ISTEK
p-ISSN: 1979-8911
Volume 13 Number 1 | June 2024: 1-6

Analytical Solutions of Single Dose Drug Models with Injection Administration: Literature Review

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Article Info

Article history:

Received April 02, 2024
Revised May 26, 2024
Accepted June 24, 2024

Keywords:

Analytical solution
Single-compartment pharmacokinetic model
Michaelis-Menten,
Endogenous production
Lambert W function
X function

ABSTRACT

This literature review aims to explore the development of the Single Dose Injection Models by finding their Analytical Solutions. The most well-known single-compartment pharmacokinetic model with first-order elimination was developed by Tang & Xiao in 2007, where the elimination part is modified by the Michaelis-Menten kinetics. Years later, in 2015 Wu, Li, & Nekka developed the model by considering simultaneous elimination and drug distribution in the body, and then they modified the more complex model by incorporating endogenous production in 2018. These three models employ differential equations to depict changes in drug concentration, and not only utilize the Lambert W function, but the models also introduce the X function to obtain the analytical solutions. The results are expected to provide a deeper understanding of drug dynamics in the body and to serve as a basis for further research and clinical applications in pharmacokinetics as well as to offer deeper insights into drug delivery within the human body.

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1. INTRODUCTION

Since ancient times, humans have used mathematics to model natural phenomena such as the movement of planets and other celestial bodies. However, the use of mathematics to model various other phenomena only began to rapidly develop in the 20th century [7].

Mathematical modeling helps in solving complex problems and provides useful information for decision-making. Through mathematical modeling, predictions about the behavior of a system in various situations can be made, the impact of changes on the system can be estimated, and understanding of complex phenomena or problems can be enhanced.

In the book "A First Course in Mathematical Modeling," Giordano & Perrier (2003) explain the stages of mathematical modeling: identifying and defining the problem, creating a mathematical model, testing the model's accuracy with empirical data or valid alternative models, using the validated model for simulation and prediction, and making decisions based on simulation results that align with initial goals and available empirical data.

Initially, mathematical modeling was primarily used by scientists and engineers in the fields of engineering and science. Over time, its use has expanded to various other fields, including the medical field, particularly pharmacokinetics. Pharmacokinetics studies the movement of drugs within the body from administration to excretion [6]. The pharmacokinetic process involves the absorption, distribution, metabolism, and elimination of drugs [6][19][5].

There are several ways to administer drugs into the body: Two of them are given extravascularly by oral and intravascularly by injection of infusion. Some researchers have investigated drug dynamics through these two routes by finding the solutions [12][17] as well as estimating the parameters that affect directly the dynamics [22][23][24].

Many studies have focused on drug elimination using mathematical models [6][10][12]. However, few have addressed drug metabolism within the body's organs. Metabolism often requires enzyme activation, with Michaelis-Menten kinetics as an important concept introduced by Michaelis and Menten (1913). This concept explains the relationship between enzyme reaction rate and

substrate concentration and is crucial in pharmacokinetic studies for understanding drug metabolism by liver enzymes that affect drug effectiveness and potential side effects [14][1][16][8].

The elimination process often follows first-order kinetics, where the elimination rate is proportional to the amount of drug in the blood [11]. Mathematical models are used to predict and understand changes in drug concentration in the body over time after dose administration.

This literature review aims to explore the development of a single-dose injection model to assist in the formulation of more effective and safer dosing strategies. The scope of this study is limited to the pharmacokinetics of single-dose administration, assuming the body as a homogeneous unit with constant endogenous production, without considering the influence of circadian rhythms. This also investigates the single-dose injection model with endogenous production and simultaneous first-order elimination and Michaelis-Menten kinetics based on three primary studies: articles written by Tang & Xiao (2007), by Wu, Li, & Nekka (2015), and by Wu, Nekka, & Li (2018).

2. INJECTION COMPARTMENT MODEL

Pharmacokinetics compartment models of drug delivery in the human body are mathematical models that describe the distribution and movement of a drug within the human body [6]. The models are crucial in understanding the processes of absorption, metabolism, distribution, and elimination of drugs, as well as predicting the toxic effects of a substance or compound in the human body. These models can also be used to develop effective and safe treatment strategies for patients.

