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Compartmental transit and dispersion model analysis of small intestinal transit flow in humans

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Abstract

The purpose of this investigation was to characterize the small intestinal transit flow in humans using quantitative and mechanistic approaches. We presented a compartmental transit model to anatomize the transit process of oral dosage forms through the human small intestinal tract. A dispersion model with constant input rate and a single-compartment model were also employed to depict the dispersion and fluid flow in the human small intestinal tract. The literature data of the small intestinal transit time were utilized to statistically construct transit flow profile. The mean small intestinal transit time in humans was found to be 199 min with a 95% confidence interval of 7 min. It was demonstrated that the small intestinal transit flow profile was well characterized by both compartmental transit and dispersion models, but not by the single-compartment model. We concluded that the compartmental transit model might be superior to the single-compartment model and less complex than the dispersion model.

Keywords: Small intestinal transit flow; Small intestinal transit time; Compartmental model; Dispersion model

1. Introduction

Despite its usefulness in pharmacokinetic modeling, the approach to treat the entire gastrointestinal tract as a single-compartment 'black box' is an oversimplification of a very complex system. This has led to the development of quantitative and mechanistic approaches to investigate gastrointestinal absorption. Currently, two physiological based approaches, namely, compartment (mixing tank) and dispersion models, are generally employed to predict dynamic oral drug absorption (Yu et al., 1996).

The compartmental model has been developed and utilized to simulate oral absorption phenomena (Goodacre and Murray, 1981). This approach

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considers the small intestinal tract as one or more serial compartments with linear transfer kinetics. Each compartment is well mixed and has an uniform concentration. Dressman et al. (1984) used a two-compartment model to simulate dose-dependent absorption; Dressman and Fleisher (1986) and Hintz and Johnson (1989) treated the gastrointestinal tract as one compartment to predict dissolution controlled drug absorption. Oberle and Amidon (1987) employed four compartments to explain plasma level double peak phenomenon. Topp (1986) and Leesman et al. (1989) proposed a physiological flow model and have demonstrated its utilization in the dosage form design and evaluation. Recently, Luner and Amidon (1993) employed four compartments to study the effect of bile sequestrants on bile salt excretion. Since the number of compartments most likely influences the simulation results, there is a need to determine how many compartments are most appropriate to predict oral drug absorption.

In addition to the compartmental model approach, the dispersion model approach can also be used to simulate oral drug absorption (Ho et al., 1983a). The dispersion model approach considers the small intestine as an uniform tube with constant axial velocity, constant dispersion behavior, and constant concentration profile across the tube diameter. Although it has to be solved numerically in most cases (Zipp and Ho, 1993), analytical solutions in some limited situations have been obtained. The dispersion model has been utilized in interrelating rate-determining steps and factors in absorption, establishing the anatomical reserve length concept (Ho et al., 1983b), and predicting the effect of bile sequestrants on human bile slat excretion (Leipold, 1995).

Despite these advances in physiological modeling and simulation of drug absorption from the gastrointestinal tract, however, the fundamental process, small intestinal transit flow, has not been characterized. The detailed knowledge of the transit flow is, to a certain extent, a prerequisite for prediction of intestinal absorption kinetics. The purpose of this investigation was to parameterize compartment and dispersion models to describe the small intestinal transit process of pharmaceutical dosage forms through the human small intestinal tract.

2. Theoretical

2.1. Compartmental transit model

As illustrated in Fig. 1, we view a drug to pass through the small intestine as a process to flow through a series of segments. Each segment can be described by a single compartment with linear transfer kinetics. All compartments may have the different volume and flow rate, but have the same residence time:

$$\frac{V_1}{Q_1}=\frac{V_2}{Q_2}=\cdots=\frac{V_n}{Q_n}\cdots=\frac{V_N}{Q_N}=\frac{1}{K_t}=\frac{\langle T_{si}\rangle}{N} \tag{1}$$

where V is the volume, Q is the flow rate, K_t is the transit rate constant, N is the number of compartments, and $\langle T_{si}\rangle$ is the mean small intestinal transit (residence) time. It is assumed that a drug is neither absorbable nor degradable. Therefore, the small intestinal transit flow can be depicted by

