Pharmacokinetic of Oral Drug Absorption using Modified Compartmental Absorption and Transit Model in Small Intestine

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Abstract. The compartment analysis and transit (CAT) model to predict oral drug absorption is presented by Yu and co-author. The transit equation in the small intestine of the CAT model is a linear equation. In this research, the transit equation in the small intestine of our present model is a nonlinear equation. Therefore, we included a nonlinear factor in the transit equation of small intestine seven compartment. To modify the small intestine equation, the first and fourth to seventh compartment equations are made nonlinear, while the second and third compartments are twice from the initial model. The prediction of plasma drug concentration was adjusted with secondary data so that the parameters used were the time of gastric emptying and the microscopic rate constant for each dose of drug that is atenolol. The accuracy of the deterministic coefficient ($R^2$) results will be used to compare between our present model and the CAT model. The equation is made nonlinear as it is close to the gastric organs so the calculated amount of mass absorbed in the small intestine. The results of deterministic coefficients to atenolol for dose masses 25, 50 and 100 mg were above 90% for this present model. The $R^2$ value of between experimental and the modified CAT model time courses are above 90% indicates the modified CAT model results are good agreement.

1. Introduction
The most important part of pharmaceutical sciences is the pharmacokinetics. It bridges the gap between the fundamental and applied sciences, especially the clinical application of drugs and the pharmaceutical industry. Many conventional formulations of orally administered drugs are already absorbed during their passage through the small intestine, due to its anatomical location right after the stomach. The small intestine is the important site of drug absorption. It is composed by one duodenum, two jejunum, and four ileum [1].

After the release of the drug from the dosage form in the stomach, several different processes of the absorption of drugs in the small intestine fluids are dissolution, degradation, adsorption or complex binding of the drug. The first step in the absorption process of a drug is the release and dispersion of the solid dosage form in the small intestine fluids. In this process, an administered drug of the solid dosage form is disintegrated physically as well as forming of the drug powder. These mechanism processes are not easily described using mathematical models to predict absorption, due to the physical disintegration from the dosage compound form is commonly assumed to be fast[2]. Moreover, the complex process of oral absorption in most drugs is administered orally that is
difficult to predict. Because of this complexity, a simulation of the pharmacokinetic model has developed as a tool to incorporate these different processes in an attempt to mechanistically capture the process of oral drug absorption. To predict the pharmacokinetic behavior of oral drugs in the human body, the small intestine is characterized as a series of compartments through which the drug transits and absorbs [3]. Several different processes of the absorption of drugs in the small intestine fluids also depend on gastrointestinal pH, volume, transit time and morphology [4].

Yu and co-author proposed the CAT model using many couple first-order ordinary differential equation that the mathematical model can easily simulate to predict absorption of oral drugs in the human body. These processes of oral drug passing through the small intestine fluids were described as transit and absorb through a linear of compartments. In this model, each compartment may have linear transfer kinetics, different volume, and flow-rates, but it has the same transit rate constant. However, this model assumed that the compartment of stomach and colon cannot either absorb nor degradable, although just minor absorption from an oral drug. Due to the transit time in a small intestine is independent of drug dosage forms, gender, age, body weight and the presence of food. The small intestine was proposed in seven compartments that gave the smallest error between the cumulative percentage of the small intestine transit time and the predicted results. Therefore, seven compartments were determined to be the best compartmental model to present the small intestine transit process and then the seven compartment model was calculated as the compartmental transit model thereafter. The compartment transit times in the duodenum, jejunum, and ileum are 14.71 and 114 min, respectively [5].

The CAT model was applied to obtain absorption data in vivo as well as in vitro. This data has been shown to be a useful tool to evaluate potential controlled-release drug candidates. The simulation results of this model can be used to optimize existing formulations as well as the development of new dosage forms for therapeutic agents. This model also can be directly formed to relate between pharmacokinetic models and predict plasma concentration profiles. The advantage of this model can be used to design the controlled-release delivery systems and to investigate the effect of physicochemical properties (such as compound solubility and permeability), physiological properties (including the pH environment and metabolic enzymes in the gastrointestinal tract) and dosage form variables on the oral drug absorption [5, 6].

