# A compartmental absorption and transit model for estimating oral drug absorption

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## Abstract

This report describes a compartmental absorption and transit model to estimate the fraction of dose absorbed and the rate of drug absorption for passively transported drugs in immediate release products. The model considers simultaneous small intestinal transit flow and drug absorption. Both analytical and numerical methods were utilized to solve the model equations. It was found that the fraction of dose absorbed can be estimated by $F_a = 1 - (1 + 0.54\ P_{eff})^{-7}$, where $P_{eff}$ is the human effective permeability in cm/h. A good correlation was found between the fraction of dose absorbed and the effective permeability for ten drugs covering a wide range of absorption characteristics. The model was able to explain the oral plasma concentration profiles of atenolol. © 1999 Elsevier Science B.V. All rights reserved.

*Keywords:* Drug absorption kinetics; Fraction of dose absorbed; Permeability; Compartmental modeling

## 1. Introduction

Estimating intestinal drug absorption kinetics can greatly facilitate lead drug candidate selection and support formulation strategies. Quantitative and mechanistic approaches have been developed since the traditional approach to treat the entire gastrointestinal tract as a single-compartment 'black box' does not suffice (Ho et al., 1983; Dressman et al., 1984; Sinko et al., 1991). The utilities and limitations of these quantitative and mechanistic models have been discussed in a recent review article (Yu et al., 1996a). Although gastric emptying and small intestinal transit flow can influence the rate and extent of drug absorption after oral administration, none of the previous models have fully considered these factors. The aim of this report was to develop a compartmental absorption and transit (CAT) model for estimating the fraction of dose absorbed and the rate of drug absorption based on the transit models (Yu et al., 1996b; Yu and Amidon, 1998). We derived an equation to correlate the fraction of dose absorbed with the human effective permeability. The CAT model was related to compartmental pharmacokinetic models to evaluate the

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effect of gastric emptying on plasma concentration profiles.

## 2. Theoretical

Fig. 1 illustrates the CAT model to account for the transit flow in the stomach, duodenum, jejunum, and ileum, and the passive absorption in the duodenum, jejunum, and ileum. The gastrointestinal tract is divided into three segments: stomach, small intestine, and colon. The transit flow in the human small intestine can be described by seven compartments, where a drug transfers from one compartment to the next one in a first-order fashion (Yu et al., 1996b). The colon is considered only as a reservoir and the colonic transit flow was not considered in this model. The assumptions for the CAT model include:

1. Absorption from the stomach and colon is insignificant compared with that from the small intestine;
2. Transport across the small intestinal membrane is passive;
3. Dissolution is instantaneous; and
4. A 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 residence times (Yu and Amidon, 1998).

Therefore, for a non-degradable drug dosed in an immediate release dosage form, the absorption and transit in the gastrointestinal tract can be depicted as follows.

### 2.1. Stomach

$$\frac{dM_s}{dt} = -K_s M_s. \tag{1}$$

### 2.2. Small intestine

$$\frac{dM_n}{dt} = K_t M_{n-1} - K_t M_n, \quad n = 1, 2, ..., 7. \tag{2}$$

### Colon

$$\frac{dM_c}{dt} = K_t M_N \tag{3}$$

where $M_s$ is the amount of drug in the stomach, $M_c$ is the amount of drug in the colon, $M_n$ is the amount of drug in the $n$th compartment, $t$ is the time, $K_s$, $K_t$, and $K_a$ are the rate constants of gastric emptying, small intestinal transit, and intrinsic absorption, respectively. In Eq. (2), when $n = 1$, the term $K_t M_0$ is replaced by $K_s M_s$. The rate of drug absorption from the small intestine into the plasma is calculated by

$$\frac{dM_a}{dt} = K_a \sum_{n=1}^{7} M_n \tag{4}$$

where $M_a$ is the amount of drug absorbed. From mass balance, we have

$$M_s + \sum_{n=1}^{7} M_n + M_c + M_a = M_0. \tag{5}$$

As $t \to \infty$, $M_s$ and $M_n$'s approach zero, so

$$M_c + M_a = M_0. \tag{6}$$

The fraction of dose absorbed, $F_a$, can then be estimated by

$$F_a = \frac{M_a}{M_0} = \frac{1}{M_0} \int_0^\infty K_a \sum_{n=1}^{7} M_n \, dt. \tag{7}$$

Coupling with Eqs. (1) and (2), the analytical solution of Eq. (7) is

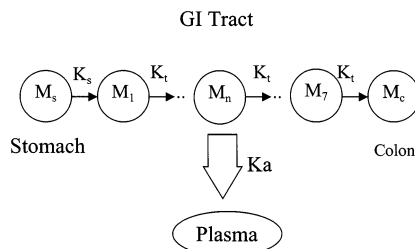$$F_a = 1 - \left(1 + \frac{K_a}{K_t}\right)^{-7}. \tag{8}$$

GI Tract



Fig. 1. A schematic diagram of the CAT model with linear transit and passive absorption kinetics. This model accounts for the transit in the stomach, duodenum, jejunum, and ileum, and the absorption in the duodenum, jejunum, and ileum.

