ELSEVIER

International Journal of Pharmaceutics 171 (1998) 157–163

international journal of pharmaceutics

Characterization of small intestinal transit time distribution in humans

Lawrence X. Yu [a,*], Gordon L. Amidon [b]

[a] *Glaxo Wellcome Inc., Five Moore Drive, Research Triangle Park, NC 27709, USA*
[b] *College of Pharmacy, The University of Michigan, 428 Church St., Ann Arbor, MI 48109, USA*

Received 14 November 1997; received in revised form 19 May 1998; accepted 19 May 1998

Abstract

This report is aimed at characterizing small intestinal transit time distribution and presenting a slope-based method to determine compartmental transit and dispersion model parameters. The intradose, intrasubject, and intersubject means and variances were defined to examine small intestinal transit time distribution in individuals and populations. Equations were derived to determine the optimum number of compartments and the dispersion coefficient. It was found that the intra- or intersubject variance was significantly smaller than the intradose variance. The optimum number of compartments and the dispersion coefficient were estimated to be seven and 0.78 cm^2/s, respectively, in agreement with the literature data.

Keywords: Transit time distribution; Transit time mean and variance; Compartmental transit model; Dispersion model

1. Introduction

Although the importance of small intestinal transit time in oral drug absorption is well recognized and documented (Mayersohn, 1990; Yu et al., 1996a), only a few have addressed variations in transit times among individuals and populations (Coupe et al., 1991; Argenyi et al., 1995). In our previous publication (Yu et al., 1996b), the population variation of small intestinal transit time was analyzed and the standard deviation was found to be 78 min, along with a mean small intestinal transit time of 199 min. Both compartmental transit and dispersion models were then used to characterize the population variation.

The aim of this report is to analyze the individual variation of small intestinal transit time and to determine model parameters based on the individual variation. The intradose, intrasubject, and in-

* Corresponding author. Tel.: +1 919 4830445; fax: +1 919 3150128; e-mail: lxy33016@glaxowellcome.com

0378-5173/98/$ - see front matter
PII: S0378-5173(98)00174-4

tersubject means and variances are defined to characterize the small intestinal transit time distribution. A slope-based method is described to determine the optimum number of compartments and the dispersion coefficient.

2. Theoretical

2.1. Compartmental transit model

The compartmental transit model has been detailed in our previous publication (Yu et al., 1996b). In brief, we view a drug passing through the small intestine as a process flowing through a series of segments. A single compartment can describe each segment with linear transfer kinetics from one to the next. From mass balance, we have

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

where M_n is the amount of the drug in the nth compartment, t is time, N is the total number of compartments, and K_t is the transit rate constant, $K_t = N/ < T_{si} >$. Solving Eq. (1) gives a cumulative transit time distribution curve:

$$F(t) = 1 - e^{-K_t t}\left(1 + K_t t + \frac{(K_t t)}{2} + ... + \frac{(K_t t)^{N-1}}{(N-1)!}\right) \tag{2}$$

If the cumulative transit time distribution function given by Eq. (2) is differentiated, we obtain an equation for the slope of the curve from which the compartment number N may be determined by comparison with the experimental transit time distribution curve.

$$\frac{dF(t)}{d(t/ < T_{si} >)} = \frac{N e^{-Nt/ < T_{si} >}}{(N-1)!}\left(\frac{Nt}{< T_{si} >}\right)^{N-1} \tag{3}$$

At $t/ < T_{si} > = 1$, the slope is equal to

$$\left[\frac{dF(t)}{d(t/ < T_{si} >)}\right]_{t = < T_{si} >} = \frac{N^{N+1} e^{-N}}{N!} \tag{4}$$

For $N > 5$, Stirling's approximation may be used with an accuracy of 2% (Stirling, 1998):

$$N! \cong N^N e^{-N}\sqrt{2\pi N} \tag{5}$$

Therefore, Eq. (4) becomes

$$\left[\frac{dF(t)}{d(t/ < T_{si} >)}\right]_{t = < T_{si} >} = \sqrt{\frac{N}{2\pi}} \tag{6}$$

For $N < 5$, approximate values of the slope at $t/ < T_{si} > = 1$ are 0.368, 0.541, 0.672, 0.781, and 0.877 for one, two, three, four, and five compartments, respectively.

2.2. Dispersion model

In addition to the compartmental transit model, the dispersion model was also used to characterize transit time distribution. The fundamental equation of the dispersion model is

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

where C is concentration, z is the axial distance from the stomach, v is velocity in the axial direction, and α is the dispersion coefficient (Ho et al., 1983). 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, an analytical solution at the end of the small intestine can be obtained. The second term in the solution (Eq. (8); Yu et al., 1996b) is relatively small and the final form is

$$F(t)\frac{C}{C_0} = \frac{1}{2} erfc\left(\frac{L - vt}{\sqrt{4\alpha t}}\right) \tag{8}$$

where L is the length of the small intestine, about 350 cm (Ho et al., 1983), and *erfc* is the argument of the error function.