However, the CAT model inappropriately explains the experimental results. This implies that the model needs to be refined and also the model assumptions have not been met. One source of incompatibility is not all compartmental models of the small intestine in processes of the oral kinetics rate that occur in oral absorption phenomena is non-homogeneous. In other words, the compartmental analysis can include not non-homogeneous phenomena in the compartment of the small intestine. The focus of this research is the development of the small intestine model, especially to obtain a set of differential equations describing non-homogeneous mechanisms. Non-homogeneous compartmental analysis can be applied to model the system transit. In this present study, non-homogeneous compartmental analysis can be implied to remodel the linear compartment to the non-linear compartment in the CAT model. The coefficient of determination, $R^2$, is used to calculate parameter estimation of the best-fit curve between simulation results and the experimental data.

2. Mathematical Modelling

2.1. Compartmental Absorption and Transit Model

The transit flow in the stomach, duodenum, jejunum, ileum, and colon and also the passive absorption in the duodenum, jejunum, and ileum can be calculated using the CAT model. The gastrointestinal tract in the CAT model is divided into three segments: stomach, small intestine, and colon. The human small intestine transit flow can be described by seven compartments, where a drug transfers from one compartment to the next one is presented by a linear first-order ordinary differential equation. In the linear CAT model, the transit flow of the colon was not considered, due to the colon is considered only
as a reservoir. The linear CAT model assumptions that were proposed: (1) drug absorption from the small intestine was more significant compared with that from the stomach and colon; (2) the small intestine transit and absorption in the small intestine membrane were passive; (3) dissolution was very fast, so this process was ignored; and (4) an oral drug moving through the small intestine can be viewed as a process flowing through a series of segments, each described by a single compartment with linear transfer kinetics from one to next, and all compartments may have different volumes and flow rates, but have the same transit times. Therefore, the absorption and transit in the gastrointestinal tract, for a non-degradable drug dosed in an immediate release dosage form, can be depicted as follows [6]:

1) The equation in the stomach,

\[
\frac{dM_s}{dt} = -k_s M_s, \quad \text{where } k_s = \frac{1}{T_{ge}}.
\]  

2) Equation in the small intestine,

\[
\begin{align*}
\frac{dM_1}{dt} & = k_s M_s - k_t M_1, \\
\frac{dM_2}{dt} & = k_t M_1 - k_t M_2 - k_a M_2, \\
\frac{dM_3}{dt} & = k_t M_2 - k_t M_3 - k_a M_3, \\
\frac{dM_4}{dt} & = k_t M_3 - k_t M_4 - k_a M_4, \\
\frac{dM_5}{dt} & = k_t M_4 - k_t M_5 - k_a M_5, \\
\frac{dM_6}{dt} & = k_t M_5 - k_t M_6 - k_a M_6, \\
\frac{dM_7}{dt} & = k_t M_6 - k_t M_7 - k_a M_7,
\end{align*}
\]

where \( k_a = \frac{2}{P_{eff} \times R} \) and \( k_t = \frac{7}{T_{se}} \).

3) The equation in the colon,

\[
\frac{dM_c}{dt} = k_c M_c,
\]  

where \( T_{ge} \) is the time constant for gastric emptying, \( T_{se} \) is the time constant for stomach emptying, \( M_s \) is the amount of drug in the stomach, \( M_i \) is the amount of drug in the colon, \( M_n \) is the amount of drug in the \( n \)th compartment, \( r \) is the time and, \( k_s, k_t, \) and \( k_a \) are the rate constants of gastric emptying, small intestine transit, and intrinsic absorption, respectively. \( P_{eff} \) is the effective intestine permeability coefficient through a cylindrical intestine segment of radius \( R \). The intestine permeability \( (P_{eff}) \) is one of the key biopharmaceutical parameters that determine the rate and extent of intestinedrug absorption.
2.2. Modified Compartmental Absorption and Transit Model