The transit rate constant $K_t$ can be estimated from the mean small intestinal transit time (Yu et al., 1996b):

$$\frac{1}{K_t} = \frac{\langle T_{si} \rangle}{7}. \tag{9}$$

The absorption rate constant $K_a$ is proportional to the effective permeability, $P_{eff}$, (Sinko et al., 1991):

$$K_a = \frac{2P_{eff}}{R} \tag{10}$$

where $R$ is the radius of the small intestine. The substitution of Eqs. (9) and (10) into Eq. (8) gives

$$F_a = 1 - \left( 1 + \frac{2P_{eff}\langle T_{si} \rangle}{7R} \right)^{-7}. \tag{11}$$

Substitution of $\langle T_{si} \rangle$ of 3.32 h (Yu et al., 1996b) and the radius of 1.75 cm (Lennernas et al., 1992) into Eq. (11) yields

$$F_a = 1 - (1 + 0.54 P_{eff})^{-7} \tag{12}$$

where the human effective permeability $P_{eff}$ is expressed in cm/h. If there is no first pass effect, Eq. (4) can be related to intravenous pharmacokinetic models to estimate oral plasma concentration profiles. For example, in the case of the three-compartment open model with central compartment elimination (Wagner, 1993), we have the following equations:

$$\frac{dC_1}{dt} = \frac{1}{V_1} \frac{dM_a}{dt} - (k_{12} + k_{13} + k_{10}) C_1 + k_{21}C_2$$
$$+ k_{31}C_3( \tag{13}$$

$$\frac{dC_2}{dt} = k_{12}C_1 - k_{21}C_2 \tag{14}$$

$$\frac{dC_3}{dt} = k_{13}C_1 - k_{31}C_3 \tag{15}$$

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, 2, and 3, respectively. $k_{12}$, $k_{21}$, $k_{13}$, $k_{31}$, and $k_{10}$ are the microscopic rate constants.

## 3. Methods

### 3.1. Computer simulation

Model 1–3 and 13–15 are a typical initial value problem of an ordinary differential equation system. This system was numerically solved by the ADAPT pharmacokinetic and pharmacodynamic modeling package (D'Argenio and Schumitzky, 1992). A subroutine was written to accommodate the model equations.

### 3.2. Estimating fraction of dose absorbed

Ten compounds covering a wide range of absorption characteristics, from enalaprilat (the least permeable) to ketoprofen (the most permeable), were chosen to evaluate the predictability of the model. The permeability data were obtained from regional perfusion studies in humans using the regional intestinal perfusion technique (Lennernas et al., 1994; Amidon et al., 1995; Fagerholm et al., 1995; Lennernas et al., 1995; Amidon, 1996; Lindahl et al., 1995). The fraction of dose absorbed data were obtained from the literature (Paterson et al., 1970; Mason et al. 1979; Eichelbaum et al., 1982; Davies, 1984; Kubo and Cody, 1985; Tse et al., 1992; Ponto and Schoenwald, 1993; Benet et al., 1996; American Hospital Formulary Service, 1998 Edition). The fraction of dose absorbed data were corrected for first pass effects, if any. Table 1 summarizes the literature data.

### 3.3. Estimating rate of drug absorption

In conjunction with the compartmental pharmacokinetics model Eqs. (12)–(15), the CAT model was used to simulate oral plasma concentration profiles of atenolol. Atenolol is a $\beta_1$-selective $\beta$-adrenergic receptor blocking agent and essentially undergoes no first-pass metabolism (Riddell et al., 1987). Two simulations were carried out with respect to gastric emptying (monoexponential and biphasic gastric emptying). The effective permeability of atenolol was found to be 0.19 cm/h (Amidon et al., 1995). The volume of the central compartment and microscopic rate constants were taken from the intravenous pharmacokinetics study by Mason et al. (1979).

