves plotted using MATLAB. In this model, we consider excretion is only from the peripheral compartment.

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KEYWORDS

Compartment model; eigenvalue; laplace transform; residual; digoxin; oral; intravenous; normal subjects

1. Introduction

Explanation of the simplest pharmacokinetic model in accordance with data observed for human drug adaptation is a necessary step for a full understanding of distribution, elimination, activity and drug toxicity. This is becoming increasingly important with drugs that have a low therapeutic index and serious side effects such as the cardiac glycoside digoxin. In view of its narrow therapeutic window, it is important to study the drug concentration in men at various times after oral (*p.o.*) and intravenous (*i.v.*) administration. Doherty, Flanigan, and Dalrymple (1972) distinguish the pharmacokinetics of digoxin after oral administration in seven normal patients of tritium-labelled digoxin. The mean half-life from digoxin concentration was 32.7 h., while urinary elimination rates capitulated the mean half-life of 35.6 h., approximately similar values of creatinine and digoxin renal clearances were identified. Gitfrich, Bodem, and Chidsey (1974) inspect the urinary excretion of tritiated digoxin after administering intravenously and reported an average half-life value of 50.8 h. in six chronic disease patients with normal renal function. They found that the renal clearance of digoxin slightly exceeded the creatinine clearances. The steady-state volume of distribution of digoxin in normal subjects has been calculated by Reuning, Sams, and Notari (1973) from digoxin concentration data reported in three

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studies. J.J Vallner, Stewart, Kotzan, Kirsten, and Honigberg (1981) examined the elimination half-life of hydromorphone in six subjects was 2.64 ± 0.88 h and the drug distributed in a high volume of 1.22 l/kg. Also, the drug was very quickly but partially absorbed after oral administration.

Kannan, Singh, and Przekwas (2018) has shown using his Q3D-compartment multi-scale models, the effect of the solubility on the regional presence of the ICS and its absorption across the different lung tissues to the vein/artery. In particular, it was found that highly soluble drugs like Budesonide (solubility coefficient ~ 45 $\mu\text{g/ml}$) dissolves very fast, then diffuses and then is cleared to the GUT region. On the other hand, poorly soluble drugs like FP (solubility coefficient $\sim 0.5\text{--}1.5$ $\mu\text{g/ml}$) being nearly insoluble, are present in chunks even after 1–2 h after the inhalation, and thus there is hardly any diffusion along the lung axis. Consequently, we see a secondary spike in the vein concentration at around 1.25 h time-frame, when the FP chunk (and the dissolved FP molecular drug, sticking to it) entering the GUT and to the vein. Similarly, the deposition of the ICS drug on the airway walls is equally important. For instance, Kannan et al. (2017), (Kannan, Guo, & Przekwas, 2016) provides the factors affecting the deposition on the airways: (i) drug density, (ii) the inhaler geometry, (iii) the inhaled flow rate, (iv) the vorticity in the airways (causes increased deposition for smaller particles), (v) the cartilaginous ridges in the trachea and the generation-1 airways (causes increased deposition for smaller particles) and (vi) the enhanced deposition at the airway bifurcations, thereby restricting the drug to reach the lower airways and the alveoli. In cases like the FP/Budesonide drug, a significant portion of the inhaled corticosteroids (ICS) (from the dry powder inhalers) go and deposit on the alveoli (due to the factors mentioned earlier). All of the above contribute to the efficacy of the inhaled drug and the clearance effects (almost none in the alveoli).

In this present study, we formulated two-compartmental model as shown in Figure 1 which is denoted by a system of three non-linear ordinary differential equations (ODEs). The Eigenvalue and the Laplace transform methods were used to solve the system of equations. In this model, digoxin was administered to three subjects through *i.v.* and three subjects through *p.o.* then, the serum concentrations were measured respectively over a period of 6 h. The transfer coefficients were obtained from digoxin concentrations using the method of residuals and the variation of digoxin concentration–time curves plotted using MATLAB In detail, we compare the distribution of digoxin in men administered

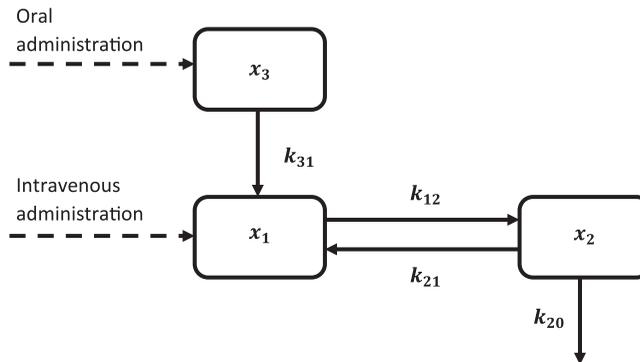


Figure 1. General scheme of the two-compartment model.

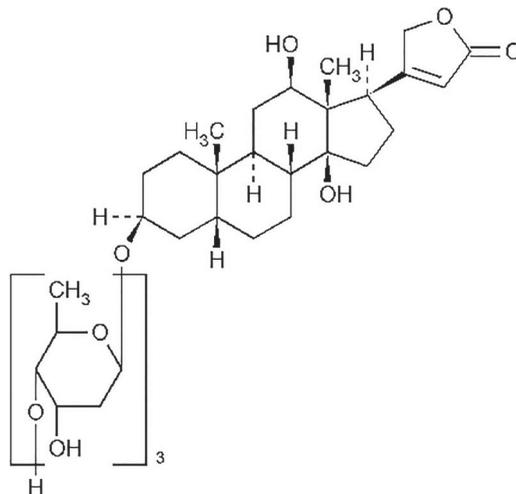
Table 1. Digoxin concentration in three subjects at various times after oral administration of 500 μg .