$$\frac{dM_n}{dt}=K_tM_{n-1}-K_tM_n, \qquad n=1,2,\ldots,N \tag{2}$$

where M is the amount of the drug and t is the time. If we define $Y=M/D$ and $\tau=K_t\times t$, where D is the dose. Eq. 2 then becomes

$$\frac{dY_n}{d\tau}=Y_{n-1}-Y_n, \qquad n=1,2,\ldots,N \tag{3}$$

The rate of the percent of dose exiting the small intestine or entering the colon is described by

$$\frac{dY_{si}}{d\tau}=Y_N \tag{4}$$

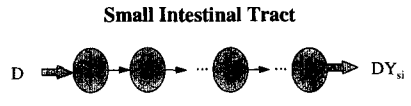

Fig. 1. A schematic diagram of a compartmental model with linear transfer kinetics. Such a model consists of N compartments accounting for transit flow in the small intestinal tract. Each compartment has the same transit time, but may have a different volume and flow rate.

Fig. 2. A schematic diagram of the dispersion flow model with constant velocity, constant dispersion behavior, and constant concentration profile across the tube diameter.

where Y_{si} is the percentage of dose entering the colon. Coupling Eqs. 1–3, the analytical solution of Eq. 4 is

$$Y_{si} = 1 - \int_{n=1}^{N} \frac{\tau^{n-1}}{(n-1)!} e^{-\tau} \quad (5)$$

Two parameters need to be determined in Eq. 5. One is the number of compartments (N) and the other is the mean small intestinal transit time $\langle T_{si} \rangle$, which is related to τ:

$$\tau = K_t \times t = \frac{Nt}{\langle T_{si} \rangle} \quad (6)$$

2.2. Dispersion model

In addition to the compartmental model approach, the dispersion model approach was also used to simulate oral drug absorption (Ho et al., 1983a). The dispersion model, as illustrated in Fig. 2, assumes the small intestine as an uniform tube with constant axial velocity, constant dispersion behavior, and constant concentration profile across the tube diameter. For a nonabsorbable and nondegradable drug, the transit of a dosage form through the small intestine can be delineated by the dispersion model as follows

$$\frac{\partial C}{\partial t} = \alpha \frac{\partial^2 C}{\partial z^2} - v \frac{\partial C}{\partial z} \quad (7)$$

where C is the concentration, z is the axial distance from stomach, v is the velocity in the axial direction, and α is the dispersion coefficient that accounts for mixing both by molecular diffusion and physiological effect, such as membrane surface solute binding, peristaltic and villous activities, and multi-S course of the small intestines (Ho et al., 1983a). Eq. 7 generally has to be solved numerically. In some cases, however, the analytical solutions may be possible (Ho et al., 1983a). If the stomach is assumed to function as an infinite reservoir with concentration of C_0 and with constant output with respect to both concentration and volume, Ho et al. (1983a) derived the following analytical solution:

$$\frac{C}{C_0} = \frac{1}{2}\left(\operatorname{erfc}\left[\frac{z}{\sqrt{4\alpha t}} - \sqrt{\frac{v^2 t}{4\alpha}}\right] + e^{vz/\alpha} \operatorname{erfc}\left[\frac{z}{\sqrt{4\alpha t}} + \sqrt{\frac{v^2 t}{4\alpha}}\right]\right) \quad (8)$$

where erfc is the error function and its definition is

$$\operatorname{erfc}(\xi) = 1 - \frac{2}{\sqrt{\pi}} \int_0^{\xi} e^{-u^2} du \quad (9)$$

The mean small intestinal transit time is given by

$$\langle T_{si} \rangle = \frac{L}{v} \quad (10)$$

where L is the length of the small intestine.