Table 1
Summary of the literature data of permeability and fraction of dose absorbed

| Drugs | $P_{eff}$ (cm/h) | $F_a$ |
|---|---|---|
| Enalaprilat | 0.079 (Lennernas et al., 1994) | 0.10 (Kubo and Cody, 1985) |
| Furosemide | 0.11 (Lennernas et al., 1995) | 0.55 (Ponto and Schoenwald, 1993) |
| Terbutaline | 0.18 (Fagerholm et al., 1995) | 0.44 (Davies, 1984) |
| Atenolol | 0.19 (Amidon et al., 1995) | 0.56 (Mason et al., 1979) |
| Metoprolol | 0.54 (Lindahl et al., 1995) | 0.88[a] |
| Propranolol | 0.97 (Amidon, 1996) | 0.92[b] |
| Fluvastatin | 1.01 (Lindahl et al., 1995) | 0.95[c] |
| Antipyrine | 2.02 (Lennernas et al., 1994) | 0.97 (Eichelbaum et al., 1982) |
| Naproxen | 2.88 (Lennernas et al., 1995) | 0.99 (Benet et al., 1996) |
| Ketoprofen | 3.06 (Lennernas et al., 1995) | 1.00 (Benet et al., 1996) |

[a] The oral bioavailability metoprolol is about 38% (Benet et al., 1996). After oral dose, about 50% of dose appears to undergo first-pass metabolism in the liver (AHFS Drug Information, 1998, pp. 1369). Thus, the fraction of dose is about 0.88.
[b] The oral bioavailability of propranolol is about 26%. However, the drug is completely absorbed following oral doses (Paterson et al., 1970).
[c] The fraction of dose absorbed of fluvastatin is 0.93–0.98 although the oral bioavailability is only 19–29% due to extensive first-pass effect (Tse et al., 1992).

## 4. Results and discussion

### 4.1. Estimating fraction of dose absorbed

Fig. 2 shows the predicted values. The fraction of dose absorbed for enalaprilat in laboratory animals was estimated to be only 5–12%; in humans, oral absorption of radiolabelled enalaprilat was probably less than 10% (Kubo and Cody, 1985). The model predicted the fraction of dose absorbed to be 26% for enalaprilat, higher than the experimental value. The fraction of dose absorbed for furosemide varies from 37 to 83% in healthy volunteers and the mean value is around 55% (Ponto and Schoenwald, 1993). The pre-

dicted fraction of dose absorbed is 34%, slightly below the experimental observations. The model predicted the fraction dose absorbed to be 48, 50, 84, and 95% for terbutaline, atenolol, metoprolol, and propranolol, respectively, based on the permeability data. The predicted results are in agreement with the experimental data (Paterson et al., 1970; Mason et al., 1979; Davies, 1984; Benet et al., 1996; American Hospital Formulary Service, 1998). Fluvastatin, antipyrine, naproxen, and ketoprofen are completely absorbed (Eichelbaum et al., 1982; Benet et al., 1996; Tse et al., 1992), as predicted by the CAT model.

### 4.2. Estimating the rate of drug absorption

Fig. 3 gives the theoretical prediction (dotted lines) for rate of drug absorption, based on monoexponential gastric emptying and the mean gastric residence time of 0.25 h for all three doses. The theoretical prediction is in fair agreement with the experimental data. The double peaks in the experimental plasma concentration profiles would not be expected from the simulation, however. Mason
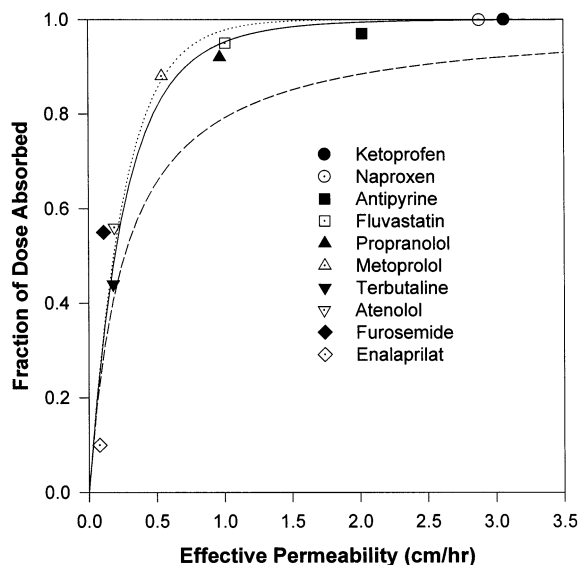