Subject 1 (Male Volunteer/Age: 52 years/Weight: 74 kg.)		Subject 2 (Male Volunteer/Age: 54 years/Weight: 80 kg.)		Subject 3 (Female Volunteer/Age: 66 years/Weight: 71 kg.)	
Time (hr.)	Drug Concentration (ng/ml)	Time (hr.)	Drug Concentration (ng/ml)	Time (hr.)	Drug Concentration (ng/ml)
0.2	9.3	0.3	1.9	0.2	0.1
0.3	9.4	0.4	2.1	0.3	0.6
0.6	6.5	0.5	2.4	0.5	1.6
0.8	4.9	0.8	2.7	0.8	1.7
1.0	3.8	1.0	2.6	–	–
1.5	1.7	1.5	1.3	1.5	1.8
2.0	1.2	2.0	0.9	2.1	1.6
3.3	1.0	3.0	0.6	3.0	1.1
6.3	0.5	6	0.3	5.8	0.6

Note: K.E. Andersson, Nyberg, Dencker, and Gothlin (1975).

through oral (p.o.) and intravenous (i.v.). Two normal male and one female adult volunteers ages 52 years, 54 years and 66 years, weights 74, 80 and 71 kg were, respectively, selected for oral (p.o.) study. Three adult subjects C.J., T.F. and W. S. ages 24 years, 26 years and 28 years, weights 75, 72.7 and 77.3 kg were also selected for the intravenous study. Digoxin was administered at a dose of 500 μg by oral (p.o.) and 1 mg dose of digoxin was administered by intravenous (i.v.), then blood samples were withdrawn over a period of 6 h. These data are shown in Table 1 (p.o.) and Table 2 (i.v.). In this study, we considered digoxin as a drug and method of residuals used for identifying the rate constants from the clinical data.

Digoxin: Digoxin is a cardiac glycoside indicated for the treatment of mild-to-moderate heart failure. Most frequently, it is used for atrial fibrillation, atrial flutter and heart failure. Digoxin is taken by mouth or by injection into a vein. Digoxin is extracted from the leaves of *Digitalis lanata*. The term 'digitalis' is used to designate the whole group of glycosides. The glycosides are composed of 2 portions: a sugar and a cardenolide. Digoxin is described chemically as (3 β , 5 β , 12 β)-3-[O-2, 6-dideoxy- β -D-ribo-hexopyranosyl-(1 \rightarrow 4)-O-2, 6-dideoxy- β -D-ribo-hexopyranosyl-(1 \rightarrow 4)-2, 6-dideoxy- β -D-ribo-hexopyranosyl oxy]-12, 14-dihydroxy-card-20(22)-enolide. Its molecular formula is $\text{C}_{41}\text{H}_{64}\text{O}_{14}$, its molecular weight is 780.95, and its structural formula is:



Method of Residuals: The method of residuals is a commonly employed technique for resolving a curve into various exponential terms. This method allows the separation of the mono-exponential constituents of a bi-exponential plot of plasma concentration against time and therefore, it is a useful procedure for fitting a curve to the experimental data of a drug.

As mentioned in this paper, a bi-exponential equation is derived, which is in the form of

$$x_1(t) = Ae^{-\lambda_1 t} + Be^{-\lambda_2 t}$$

Here the constants λ_1 and λ_2 are rate constants for the distribution phase and elimination phase, respectively. The constants A and B are intercepts on the y -axis for each exponential segment of the curve in the above equation. Clearly, for the data given the decline in the initial distribution phase is more rapid than the elimination phase. The rapid distribution phase is confirmed with the constant λ_1 being larger than the rate constants λ_2 . Therefore at a time following the attainment of distribution equilibrium, the term $Ae^{-\lambda_1 t}$ will approach to zero, while $Be^{-\lambda_2 t}$ will still have a finite value. At this later time, the above equation will reduce to

$$x_1(t) = Be^{-\lambda_2 t}$$

Which, in common logarithm, is:

$$\log x_1(t) = \log B - \frac{\lambda_2 t}{2.3}$$

Here the rate constant can be obtained from the slope ($-(\lambda_2/2.3)$) of a straight line representing the terminal exponential phase or λ_2 phase is extrapolated to the y -axis; the y intercept is equal to B . values from the extrapolated line are then subtracted from the original experimental data points and a straight line is obtained. This line represents the rapidly distributed λ_1 phase or the residual plasma concentration against time. A number of pharmacokinetic parameters derived by using rate constants λ_1 and λ_2 and y intercepts A and B .

2. Mathematical method

2.1. Assumptions and model building

A two-compartment model consists of two physiological meaningful parts (Kwon, 2001). The first central compartment x_1 is identified with the blood and organs were heavily supplied with blood like liver or kidney. The second peripheral compartment x_2 describes a tissue or the part of the body which is not heavily supplied with blood such as skin and fat tissue. Only, in the case of *p. o.* administration x_3 describes the absorption compartment in which the absorption takes place. The central and peripheral compartments are connected with each other in both directions and therefore, a distribution between the central and peripheral compartment takes place.

The main assumption in pharmacokinetics is that the drug is completely eliminated from the body through the central compartment. In most cases, the metabolism takes place in the liver and the excretion via the kidneys.

We consider two different types of drug administration, first, the drug is directly administered by intravenous bolus injection (*i.v.*) into the blood. It is assumed that the drug is immediately completely distributed in the blood. Second, the drug is orally (*p. o.*) administered by a tablet. Hence, absorption through the stomach takes place. Therefore, the distribution is not immediate further, only a part of the amount of drug will reach the blood circulation called bio-availability. A schematic overview of the two-compartment model is presented in Figure 1.

To shorten the notations, we consider *i. v.* and *p. o.* administration at once. The general form of a two-compartment model describing either *i. v.* or *p. o.* drug administration is given by the set of ODEs as follows:

$$\frac{dx_1(t)}{dt} = -k_{12}x_1 + k_{21}x_2 + k_{31}x_3; x_1(0) = k_01 \quad (1)$$

$$\frac{dx_2(t)}{dt} = k_{12}x_1 - (k_{20} + k_{21})x_2; x_2(0) = 0 \quad (2)$$

$$\frac{dx_3(t)}{dt} = -k_{31}x_3; x_3(0) = f.k_03 \quad (3)$$

Equation (1) describes the central compartment, Equation (2) the peripheral compartment and Equation (3) the absorption in the case of *p. o.* administration. Note that the third absorption compartment for *p. o.* does not count for the nomenclature of the model. Table 3 describes the parameters and variables used in this model. Also, Table 4 describes the particular setting for Equations (1)–(3) to present either *p.o.* or *i.v* administration.

2.2. Case I: Oral administration (*p. o.*)

In matrix notation of (1)–(3), we have

$$\frac{dX(t)}{dt} = KX(t) \quad (4)$$

Table 2. Digoxin concentration in three patients C. J., T. F and W.S. at various times after intravenous administration of 1 mg.