In this work, the CAT model has been modified by assuming that the compartments of the small intestine are not always a linear function, but it is a nonlinear function. The proposed modified CAT model in this study is as follows:

\[
\frac{dM_1}{dt} = \frac{(K_r M_2^2 - K_r M_1^2)}{M_0} - K_a M_1, \quad (10)
\]

\[
\frac{dM_2}{dt} = K_r M_1 - K_r M_2 - 2K_a M_2, \quad (11)
\]

\[
\frac{dM_3}{dt} = K_r M_2 - K_r M_3 - 2K_a M_3, \quad (12)
\]

\[
\frac{dM_4}{dt} = (K_r M_3^2 - K_r M_4^2) \alpha x \frac{F}{M_0} - K_a M_4, \quad (13)
\]

\[
\frac{dM_5}{dt} = \left( K_r M_4^2 - K_r M_5^2 \right) \alpha x \frac{F}{M_0} - K_a M_5, \quad (14)
\]

\[
\frac{dM_6}{dt} = \left( K_r M_5^2 - K_r M_6^2 \right) \alpha x \frac{F}{M_0} - K_a M_6, \quad (15)
\]

\[
\frac{dM_7}{dt} = \left( K_r M_6^2 - K_r M_7^2 \right) \alpha x \frac{F}{M_0} - K_a M_7, \quad (16)
\]

where \( a = \frac{P_{eff} \cdot t_{ileum}}{t_{ileum}^2} = 0.0475 P_{eff} \), \( t_{ileum} = 1.9 \) hours and \( l_{ileum} = 400 \) cm. Notation \( F \) is a unit less ratio, \( 0 < F \leq 1 \), that compares the drug’s availability given in a non-oral route compared with the availability obtained when the drug is given by the oral route. \( F \) is also known as the fraction of dose that reaches the small intestine transit process. Frequently, the unit less ratio pharmacokinetics parameter \( F \) will be used to represent absolute bioavailability under steady-state conditions or for medications of chronic use.

The rate of drug absorption from the small intestine into the plasma is calculated by

\[
\frac{dM_a}{dt} = k_a \sum_{n=1}^{7} M_n, \quad n = 1...7, \quad (17)
\]

where \( M_a \) is the amount of drug absorbed.

2.3. Compartmental Pharmacokinetic Modelling

In compartmental pharmacokinetic modelling, tissues having similar kinetic drug concentration profiles are lumped together into a compartment. Three compartments model frequently can be justified to describe the kinetic concentration profile of a drug accurately. A common three-compartment model may have one compartment representing the blood/plasma and other tissues that reach their steady-state concentration very rapidly (< 3 hours) for a given dose. This compartment is commonly called the central compartment and usually contains such organs as the blood/plasma, kidney, lungs, liver, and most other large internal organs. The second compartment in this three-compartment model could be called shallow tissues; these tissues do not reach their steady-state concentration as rapidly as the central compartment but still reach steady-state somewhat quickly (3 to 8 hours). The shallow compartment might be organs such as muscle, eyes, and other smaller internal organs, as well as sometimes the skin. The third compartment consists of tissues that reach their steady-state concentration slowly; examples of the deep compartment are adipose tissue, brain, and sometimes skin tissues [6, 7].
The rate of the percent of dose absorbed from the small intestine into the plasma in the linear and nonlinear CAT model is calculated using (17). It can be easily related to any compartmental pharmacokinetic model. A linear and nonlinear compartment model with elimination from the central compartment was used by the pharmacokinetic model equations [6, 7]:

\[
\frac{dC_1}{dt} = \frac{1}{V_1} \frac{dM_{a}}{dt} - (k_{12} + k_{13} + k_{10})C_1 + k_{21}C_2 + k_{13}C_3
\]

(18)

\[
\frac{dC_2}{dt} = k_{12}C_1 - k_{21}C_2,
\]

(19)

\[
\frac{dC_3}{dt} = k_{13}C_1 - k_{31}C_3,
\]

(20)

where \(V_1\) is the volume of the central compartment 1, and \(C_1\), \(C_2\), and \(C_3\) are the plasma concentrations in compartments 1 (central compartment), 2 (shallow compartment), and 3 (deep compartment), respectively. Notation \(k_{12}\), \(k_{21}\), \(k_{13}\), \(k_{31}\), and \(k_{10}\) are the microscopic rate constants. The model equations were solved using the MATLAB software. The coefficient of determination, \(R^2\), is calculated from parameter estimates. The residuals between the best-fit curve and the experimental data are used:

\[
R^2 = \left(1 - \frac{X^2}{SST}\right) \times 100\%,
\]