3. Methods

3.1. Small intestinal transit time

Since the small intestinal transit flow is difficult to be measured accurately as a function of time and location, the small intestinal transit data were utilized to statistically construct the transit flow. It appears that the small intestinal transit time is independent of dosage forms, gender, age, body weight, and the presence of food in the stomach (Davis et al., 1986a; Madsen, 1992). Therefore, a total of over 400 human small intestinal transit time data were collected and compiled as a data set from various publications (Davis et al., 1984a,b, 1986a,b, 1987, 1988; Christensen et al., 1985; Khosla et al., 1989; Madsen and Jensen, 1989; Coupe et al., 1991; Madsen, 1992; Wilding et al., 1992).

3.2. Data processing and model simulation

Small intestinal transit time data set were processed and plotted using Microsoft Excel 5.0® and Sigma-Plot®. The model equations were solved using the ADAPT pharmacokinetic and pharma-

codynamic modeling package, kindly provided by the University of Southern California (D'Argenio and Schumitzky, 1992).

3.3. Model selection criteria

The compartmental model, Eq. 5, involves two parameters: the number of compartments, N, and the mean small intestinal transit time, $\langle T_{si} \rangle$. The mean small intestinal transit time can be experimentally determined and the number of compartments then becomes the sole parameter in the compartmental model. Jacquez (1984) discussed compartmental analysis and suggested adding compartments until the reduction in residual (error) sum of squares (SSE) with an additional compartment becomes small. It was suggested to use F-test to decide whether the last compartment added significantly reduces the residual variance. Because the compartmental model with the fixed number of compartments contains none of parameters, F-test was not used and SSE then became only criterion to select the best compartmental model.

The dispersion model, Eq. 8, requires two parameters: the velocity, v, and the dispersion coefficient, α. Once the mean small intestinal transit time is determined, the velocity can be calculated from Eq. 10. Consequently, the dispersion coefficient becomes the only parameter. The value of the dispersion coefficient either was from literature or was fitted. F-test was performed to examine whether the fitting was significant.

4. Results and discussion

4.1. Small intestinal transit flow

The descriptive statistics showed that the mean small intestinal transit time was 199 min with a 95% confidence interval of 7 min and a standard deviation of 78 min. The median small intestinal transit time was 191 min, the minimum 30 min, and the maximum 570 min. The probabilities of normality or log normality tests for the data set were less than 0.001, suggesting that small intestinal transit time distribution could not be simply depicted by normal or log normal distribution.

The data set of the small intestinal transit time was analyzed by arranging these data into 14 classes, each with a width of 40 min. The 14 classes were selected based on the rule that classes should have no fewer than 5 and no more than 15 (Ostle and Malone, 1988). However, we also evaluated 7 classes with a width of 80 min and 10 classes with a width of 60 min. It was found that the cumulative distribution curves essentially overlapped for all three cases. Figs. 3 and 4 show the small intestinal transit time distribution and cumulative distribution. The cumulative distribution of this data set can be viewed as the percent of dose across a typical human small intestine upon oral administration of a pharmaceutical dosage form. Consequently, the cumulative distribution of the small intestinal transit time represents the percentage of dose entering the colon in the case of the compartmental models and C/C_0 in the case of the dispersion model.

4.2. Compartmental transit model analysis

From the descriptive statistics of small intestinal transit time data, the 95% confidence interval for the mean small intestinal transit time was only 7 min. Therefore, 199 min can be considered to be

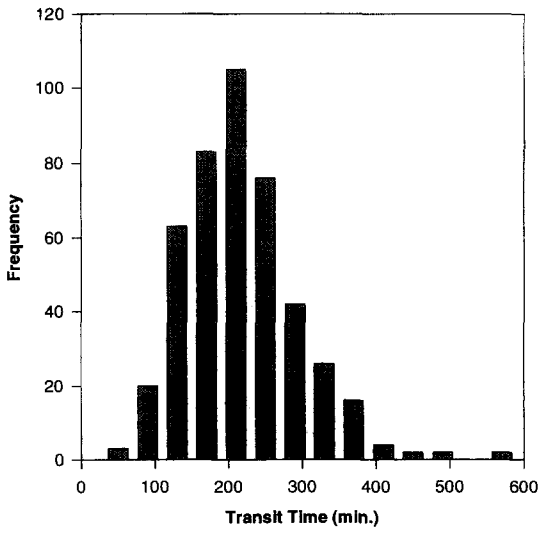

Fig. 3. Small intestinal transit time distribution based on the frequency.