C. J.		T. F.		W. S.	
Time (hr.)	Digoxin Concentration (ng/ml)	Time (hr.)	Digoxin Concentration (ng/ml)	Time (hr.)	Digoxin Concentration (ng/ml)
0.03	21.0	0.03	26.5	0.03	22.0
0.07	22.0	0.07	21.0	0.07	18.0
0.10	18.0	0.10	18.8	0.10	20.5
0.13	15.0	0.13	16.5	0.13	18.5
0.17	15.5	0.17	14.3	0.17	16.5
0.23	14.0	0.23	14.0	0.23	16.5
0.30	11.3	0.30	13.0	0.30	11.5
0.37	13.5	0.37	12.3	0.37	13
0.50	12.5	0.50	10.3	0.50	9.8
0.75	9.1	0.75	7.6	0.75	7.3
1.00	6.7	1.00	5.8	1.00	5.5
2.00	3.6	2.00	3.3	2.00	2.8
3.00	2.6	3.00	2.2	3.00	2
4.00	2.2	4.00	1.9	4.00	1.4
6.00	1.2	6.00	0.52	6.00	0.73

Note: William G. Kramer et al. (1974).

Table 3. Parameters and variables present in the model.

Parameters and variables	Description
k_{12}	the rate of flow of digoxin from the central compartment to the peripheral compartment
k_{21}	the rate of flow of digoxin from the peripheral compartment to the central compartment
k_{20}	the excretion from the peripheral compartment
k_{31}	the absorption rate of digoxin in case of <i>p. o.</i>
k_{01}	the dose of digoxin either in the <i>p. o.</i> or <i>i. v.</i> administration
$x_1(t)$	the digoxin concentration in the central compartment at a time t
$x_2(t)$	the digoxin concentration in the peripheral compartment at a time t
$x_3(t)$	the digoxin concentration in the absorption compartment at a time t
$0 < f \leq 1$	Fraction parameter regulating the amount of drug which effectively reaches the blood in case of <i>p. o.</i> administration. We set $f = 1$ without loss of generality for our mathematical consideration.

Table 4. Particular settings for Equations (1)–(3) to present either *p. o.* or *i. v.* administration.

<i>p. o.</i> administration	<i>i. v.</i> administration
$k_{12}, k_{21}, k_{20}, k_{31} > 0$ $X(0) = (0, 0, k_{03})^T$	$k_{12}, k_{21}, k_{20} > 0$ and $k_{31} = \text{does not exit}$ $X(0) = (k_{01}, 0)^T$

where

$$X(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{bmatrix} \text{ and } K = \begin{bmatrix} -k_{12} & k_{21} & k_{31} \\ k_{12} & -(k_{20} + k_{21}) & 0 \\ 0 & 0 & -k_{31} \end{bmatrix} \tag{5}$$

The Laplace transform (Doetsch 1976; Widder, 1966) is an integral transform where the linear operator $\mathcal{L}\{f(t)\}$ transform a function $f(t)$ with $t \in \mathbb{R}$ from the time domain to a function $F(s)$ with $s \in \mathbb{C}$ in an image domain. The advantage of this transformation is that differentiation and integration in the time domain correspond to simple algebraic operations in the image domain.

To solve (4), apply Laplace Transform, which gives

$$\begin{aligned} \mathcal{L}\{X'(t)\} &= \mathcal{L}\{KX\} \Leftrightarrow s\mathcal{L}\{X(t)\} - X(0) = K\mathcal{L}\{X(t)\} \\ &\Leftrightarrow (sI - K)\mathcal{L}\{X(t)\} = X(0) \\ &\Leftrightarrow \begin{bmatrix} s + k_{12} & -k_{21} & -k_{31} \\ -k_{12} & s + k_{20} + k_{21} & 0 \\ 0 & 0 & s + k_{31} \end{bmatrix} \begin{bmatrix} \mathcal{L}\{x_1(t)\} \\ \mathcal{L}\{x_2(t)\} \\ \mathcal{L}\{x_3(t)\} \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ k_{03} \end{bmatrix} \\ &\Leftrightarrow L(s).\mathcal{L}\{X(t)\} = X(0) \end{aligned} \tag{6}$$

where

$$L(s) = \begin{bmatrix} s + k_{12} & -k_{21} & -k_{31} \\ -k_{12} & s + k_{20} + k_{21} & 0 \\ 0 & 0 & s + k_{31} \end{bmatrix} \tag{7}$$

We solve the system of Equation (6) by Cramer's rule.

$$\begin{aligned}\det(L(s)) &= \det(sI - K) = (s + k_{31})[(s + k_{12})(s + k_{20} + k_{21}) - k_{12}k_{21}] \\ &= (s + k_{31})[s^2 + (k_{12} + k_{21} + k_{20})s + k_{12}k_{20}] \\ &= (s + k_{31})[s^2 + (\lambda_1 + \lambda_2)s + \lambda_1\lambda_2] \\ &= (s + k_{31})(s + \lambda_1)(s + \lambda_2)\end{aligned}$$

where $\lambda_1 > 0, \lambda_2 > 0$ and are real therefore, $\det(L(s)) = (s + k_{31})(s + \lambda_1)(s + \lambda_2) > 0 \forall s \geq 0$

$$\lambda_1 + \lambda_2 = k_{12} + k_{21} + k_{20} \text{ and } \lambda_1\lambda_2 = k_{12}k_{20} \quad (8)$$

To calculate the solution of the central compartment $x_1(t)$, peripheral compartment $x_2(t)$ and absorption compartment $x_3(t)$ in *p.o.* case, we substitute the vector $X(0)$ from Table 4 into the first column, second column and third column of the matrix $L(s)$ and denote the resulting matrices by $L_1(s), L_2(s)$ and $L_3(s)$ respectively, the quotient from Cramer's rule, we obtain.

$$\mathcal{L}\{x_1(t)\} = \frac{\det(L_1(s))}{\det(L(s))}, \mathcal{L}\{x_2(t)\} = \frac{\det(L_2(s))}{\det(L(s))} \text{ and } \mathcal{L}\{x_3(t)\} = \frac{\det(L_3(s))}{\det(L(s))} \quad (9)$$