One of the simplest compartment models is the single compartment model for which the body is considered as a single unit with homogeneous characteristics. For instance, organs or tissues responsible for drug elimination are assumed to have the same blood flow rate [6].

When a drug is administered by injection, it enters the bloodstream without absorption processes, the drug is directly distributed within the body, and eliminated following a first-order reaction process [6]. Mathematically, the rate of change of drug concentration in the blood when the drug is administered by injection can be modeled as

$$\frac{dC}{dt} = -kC, \tag{2.1}$$

with the initial condition

$$C(0) = \frac{D}{V}, \tag{2.2}$$

where C is the drug concentration in the blood plasma that depends on time t, D is the dose of the drug given, V_d is the volume of drug distribution in the body, and k is the constant rate of drug elimination. By using the separation of variables in the equation and using the initial condition given in (2.2), the solution of (2.1) can be obtained as

$$C(t) = \frac{D}{V_d} e^{-kt} \tag{2.3}$$

3. SINGLE DOSE INJECTION MODELS

This section further discusses the model reviews of Single doses when the drug is given by injection. Initially, it only considered metabolism within the body, then it was further developed to consider the distribution of the drug within the body. Subsequently, it was expanded to consider the presence of endogenous substances naturally produced in the body.

3.1. The Model with Michaelis-Menten Drug Elimination

Wagner (1973) conducted extensive research on evidence of nonlinearity in pharmacokinetics (the phenomenon where changes in drug dosage do not result in proportional changes in drug concentration within the body), including drug metabolism and renal excretion. He also considered the nature of the Michaelis-Menten equation and conducted simulations to illustrate it. Several compartmental models have been used in recent studies to fit Michaelis-Menten parameters, including phenomena in single-dose response data [15].

Tang and Xiao (2007) modeled a single-compartment model with Michaelis-Menten elimination and drug administration with a single dose (D) given impulsively at time t_0 (drug administration

occurs in a very short period, and there is no change in dosage during the observation time, $\boldsymbol{t_0 = 0}$, concentration for $\boldsymbol{t > t_0}$ can be represented by the following differential equation:

$$\frac{dC(t)}{dt} = \frac{V_{max}C(t)}{K_m + C(t)}, \qquad C(t_0^+) = C(0) = \frac{D}{V_d}, \tag{3.1}$$

where $\boldsymbol{V_{max}}$ is the maximum rate of concentration change (in concentration units per time), $\boldsymbol{K_m}$ is the Michaelis-Menten constant (in concentration units), and $\boldsymbol{V_d}$ is the volume of drug distribution. To find the analytical solution of equation (3.1), the separation of variables method is used so that we gain,

$$\frac{1}{V_{max}}\left(K_m\left(\ln\left(\frac{D}{V_d}\right) - \left(\ln\left(C(t)\right)\right) + \frac{D}{V_d} - C(t)\right) = t - t_0. \tag{3.2}$$

The form of equation (3.2) has been extensively studied by Beal (1982). The results suggested that the solution of equation (3.1) can be solved analytically through several implicit functions, and in his study, there is also a table to calculate $C(t)$ for given values of t. Thus, equation (3.2) is not a fully analytical solution of equation (3.1) and is not a solution to compute continuous solutions for specific time intervals. However, the analytical solution of equation (3.1) can be obtained with the definition and properties of the Lambert *W* function.

Before using the method to solve the model, we first write some properties of the Lambert *W* function. In the article written by Corless (1996), by definition, the Lambert *W* function (logarithmic product) is a multi-valued inverse function of the equation $\boldsymbol{f(z) = ze^z}$ or mathematically expressed as:

$$W(z) = f^{-1}(z) \; where \; f(z) = ze^z.$$

From this statement, we can conclude that

$$W\left(f(z)\right) = W(ze^z) = z.$$

and

$$f\left(W(z)\right) = W(z)\exp(W(z)) = z.$$

By this definition, we can proceed to find the analytical solution of equation (3.1) by using the exponential term to (3.2) and performing algebraic manipulations. we obtain

$$\frac{C(t)}{K_m}\exp\left(\frac{C(t)}{K_m}\right) = \left(\frac{C(0)}{K_m}\exp\left(\frac{C(0) - V_{max}(t - t_0)}{K_m}\right)\right). \tag{3.3}$$