(21)

where \(X^2\) and SST are:

\[
X^2 = \sum_{i=1}^{N} (y_{\text{exp}} - y_{\text{sim}})^2,
\]

(22)

\[
\bar{y} = \frac{\sum_{i=1}^{N} (y_{\text{sim}} + y_{\text{exp}})}{2N},
\]

(23)

\[
SST = \sum_{i=1}^{N} (y_i - \bar{y})^2,
\]

(24)

where \(y_{\text{exp}}\) is experimental data, \(y_{\text{sim}}\) is the simulation results of the nonlinear pharmacokinetic model equations and \(\bar{y}\) is the averaged data.

3. Result and Discussion

The simulation results are shown in Fig. 1-3. This simulation results of the nonlinear CAT based pharmacokinetic model was able to incorporate gastric emptying and predict plasma concentration profiles that is good compared the linear CAT. Due to the coefficient of determination value, \(R^2\), for plasma concentrations for these three doses of atenolol, is above 90%; this means that the nonlinear CAT model is good agreement with the experimental data compared than the linear CAT. This could be explained that the nonlinear transfer rates and nonlinear time-varying compartmental does occur in the small intestine, because of the assumption that the compartmental transit and absorption rate is not always a first-order process. In other word, the processes of small intestine compartmental model are
considered as consisting of compartments in the same location a different chemical form of the oral drug molecule administered. To model the compartmental, the compartmental model must include chemical reaction kinetics. Because of one source of nonlinear compartmental models is processes of chemical reaction kinetics that occur in small intestine cells. Traditional compartmental analysis cannot be applied to model chemical reaction kinetics, but the law of mass-balance allows us to obtain a set of differential equations describing mechanisms implied in such reactions [1].

The nonlinear compartmental models occur in several processes dealing with transport of oral drug materials across cell membranes that represent the transfers between compartments. The several processes of each small intestine compartments in the extracellular and intracellular spaces separated by membranes may be sufficiently distinct kinetically to act like nonlinear compartments.

Pharmacokinetics described the rate of absorption owing to simultaneous kinetic mixing of passive and active transit and absorption. The ratio pharmacokinetics parameter \( F \) represent absolute bioavailability under steady-state conditions. Bioavailability is made up of both extent and rate of absorption. Parameter \( F \) is also known as the fraction of dose that reaches the plasma concentrations in system central compartment. Hence, the rate of absorption tends to be more important in small intestine, then Eq. (10-16) add a bioavailability parameter.

Nonlinear pharmacokinetics simply means that the relationship between dose and the plasma concentrations in system central compartment is not directly proportional for all doses. In nonlinear pharmacokinetics, drug concentration does not directly proportional to doses that also known as dose-dependent kinetics.

Many time-dependent processes appear to be nonlinear, when the oral drug concentration is measured carefully relative to the time of dose. Therefore, to make mathematical model of dose-to-drug concentration relationship is easy and directly proportional to the dose, its used model is linear.
Figure 1. The CAT [6] and nonlinear CAT (present model) simulation results of plasma concentration profiles of atenolol at the 25 mg oral doses the coefficient of determination, $R^2$ is 78% and 92%, and red circle symbols represent the experimental data from Mason et al. [8].
Figure 2. The CAT [6] and nonlinear CAT (present model) simulation results of plasma concentration profiles of atenolol at the 50 mg oral doses the coefficient of determination, $R^2$ is 78% and 92%, and red circle symbols represent the experimental data from Mason et al. [8].
4. Conclusion

The nonlinear CAT model accurately describes the small intestinetransit and absorption process if the assumptions of the nonlinear compartment model and oral bioavailability kinetics are satisfied. This new first-order ordinary differential equations (10) - (16) can be used to determine the human small intestinepermability during the normal human drug absorption process. Its main results from the heterogeneity in the small intestinepermability of seven compartments produced by the variation in oral bioavailability. The $R^2$ value of between experimental and simulation time courses are above 90% indicates the simulation results are a good agreement.

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