Making use of inverse Laplace Transform, Equations (7) and (9) give

$$x_1(t) = \mathcal{L}^{-1} \left\{ \frac{k_{03}k_{31}(s + k_{20} + k_{21})}{(s + k_{31})(s + \lambda_1)(s + \lambda_2)} \right\} \quad (10)$$

$$x_2(t) = \mathcal{L}^{-1} \left\{ \frac{k_{12}k_{03}k_{31}}{(s + k_{31})(s + \lambda_1)(s + \lambda_2)} \right\} \quad (11)$$

$$x_3(t) = \mathcal{L}^{-1} \left\{ \frac{k_{03}}{(s + k_{31})} \right\} \quad (12)$$

Applying Heaviside's Theorem to Equations (10)–(12) to obtain the solution

$$\begin{aligned}x_1^{po}(t) &= \frac{k_{03}k_{31}(k_{20} + k_{21} - \lambda_1)}{(k_{31} - \lambda_1)(\lambda_2 - \lambda_1)} e^{-\lambda_1 t} + \frac{k_{03}k_{31}(k_{20} + k_{21} - \lambda_2)}{(k_{31} - \lambda_2)(\lambda_1 - \lambda_2)} e^{-\lambda_2 t} \\ &\quad + \frac{k_{03}k_{31}(k_{20} + k_{21} - k_{31})}{(\lambda_1 - k_{31})(\lambda_2 - k_{31})} e^{-k_{31} t}\end{aligned} \quad (13)$$

$$\begin{aligned}x_2^{po}(t) &= \frac{k_{12}k_{03}k_{31}}{(k_{31} - \lambda_1)(\lambda_2 - \lambda_1)} e^{-\lambda_1 t} + \frac{k_{12}k_{03}k_{31}}{(k_{31} - \lambda_2)(\lambda_1 - \lambda_2)} e^{-\lambda_2 t} \\ &\quad + \frac{k_{12}k_{03}k_{31}}{(\lambda_1 - k_{31})(\lambda_2 - k_{31})} e^{-k_{31} t}\end{aligned} \quad (14)$$

Equation (12) gives the solution of absorption compartment.

$$x_3^{po}(t) = k_{03}e^{-k_{31}t} \quad (15)$$

2.2.1. Case II: Intravenous administration (i. v.)

Since the third compartment does not exist for the intravenous administration, the matrix notation of Equations (1) and (2) from Equation (4), we have.

$$X(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \end{bmatrix} \text{ and } K = \begin{bmatrix} -k_{12} & k_{21} \\ k_{12} & -(k_{20} + k_{21}) \end{bmatrix} \quad (16)$$

From Equation (6),

$$L(s) = \begin{bmatrix} s + k_{12} & -k_{21} \\ -k_{12} & s + k_{20} + k_{21} \end{bmatrix} \quad (17)$$

where

$$\begin{aligned} \det(L(s)) &= \det(sI - K) = (s + k_{12})(s + k_{20} + k_{21}) - k_{12}k_{21} \\ &= s^2 + (k_{12} + k_{21} + k_{20})s + k_{12}k_{20} \\ &= s^2 + (\lambda_1 + \lambda_2)s + \lambda_1\lambda_2 \\ &= (s + \lambda_1)(s + \lambda_2) \end{aligned}$$

Here, $\lambda_1 > 0, \lambda_2 > 0$ and are real therefore, $\det(L(s)) = (s + \lambda_1)(s + \lambda_2) > 0 \forall s \geq 0$

To calculate the solution of the central compartment $x_1(t)$, peripheral compartment $x_2(t)$ in *i.v.* case. We substitute the vector $X(0)$ from Table 4 into the first column and second column of the matrix $L(s)$ in (16) and denote the resulting matrices by $M_1(s), M_2(s)$ respectively, the quotient from Cramer's rule, we obtain.

$$\mathcal{L}\{x_1(t)\} = \frac{\det(M_1(s))}{\det(L(s))}, \mathcal{L}\{x_2(t)\} = \frac{\det(M_2(s))}{\det(L(s))} \quad (18)$$

Making use of inverse Laplace Transform,

$$x_1(t) = \mathcal{L}^{-1} \left\{ \frac{k_{01}(s + k_{20} + k_{21})}{(s + \lambda_1)(s + \lambda_2)} \right\} \quad (19)$$

$$x_2(t) = \mathcal{L}^{-1} \left\{ \frac{k_{01}k_{12}}{(s + \lambda_1)(s + \lambda_2)} \right\} \quad (20)$$

Applying Heaviside's Theorem to Equations (19) and (20) to obtain the solution

$$x_1^{iv}(t) = \frac{k_{01}(\lambda_2 - k_{12})}{(\lambda_2 - \lambda_1)} e^{-\lambda_1 t} + \frac{k_{01}(\lambda_1 - k_{12})}{(\lambda_1 - \lambda_2)} e^{-\lambda_2 t} \quad (21)$$

$$x_2^{iv}(t) = \frac{k_{01}k_{12}}{(\lambda_2 - \lambda_1)} e^{-\lambda_1 t} + \frac{k_{01}k_{12}}{(\lambda_1 - \lambda_2)} e^{-\lambda_2 t} \quad (22)$$

3. Clinical application

3.1. Results – oral administration

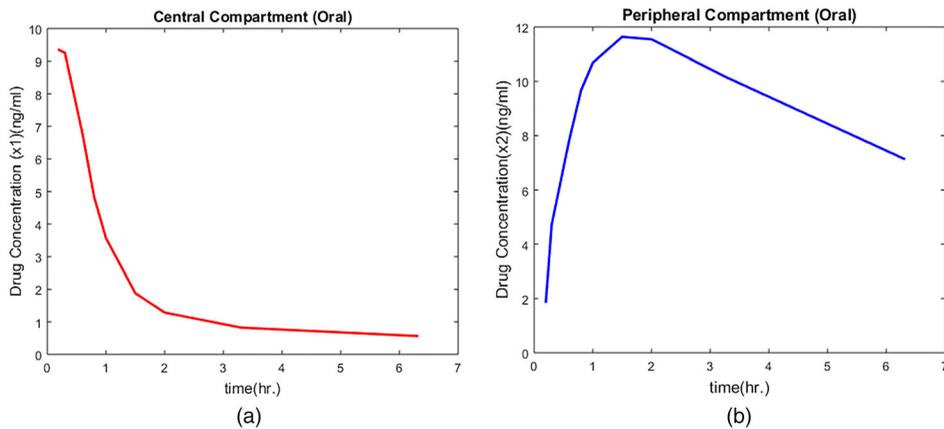
Once the pharmacokinetic parameters in Table 5 are determined using the method of residuals for an individual, the amount of drug remaining in the central and peripheral

Table 5. Parameters and RMSE of Subject 1, Subject 2 and Subject 3.