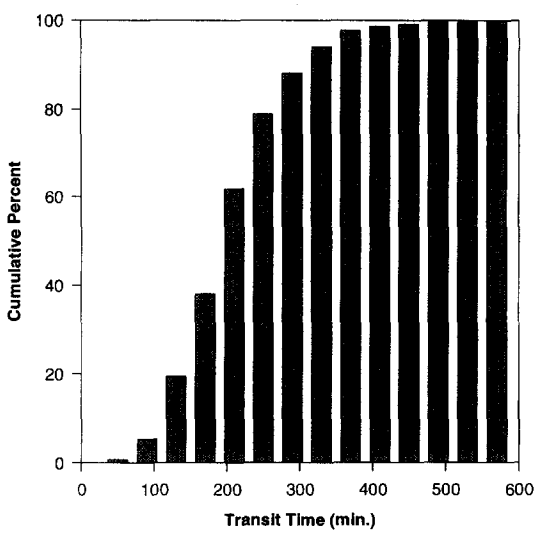

Fig. 4. A cumulative percent graph of the small intestinal transit time based on its distribution.

the true mean transit time in humans. Based on this value and Eq. 1 the rate constant K_t for each compartment was calculated and used to predict the percent of dose in colon using Eq. 5 of the compartmental models. Fig. 5 shows three predicted curves with respect to the number of compartments. The SSE was found to be 79, 8, and 52 for 5, 7, and 9 compartments, respectively. Considering the SSE values, seven compartments were determined to be the best compartmental model to depict the small intestinal transit process. The seven-compartment model is referred to as the compartmental transit model thereafter.

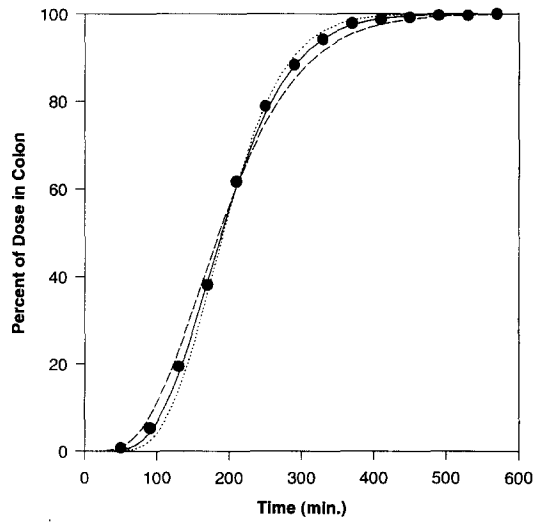

Fig. 5. Estimating human small intestinal transit flow using compartmental models, where (——) seven compartment, (– – –) five compartment, (···) nine compartment, (●) cumulative percentage of small intestinal transit time.

The seven-compartment transit model may be physiologically sound. We may visualize that the first half of the first compartment represents the duodenum, the second half of the first compartment, along with the second and third compartments, does the jejunum, and the rest of the compartments do the ileum. The transit time in the duodenum is short and variable, and, therefore, it was incorporated in the jejunum compartments. The corresponding transit times in the duodenum, jejunum, and ileum are 14, 71, and 114 min. Considering the volumes and flow rates in these three segments (Weisbrodt, 1989; Kerlin et al., 1982), such an assignment sounds reasonable.