Applying the Lambert *W* function, the analytical solution is obtained as

$$C(t) = K_m W\left(\frac{C(0)}{K_m}\exp\left(\frac{C(0) - V_{max}(t - t_0)}{K_m}\right)\right), \tag{3.4}$$

and the drug's half-life is given by:

$$t_{1/2} = \frac{K_m}{V_{max}}\ln(2) + \frac{1}{2V_{max}}C(0). \tag{3.5}$$

3.2. The Model with Simultaneous Elimination and Michaelis-Menten Kinetics

Tang and Xiao (2007) modeled a single-compartment injection model with Michaelis-Menten elimination kinetics in their research, as previously discussed. However, that model only considered drug metabolism at the injection site. This model needs to be further developed to provide more comprehensive information about drug kinetics in the body and assist in designing effective and safe drug dosages.

Wu, Li, and Nekka (2015) expanded the model by considering the elimination of the drug from the body through the kidneys or liver. Their research not only considered the kinetics of drug metabolism and the rate of drug absorption but also the distribution of the drug throughout the body via the circulatory system, which can be represented by the following differential equation:

$$V_d\frac{dC(t)}{dt} = -CL_l - \frac{V_{max}C(t)}{K_m + C(t)}, \tag{3.6}$$

With the initial condition

$$C(0^+) = \frac{D}{V_d} = C_0, \tag{3.7}$$

Noticing the inconsistency of the dimensions of the right and the left-hand side equation (3.6), we rewrite the equation as

$$\frac{dC(t)}{dt} = -\frac{CL_l}{V_d}C(t) - \frac{V_{max}C(t)}{K_m + C(t)}, \quad t > 0. \tag{3.8}$$

By using partial fraction decomposition and rearranging, we obtain:

$$\left(\frac{p1}{C(t)} + \frac{p2}{C(t) + \beta}\right)dC(t) = -dt, \tag{3.9}$$

where

$$p1 = \frac{1}{k_{el} + CL_{int}}, \quad p2 = \frac{CL_{int}}{k_{el}}\frac{1}{k_{el} + CL_{int}}, \; \beta = K_m\frac{k_{el} + CL_{int}}{k_{el}}. \tag{3.10}$$

Here $Kel = CL_l/V_d$ is the first-order elimination rate constant, and $CL_{int} = V_{max}/K_m$ represents the intrinsic clearance of Michaelis-Menten kinetics [9]. Then, $\boldsymbol{p1}$ represents the corresponding time for

the drug to be eliminated, and $\boldsymbol{p2}$ is the same as $\boldsymbol{p1}$, but considering the ratio of intrinsic clearance of Michaelis-Menten kinetics ($\boldsymbol{CL_{int}}$) and the first-order elimination rate constant ($\boldsymbol{_{Kel}}$). Meanwhile, $\boldsymbol{\beta}$ is a concentration obtained by multiplying the Michaelis-Menten constant ($\boldsymbol{K_m}$) by a fraction involving the first-order elimination rate constant ($\boldsymbol{k_{el}}$) and the intrinsic clearance of Michaelis-Menten kinetics ($\boldsymbol{CL_{int}}$).

By integrating equation (3.9) from time $\mathbf{0}^+$ to time t, we obtain:

$$\boldsymbol{C(t)^{p1}(C(t)+\beta)^{p2} = (C_0)^{p1}(C_0+\beta)^{p2}\exp(-t)}. \qquad \textbf{(3.11)}$$

Equation (3.11) is a transcendental equation (a type of equation that is difficult to solve using conventional methods). The solution to this equation cannot be easily expressed. However, to help find the solution to this equation, Wu, Li, and Nekka (2015) introduced a new function called the X function, inspired by the Lambert W function. This function has been used in cases of Michaelis-Menten elimination pathways. By using this function, the solution to the equation can be found more easily and efficiently.