Parameters	Subject 1	Subject 2	Subject 3
k_{12}	1.8722	1.4443	1.5716
k_{20}	0.1327	0.0704	0.1972
k_{21}	0.1323	1.0971	0.8712
k_{31}	8.2753	2.0550	2.1966
RMSE	0.1697	0.0974	0.1282

Table 6. Simulated and actual digoxin concentrations in the central compartment of Subject 1, Subject 2 and Subject 3 after oral administration of 500 μg .

Subject 1 (Male volunteer /Age: 52 years/Weight: 74 kg.									
Time (hr.)	0.2	0.3	0.6	0.8	1.0	1.5	2.0	3.3	6.3
Actual (ng/ml)	9.3	9.4	6.5	4.9	3.8	1.7	1.2	1.0	0.5
x1-Simulated (ng/ml)	9.3435	9.2553	6.7675	4.8199	3.5665	1.8801	1.2865	0.8239	0.5645
Subject 2 (Male Volunteer/Age: 54 years/Weight: 80 kg.									
Time (hr.)	0.3	0.4	0.5	0.8	1.0	1.5	2.0	3.0	6
Actual (ng/ml)	1.9	2.1	2.4	2.7	2.6	1.3	0.9	0.6	0.3
x1-Simulated (ng/ml)	1.9918	2.1406	2.4461	2.7466	2.5085	1.3948	1.0949	0.5217	0.2921
Subject 3 (Female volunteer / Age: 66 years/Weight: 71 kg.									
Time (hr.)	0.2	0.3	0.5	0.8	-	1.5	2.1	3.0	5.8
Actual (ng /ml)	0.1	0.6	1.6	1.7	-	1.8	1.6	1.1	0.6
x1-Simulated (ng /ml)	0.0442	0.7859	1.3681	1.8467	-	1.7566	1.5208	1.1973	0.5701

**Figure 2.** Subject 1: Digoxin concentration in the central compartment (a) and peripheral compartment (b) after oral administration of 500 μg .

compartments is calculated using Equations (12) and (13). The pharmacokinetic data for digoxin are calculated in Subject 1, Subject 2 and Subject 3. Simulated and actual digoxin concentrations in the central compartment of Subject 1, Subject 2 and Subject 3 are tabulated in Table 6 and plotted for Subject 1 in Figure 2(a) (Central Compartment), Figure 2(b) (Peripheral Compartment) and Figure 5(a) (Actual and Simulated data in Central Compartment). For Subject 2, Figure 3(a) (Central Compartment), Figure 3(b) (Peripheral Compartment) and Figure 5(b) (Actual and Simulated data in Central Compartment) are plotted. Also, plotted for Subject 3 in Figure 4(a) (Central Compartment), Figure 4(b) (Peripheral Compartment) and Figure 5(c) (Actual and Simulated data in Central Compartment). During the first hour after oral administration of digoxin, a peak was

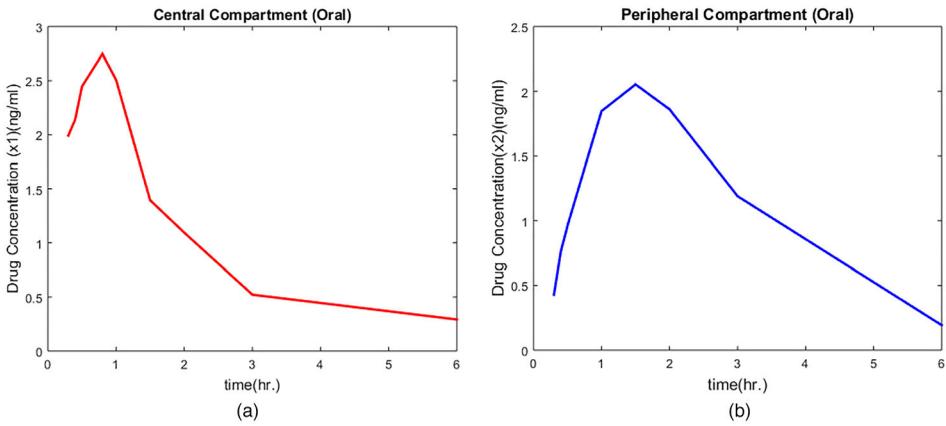


Figure 3. Subject 2: Digoxin concentration in the central compartment (a) and peripheral compartment (b) after oral administration of 500 µg.

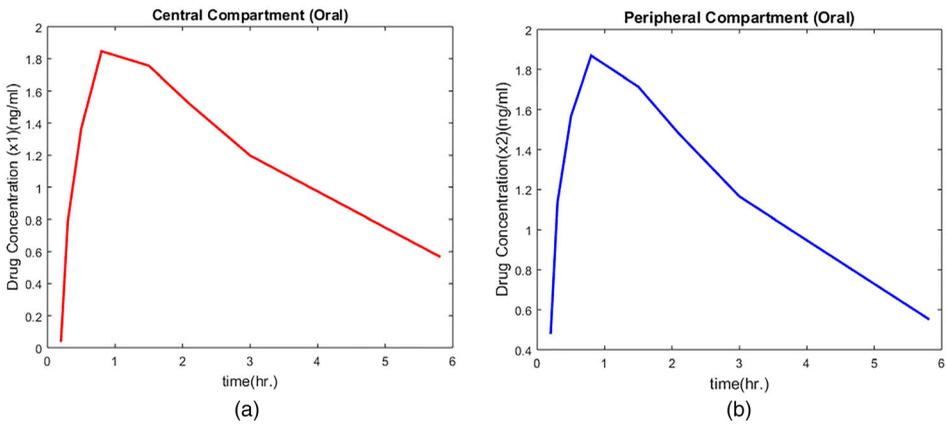


Figure 4. Subject 3: Digoxin concentration in the central compartment (a) and peripheral compartment (b) after oral administration of 500 µg.