Fig. 2. The fraction of dose absorbed as a function of the human effective permeability, where (—) represents the prediction of the compartmental absorption and transit model, (---) represents the single compartment model, and (···), the plug flow model.
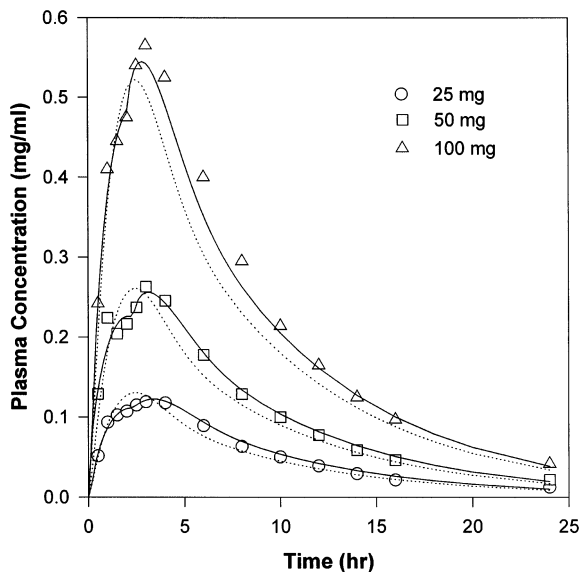
Fig. 3. Prediction of plasma concentration profiles of atenolol at the 25, 50, and 100 mg oral doses, where dotted lines represent the prediction with monoexponential gastric emptying, solid lines represent the prediction with biphasic gastric emptying (two intervals of monoexponential emptying, interrupted by an interval with no emptying), and symbols represent the experimental results from Mason et al. (1979).

et al. (1979) postulated that the biphasic gastric emptying contributed to the double peaks.

In the next simulation, therefore, we assumed that the drug was emptied from the stomach in a biphasic fashion. The simulation results are also shown in Fig. 3. Evidently, there exist double peaks in the simulated curves (solid lines). Based on the $F$-test, the pharmacokinetic model with biphasic gastric emptying was found to be a significant improvement over the model with monoexponential emptying.

The parameters in the biphasic gastric emptying include two rate constants and the interval between the two phases (Clements et al., 1978, type 3). The first phase of the biphasic gastric emptying was assumed to have the same rate constant as the monoexponential emptying. The values of the second emptying phase and the interval were determined by curve fitting. In a typical simulation, approximately 77% of the dose was evacuated from the stomach during the first phase. The emptying was then interrupted by an interval of

almost two hours of no emptying. The remaining drug was completely cleared from the stomach in the second phase of the emptying, producing the second peak in the plasma concentration profile. Nevertheless, no gastric emptying for 2 hours is physiologically questionable although not impossible despite the fact that the biphasic gastric emptying model is better than the monoexponential model for fitting the experimental data.

### 4.3. Model comparison

Several approaches to predicting the fraction of dose absorbed have been discussed in the literature (Yu et al., 1996a). Ho et al. (1983) developed a dispersion model and proposed an anatomical reserve length concept. The dispersion model is physically more plausible than the CAT model. However, the current dispersion model is probably unable to account for gastric emptying and to simulate the effect of gastric emptying on absorption (Yu et al., 1996b). The dispersion model also appears to be difficult to incorporate into pharmacokinetic models to estimate plasma concentration profiles.

Sinko et al. (1991) developed a macroscopic mass balance approach and showed the relationship between the fraction of dose absorbed and the absorption number (effective permeability) under steady-state conditions. Two flow models were considered in the mass balance approach: the single mixing tank model and the plug flow model. The single mixing tank model, as the name suggests, considers the small intestinal tract a mixed tank with uniform concentration. The plug flow model considers the small intestinal tract a uniform tube without axial mixing. In the case of the single mixing tank model, the mass balance approach gives

$$F_a = \frac{3.87 \, P_{\text{eff}}}{1 + 3.87 \, P_{\text{eff}}} \tag{16}$$

In the case of the plug flow model, the mass balance approach gives

$$F_a = 1 - e^{-3.87 \, P_{\text{eff}}}. \tag{17}$$

Fig. 2 shows the fraction of dose absorbed calculated by Eqs. (16) and (17). The single com-

partment model underestimates the fraction of dose absorbed whereas the plug flow and the CAT models give a much closer fit to the data. We have shown that the CAT based pharmacokinetic model was able to incorporate gastric emptying and predict plasma concentration profiles. This appears to be difficult to achieve by the plug flow model because of its steady state assumption.

## 5. Conclusions

This report describes a compartmental absorption and transit model to estimate oral drug absorption of passively transported drugs. A simple equation was derived which predicts the fraction of dose absorbed reasonably well. The CAT model offers the advantages of being able to estimate the rate of drug absorption and couple easily with compartmental pharmacokinetics models. The simulation study showed that gastric emptying could cause double peaks in oral plasma concentration profiles.

## Acknowledgements

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