Definition 1: $X(t,p,q)$ is defined as the solution to the following equation:

$$\boldsymbol{(X(t,p,q))^p \cdot \big(X(t,p,q)\big)^q = t}, \qquad \textbf{(3.12)}$$

where $\boldsymbol{p > 0}$ and $\boldsymbol{q \geq 0}$ are given constant. The left-hand side of equation (3.12) has the form $\boldsymbol{f(x,p,q) = x^p(1+x)^q}$ which is positive and monotonically increasing for $\boldsymbol{x > 0}$ ensuring that $\boldsymbol{X}$ is a well-defined function. Additionally, its derivative is given by:

$$\boldsymbol{\frac{d}{dt}X(t,p,q) = \frac{1}{t}\left(\frac{p}{X(t,p,q)} + \frac{q}{1+X(t,p,q)}\right)^{-1} > 0}.$$

This indicates that the function X is smooth and strictly increasing for $t > 0$. In this review, the function X is used to find a closed-form solution of equation (3.8).

Returning to the previous problem, by dividing both sides of equation (3.11) by $\boldsymbol{\beta^{p1+p2}}$ we obtain:

$$\boldsymbol{\left(\frac{C(t)}{\beta}\right)^{p1}\left(\frac{C(t)}{\beta}+1\right)^{p2} = \left(\frac{C_0}{\beta}\right)^{p1}\left(\frac{C_0}{\beta}+1\right)^{p2}\exp(-t)}. \qquad \textbf{(3.13)}$$

Using the function X, the solution to the Single Compartment Injection Model with Simultaneous Elimination and Michaelis-Menten Elimination Kinetics is as follows:

$$\boldsymbol{C(t) = \beta \cdot X\left(\left(\frac{C_0}{\beta}\right)^{p1}\left(\frac{C_0}{\beta}+1\right)^{p2}\exp(-t), p1, p2\right),\ t > 0}, \qquad \textbf{(3.14)}$$

where $\boldsymbol{C_0 = D/V_d}$ and $\boldsymbol{p1, p2, \beta}$ are as defined in equation (3.10).

3.3. The Model with Endogeneous Production Simultaneous First-Order and Michaelis-Menten Elimination

Exogenous and endogenous substances refer to the source or origin of a substance in the human body. Exogenous substances are those originating from outside the human body, such as food, beverages, inhaled air, or externally administered drugs. For example, drugs consumed to treat diseases are exogenous substances [4].

Endogenous substances are those naturally produced within the human body by organs or internal biological processes, such as the insulin hormone produced by the pancreas. Endogenous production can occur in response to internal or external stimuli, involving various biochemical processes in the body [4].

In some cases, drugs administered from outside the body (exogenous) can also be naturally produced by the body (endogenous). This means that externally administered drug substances may also exist in the body as a result of natural production and be eliminated through parallel pathways. Indeed, elimination may involve first-order processes typically through the kidneys, in a manner proportional to drug plasma concentration, accompanied by nonlinear Michaelis-Menten kinetics, most likely due to metabolism mediated by the drug or internalization [4].

In this regard, Wu, Li, and Nekka (2018) further developed their previous model by considering the presence of endogenous substances within the body, assuming that the endogenous production of drug substances occurs at a constant rate, denoted by r_{prod} if circadian effects (influence of daily biological rhythms, such as sleep patterns, body temperature, blood pressure, and hormone production) can be neglected. This can be modeled by the following differential equation

$$\frac{d}{dt}C(t) = r_{prod} - k_{el}C(t) - \frac{1}{V_d}\frac{V_{max}C(t)}{K_m+C(t)},\ t > 0. \qquad \textbf{(3.15)}$$

Like in the previous section, the inconsistency of the dimension of the right and left-hand sides in equation (3.15) is found, so we rewrite it as

$$\frac{d}{dt}C(t) = r_{prod} - k_{el}C(t) - \frac{V_{max}C(t)}{K_m+C(t)}, t > 0, \qquad \textbf{(3.16)}$$

with

$$C(0^+) = C_{hs} + {}^{D}/_{V_d} = C_0 \quad at \quad t = 0^+, \tag{3.17}$$

where $_{Kel}, V_{max}, K_m, V_d, D$ are as defined previously, and C_{hs} has the form

$$C_{hs} = \left(\frac{1}{2}\left(\frac{r_{proud}}{k_{el}} - C_\beta + \sqrt{\left(\frac{r_{proud}}{k_{el}} - C_\beta\right)^2 + 4\frac{r_{proud}}{k_{el}}K_m}\right)\right). \tag{3.18}$$

That denotes the initial concentration calculated from the system at homeostasis conditions (the body in a constant state).