found in all the three subjects and the same is illustrated in Figure 2(a). and Figure 3(a). In Subject 1 it takes 0.2 h to reach the high concentration of 9.3435 ng/ml whereas, in Subject 2 and Subject 3 it takes 0.8 h to reach the high concentration of 2.7466 ng/ml and 1.8467 ng/ml, respectively. However, within 1.5 h the digoxin concentration falls to 1.8801 ng/ml and 1.3948 ng/ml for Subject 1 and Subject 2, respectively and also within 2.1 h the digoxin concentration falls to 1.5208 ng/ml for Subject 3. The rate of disintegration of digoxin is very slow after 1.5 hours in both Subject 1 and Subject 2, whereas in Subject 3 it is slow down after 2.1 h. It takes almost 6–7 h to reduce from 1.8801 ng/ml to 0.5645 ng/ml in Subject 1 and 1.3948 ng/ml to 0.2921 ng/ml in Subject 2 also, in Subject 3 it reduces from 1.5208 to 0.5701 ng/ml. In the peripheral compartment of three subjects, the digoxin concentration quickly raises in the span of 1–1.5 h, then slowly decreases in the next 4.5 h. More clearly, the digoxin concentration of Subject 1 in the peripheral compartment (Figure 2(b)) increases from 1.8881 to 11.6384 ng/ml in the span of 1.5 h and takes 4.8 h to reduce 7.1440 ng/ml. In Subject 2, the digoxin concentration in the peripheral

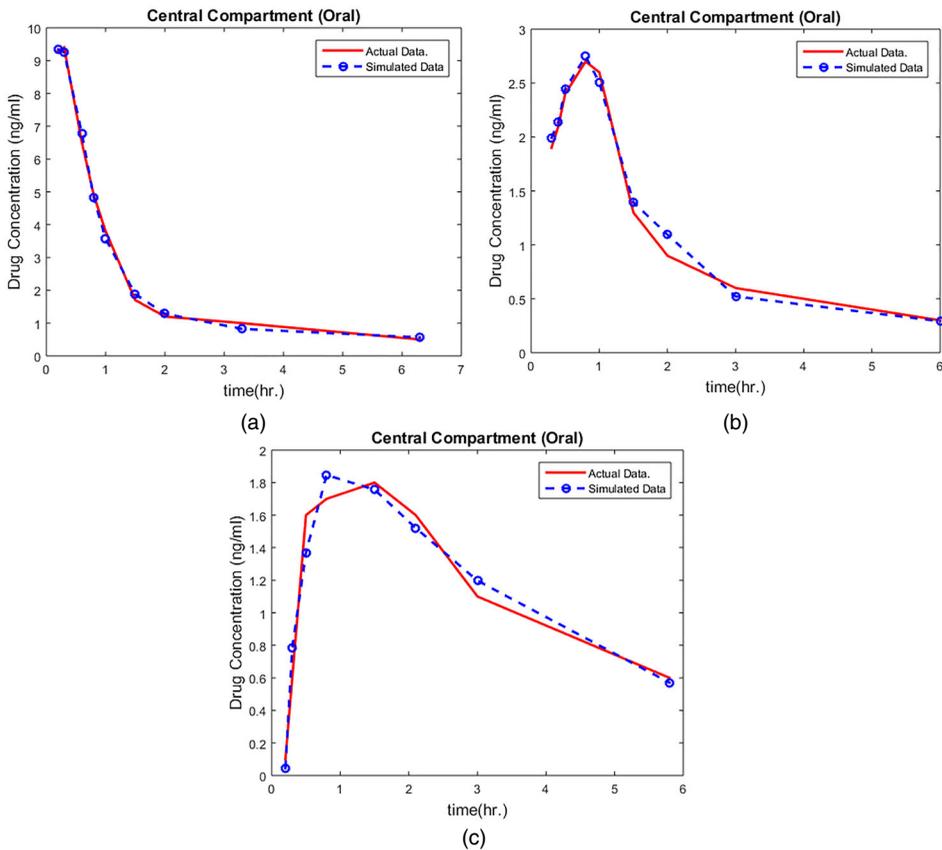


Figure 5. Simulated and actual digoxin concentrations in the central compartment of Subject 1 (a), Subject 2 (b) and Subject 3 (c) after oral administration of 500 μg .

compartment (Figure 3(b)) increases from 0.4293 to 2.0535 ng/ml in 1.5 h and takes 4.5 h to reduce 0.1936 ng/ml. However, in Subject 3, the digoxin concentration in the peripheral compartment (Figure 4(b)) increases from 0.4845 to 1.8689 ng/ml in 0.8 h and takes 5.8 h to reduce 0.5548 ng/ml.

3.2. Results – intravenous administration

The pharmacokinetic parameters in Table 7 are determined using the method of residuals for an individual, the amount of drug remaining in the central and peripheral compartments is calculated using Equations (20) and (21). The pharmacokinetic data for

Table 7. Parameters and RMSE of C. J., T. F. and W. S.

Parameters	C. J.	T. F.	W. S.
k_{12}	2.8421	8.0646	2.8366
k_{20}	2.7418	3.1652	3.3874
k_{21}	3.3865	4.1291	3.3513
RMSE	0.4993	0.4950	0.9543

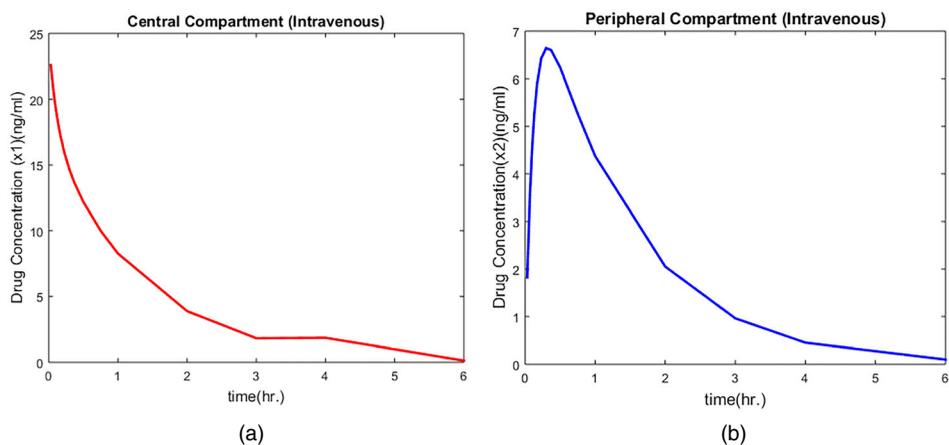


Figure 6. C. J.: Digoxin concentration in the central compartment (a) and peripheral compartment (b) after intravenous administration of 1 mg.