4.3. Dispersion model analysis

From the analytical solution Eq. 8 of the dispersion model, we have two parameters to be determined: velocity v and dispersion coefficient α. If we assume that the total length of the small intestine is 350 cm (Ho et al., 1983a), v was then calculated to be 1.76 cm/min from Eq. 10. The experimental value of α varies from 0.33 to 0.61 cm^2/s for the jejunum and 0.3 cm^2/s for the ileum in the literature (Ho et al., 1983a). A typical value of 0.49 cm^2/s was used for the prediction. The results are shown in Fig. 6 and the SSE was calculated to be 130. In order to improve the prediction accuracy of the dispersion model, α was estimated by curve fitting Eq. 8 to the cumulative percentage of the small intestinal transit time. α was found to be 0.78 cm^2/s and the SSE was then reduced to 20. F-test showed that this improvement was significant ($P < 0.001$). Since molecular diffusion coefficient in liquid is usually in the order of 10^{-5} cm^2/s, the contribution of molecular diffusion is negligible, suggesting that the axial mixing is mainly due to biological effects, such as peristaltic and villous activities as well as membrane surface solute binding.

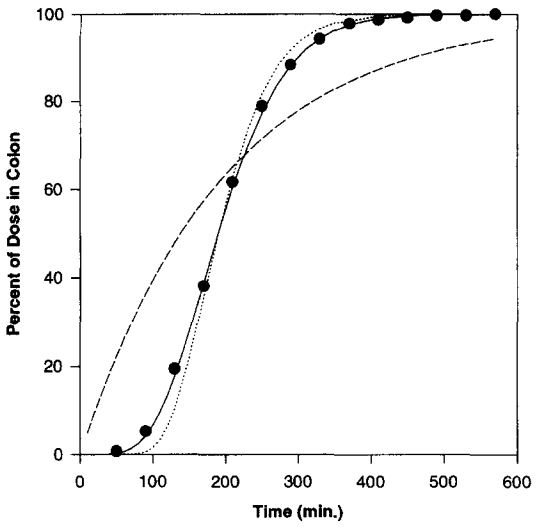

Fig. 6. Predicting human small intestinal transit flow, where (——) compartmental transit model, (···) dispersion model with dispersion coefficient of 0.49 cm^2/s, predicted results using estimated dispersion coefficient of 0.78 cm^2/s are similar to those of the compartmental transit model, (– –) single-compartment model, and (●) cumulative percentage of the small intestinal transit time.

4.4. Model comparison

A single-compartment model is often used in the literature to simulate oral drug absorption. It is interesting to see how this model fits the intestinal transit flow profile in humans. In case of the single-compartment model, the percent of dose exiting the small intestine or entering the colon can be expressed by

$$Y_{si} = 1 - e^{-t/\langle T_{si}\rangle} \quad (11)$$

The predicted transit flow by Eq. 11 is also shown in Fig. 6. The SSE for the single-compartment model was 3543 that is significantly larger than those of both dispersion and compartmental transit models. Therefore, it was concluded the dispersion and compartmental transit models were superior to the single-compartment model.

Both compartmental transit and dispersion models well characterized the human small intestinal transit flow profile. The compartmental transit model has the advantage of relative simplicity, intuition, and easy correlation with pharmacokinetic models. However, it has not many physical bases that one physiological segment of the gastrointestinal tract can be considered as one or more serial compartments although such an assumption has been commonly and successfully utilized in biology and medicine (Jacquez, 1984). The dispersion model more closely resembles the small intestine physically, however, it does not distinguish physiological differences throughout the gastrointestinal tract. It is also more complex than the compartmental transit model because the dispersion model involves a partial differential equation system while the compartmental transit model is described by an ordinary differential equation system.

It is also usually difficult for the dispersion model to include gastric emptying since gastric emptying is generally described with respect to the volume and the boundary conditions of the dispersion model are with respect to concentration. A reasonable way to transfer from volume to concentration has not yet been established. The compartmental transit model, on the other side, could include gastric emptying in the model equations.

5. Conclusions

We presented a compartmental transit model to anatomize the transit flow of oral dosage forms through the human small intestinal tract. It was demonstrated that the small intestinal transit flow profile was well characterized by both compartmental transit and dispersion models, but not by the single-compartment model. The compartmental transit model may be more complex than the single-compartment model. But, the compartmental transit model has no more parameters than the single-compartment model. We concluded that the compartmental transit model might be superior to the single-compartment model and less complex than the dispersion model. The compartmental transit model laid a foundation for predicting oral drug absorption (Yu et al., 1995a and Yu et al., 1995b).

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