It should be noted that the initial concentration can be estimated before drug administration. When $r_{proud} = 0$, the current model reverts to the model with simultaneous first-order and Michaelis-Menten elimination studied in the previous discussion. Additionally, the concentration value immediately after drug administration is referred to as the concentration at time zero (Equation (3.17)).

To find the solution to this model, we can first use partial fraction decomposition. Since a single dose is added to the system, it is obtained that $C(t) > C_{hs}$, so Equation (3.16) can be modified to:

$$\left(\frac{p}{C(t)-C_{hs}} + \frac{q}{C(t)+C_\beta^{en}}\right) dC(t) = -dt, \tag{3.19}$$

where

$$p = \frac{1}{k_{el}}\frac{C_{hs}+K_m}{C_{hs}+C_\beta^{en}}, \qquad q = \frac{1}{k_{el}}\frac{C_\beta^{en}-K_m}{C_{hs}+C_\beta^{en}}, \qquad C_\beta^{en} = C_{hs} - \frac{r_{proud}}{k_{el}} + C_\beta. \tag{3.20}$$

The notation p and q are the coefficients that determine the drug elimination time, and k_{el} is the elimination constant, which is the rate at which the drug is eliminated from the body. Furthermore $_{en}, C_\beta$ is the drug concentration obtained by subtracting the initial concentration calculated from the system at homeostasis (C_{hs}) with the endogenous production of the drug occurring at a constant rate (r_{prod}) divided by the elimination constant (k_{el}), then added to C_β (β as discussed previously). Integrating Equation (3.19) from 0^+ to t and using exponential term, yields

$$(C(t) - C_{hs})^p \left(C(t) + C_\beta^{en}\right)^q = (C_0 - C_{hs})^{\,p} \left(C_0 + C_\beta^{en}\right)^q \boldsymbol{e^{-t}}. \tag{3.21}$$

By dividing both sides of the equation by ($C_{hs} + C_\beta^{en}$), we obtain

$$\left(\frac{C(t)-C_{hs}}{C_{hs}+C_\beta^{en}}\right)^p \left(\frac{C(t)-C_{hs}}{C_{hs}+C_\beta^{en}} + 1\right)^q = \left(\frac{C_0-C_{hs}}{C_{hs}+C_\beta^{en}}\right)^p \left(\frac{C_0+C_\beta^{en}}{C_{hs}+C_\beta^{en}}\right)^q \boldsymbol{e^{-t}}. \tag{3.22}$$

The closed-form solution of the single dose injection model with endogenous production and simultaneous first-order and Michaelis-Menten elimination can be obtained using the X function and applying the initial conditions from Equation (3.17) as follows

$$C(t) = C_{hs} + \left(C_{hs} + C_\beta^{en}\right) \cdot X\left(\left(\frac{{}^{D}/_{V_d}}{C_{hs}+C_\beta^{en}}\right)^p \left(\frac{{}^{D}/_{V_d}}{C_{hs}+C_\beta^{en}} + 1\right)^q e^{-t}, p, q\right), \quad t > 0. \tag{3.23}$$

4. CONCLUSION

This literature review given in this paper has successfully described the three models and their analytical solutions. The models started from the simplest model with the first-order drug elimination, then progressed into the more complex model: First considering only metabolism occurs within the body, then further developed by also considering the drug distribution, and last, by taking into account the endogenous substances that are produced by the body.

The paper has explored the closed-form analytic solutions of the models, encompassing aspects of simultaneous elimination and endogenous production. The Lambert W function has an important role in obtaining the analytical solutions for the Michaelis-Menten elimination model, while the X function has been introduced to find the closed-form solutions in the more complex models, that is when simultaneous elimination is assumed to occur as well as when the endogen production is assumed to appear.

Finally, this study is expected to enhance the understanding of drug dynamics through the solution of the model and hopefully provide useful analytical tools for evaluating dosing strategies in future medical treatments. The models given in this paper as well as the solutions can serve as a foundation for further research and clinical applications in pharmacokinetics and offer deeper insights into drug delivery within the human body.

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