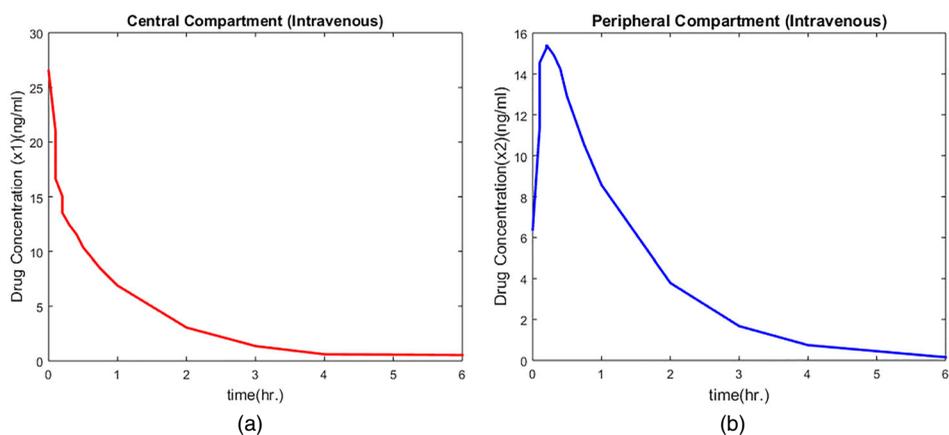


Figure 7. T. F.: Digoxin concentration in the central compartment (a) and peripheral compartment (b) after intravenous administration of 1 mg.

digoxin are calculated in subjects C.J. and T.F. Simulated and actual digoxin concentrations in the central compartment of subjects C.J. and T.F. are given in Table 8 and plotted for C. J. in Figure 6(a) (Central Compartment), Figure 6(b) (Peripheral Compartment) and Figure 9(a) (Actual and Simulated data in Central Compartment), also plotted for T.F. in Figure 7(a) (Central Compartment), Figure 7(b) (Peripheral Compartment) and Figure 9(b) (Actual and Simulated data in Central Compartment). When an intravenous dose of digoxin is administered, the digoxin enters directly into the central compartment. It can be seen that digoxin concentration of the central compartment declines rapidly during the initial distribution phase, while digoxin amount in the peripheral compartment equilibrates more slowly in C.J., T.F. and W.S. The digoxin concentration in the central compartment of C.J. (Figure 6(a)), T.F. (Figure 7(a)) and W.S. (Figure 8(a)) decreases rapidly within 1 h from 22.58 to 8.26 ng/ml, 26.50 to 6.88 ng/ml and 21.56 to 5.48 ng/ml, respectively. In the next 6 hours, the concentration of digoxin slowly decreases to 0.12 ng/ml,

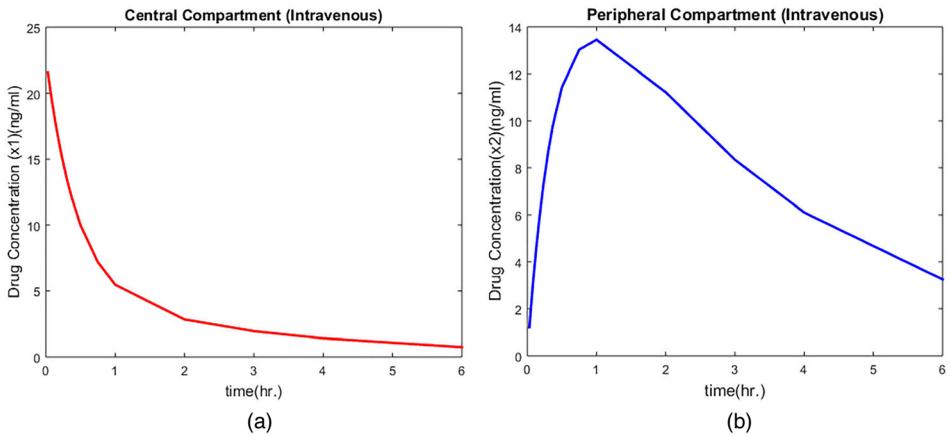


Figure 8. W. S.: Digoxin concentration in the central compartment (a) and peripheral compartment (b) after intravenous administration of 1 mg.

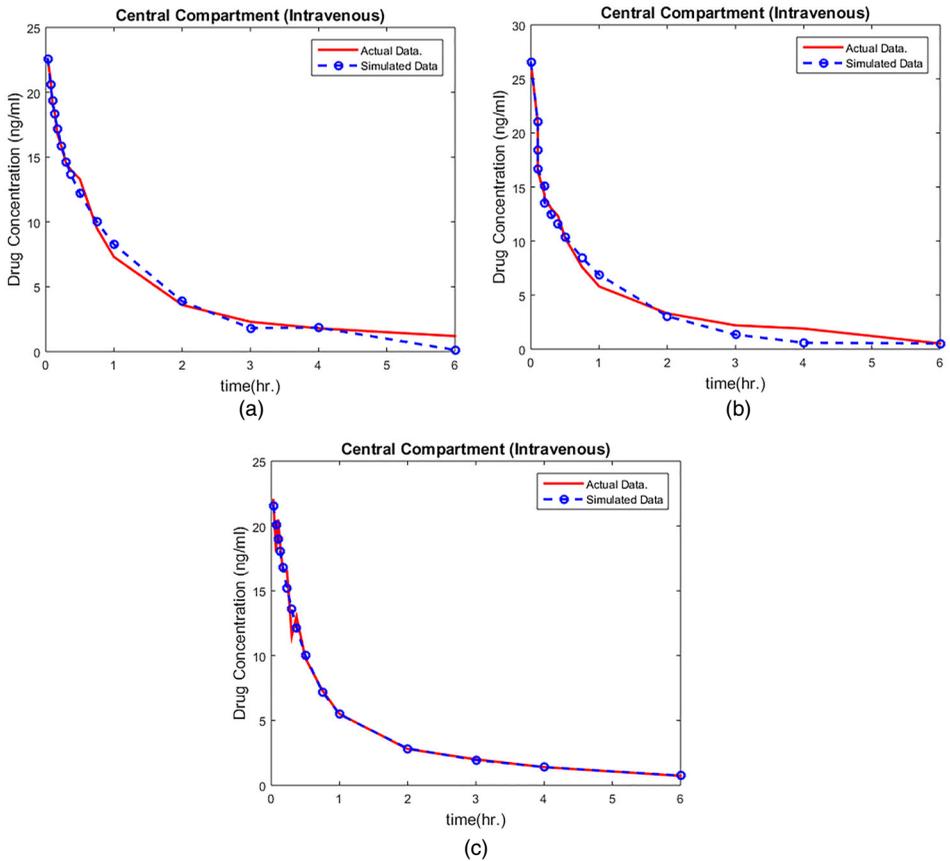


Figure 9. Simulated and actual digoxin concentrations in central compartment of C. J. (a), T. F. (b) and W. S. (c) after intravenous administration of 1 mg.

Table 8. Simulated and actual digoxin concentrations in the central compartment of C. J., T. F and W. S.

C.J./Age: 24/Weight: 75															
Time (hr.)	0.03	0.07	0.10	0.13	0.17	0.23	0.30	0.37	0.50	0.75	1.00	2.00	3.00	4.00	6.00
Actual (ng/ml)	22.5	21.0	19.0	18.5	16.8	15.8	14.5	14.0	13.3	9.5	7.3	3.6	2.3	1.8	1.2
Simulated (ng/ml)	22.58	20.56	19.35	18.32	17.19	15.84	14.62	13.64	12.18	10.00	8.26	3.87	1.81	1.85	0.12
T.F./Age: 26/Weight: 72.7															
Time (hr.)	0.03	0.07	0.10	0.13	0.17	0.23	0.30	0.37	0.50	0.75	1.00	2.00	3.00	4.00	6.00
Actual (ng/ml)	26.5	21.0	18.8	16.5	14.3	14.0	13.0	12.3	10.3	7.6	5.8	3.3	2.2	1.9	0.52
Simulated (ng/ml)	26.50	21.04	18.45	16.66	15.04	13.54	12.42	11.60	10.37	8.44	6.88	3.03	1.34	0.59	0.51
W.S./Age: 28/Weight: 77.3															
Time (hr.)	0.03	0.07	0.1	0.13	0.17	0.23	0.3	0.37	0.5	0.75	1	2	3	4	6
Actual (ng/ml)	22	18	20.5	18.5	16.5	16.5	11.5	13	9.8	7.3	5.5	2.8	2	1.4	0.73
Simulated (ng/ml)	21.56	20.06	19.02	18.04	16.83	15.21	13.56	12.14	9.99	7.19	5.48	2.84	1.95	1.41	0.75

0.51 ng/ml and 0.75 ng/ml in C.J., T.F. and W.S, respectively. However, the digoxin concentration of the peripheral compartment in C.J. (Figure 6(b)) increases rapidly from 2.58 ng/ml and reaches the peak 8.98 ng/ml within 0.3 h then it starts decreasing and reaches to 3.38 ng/ml in 2 h and it equilibrates. It takes 6 h to reach 0.28 ng/ml. The digoxin concentration of the peripheral compartment in T.F. (Figure 7(b)) increases quickly from 1.83 ng/ml and reaches the highest point 6.64 ng/ml in 0.3 h and declines to 2.06 ng/ml in 2 h then slowly decrease to 0.10 ng/ml in 6 h. Also, the digoxin concentration of the peripheral compartment in W.S. (Figure 8(b)) increases quickly from 1.21 ng/ml and reaches the highest peak of 13.45 ng/ml in 1 h then slowly decreases to 3.25 ng/ml in 6 h.

4. Conclusion

In this present study, we develop a two-compartment model and consider digoxin drug administration through oral (*p.o.*) and intravenous (*i.v.*) to four volunteers. *Kramer et al* considered a two-compartmental model with excretion from the central compartment and describes the time course of drug concentration in the central compartment model after an intravenous injection, whereas the authors considered excretion from the peripheral compartment for both the oral and intravenous injection. The solution curves for clinical data and model were drawn using MATLAB. In this two-way cross-over study it was noted that the digoxin concentration in the central compartment after oral administration, our model-simulated data almost coincide with the available clinical data (Table 1) with RMSE 0.1697 (Subject 1), 0.0974 (Subject 2) and 0.1282 (Subject 3) which we can see from Figure 4 to Figure 10 of each subject. Also, after the intravenous administration, the data simulated by our model almost coincide with the available clinical data (Table 2) with RMSE 0.4993 (C.J.), 0.4950 (T.F) and 0.9543 (W.S.) which we can see from Figure 13 to Figure 19 of each subject. Eventually, our model predicts the measures of the drug concentration in the peripheral compartment for any given time in both *p.o.* administration and *i.v.* administration. Also, we were unable to demonstrate any significant relationship between digoxin doses of 500 µg and 1 mg administered through oral and intravenous respectively and the parameters k_{12} , k_{21} , k_{31} and k_{20} . This supports the observation that the pharmacokinetics of digoxin when given through oral and intravenous, are independent of dose. Also, there is no significant relation between pharmacokinetic parameters and RMSE of each subject in both the administrations. When we are using a non-linear compartment model

in pharmacokinetics, the general approach is to use ODEs. Furthermore, stochastic differential equations (SDEs) are achieved by adding a Wiener noise component. This extra noise permits handling of auto-correlated residuals originating from natural variation or a systematic model error. Auto-correlated residuals are often partly ignored in pharmacokinetic modelling although it violates the hypothesis for many standard statistical tests (Klim, Mortensen, Kristensen, Overgaard, & Madsen, 2009). Since a curved pattern occurs in the residual plots for the deterministic minimal model a stochastic approach could decrease this curve pattern and give more accurate results.

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