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

The slope of the F curve can then be estimated from the derivative of Eq. (8) at $t = < T_{si} >$:

$$\left[\frac{dF(t)}{d(t/ < T_{si} >)}\right]_{t = < T_{si} >} = \frac{1}{2}\frac{L}{\sqrt{\pi\alpha < T_{si} >}} \tag{10}$$

3. Methods

3.1. Intradose, intrasubject, and intersubject means and variances

To characterize the small intestinal transit time in individuals and populations, let us define intradose, intrasubject, and intersubject means and variances. Consider a non-absorbable drug solution dose that enters the small intestine of a normal volunteer subject as a bolus. Drug molecules will spread when traveling along the small intestine. If we measure the amount of drug at the end of the small intestine, we will have a transit time distribution of the amount of drug as a function of time, as shown in Fig. 1, which can be approximately characterized by the intradose mean and variance.

If we repeat the experiment several times on the same subject as determined over the course of many doses, we will have several intradose means since each experiment will produce an intradose mean. Several intradose means constitute a distribution which can be characterized by the intrasubject (interdose) mean and variance. The intrasubject variance describes the dose-to-dose variability of the transit time in a subject.

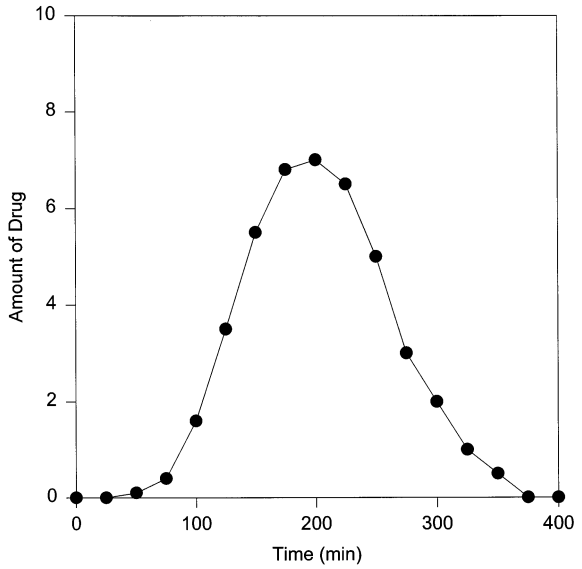

Fig. 1. Schematic representation of a typical intestinal transit time distribution profile upon administration of a pharmaceutical solution as a bolus.

If we conduct the experiment for all the subjects of a population, we then calculate the intersubject mean and variance based on intrasubject means. The intersubject mean represents the overall mean transit time in a population, and the variance describes the subject-to-subject variability of the transit time in a population.

3.2. Scintigraphic measurement of small intestinal transit time

Scintigraphy is one of the major methods used to measure small intestinal transit time (von der Ohe and Camilleri, 1992). In general, the transit time is calculated by the difference in time between 50% of the drug arriving in the colon and 50% of the drug leaving the stomach (Davis et al., 1986; Coupe et al., 1991; Argenyi et al., 1995). Such a method provides only a measure of the small intestinal transit time and does not give any indication of the distribution or range of the actual transit time.

Malagelada et al. (1984) developed a deconvolution method for quantifying the intestinal transit time distribution because of the obvious flaw in the 50% method that implicitly assumes that the small intestinal transit time is a single constant. Malagelada et al. (1984) measured the small intestinal input and output rates using scintigraphy. The input and output rates were then fitted by polynomial functions. The transit time distribution was calculated using a numerical deconvolution program. The transit time distribution over six individuals was measured for both solid and liquid (Malagelada et al., 1984). Considering the confounding effect of the ileocecal junction (Davis, 1989), only liquid data were used for this analysis.

3.3. Data processing and parameter estimation

Based on the transit time distribution curves of Malagelada et al. (1984), we calculated the intradose mean and variance. The means for six individuals were then used to calculate the intersubject mean and variance. Since the experi-

Table 1
Summary of intradose mean and standard deviation of small intestinal transit time from Malagelada et al. (1984)

Subject	Intradose mean (min)	Intradose standard deviation (min)	Slope at $t = <T_{si}>$ $dF(t)/d(t/<T_{si})$	Optimum number of compartments	Dispersion coefficient (cm^2/s)
1	210	45	1.29	10	0.47
2	154	50	0.90	5	1.30
3	238	45	1.51	14	0.30
4	180	114	0.44	1	4.66
5	227	53	1.25	10	0.46
6	212	80	0.75	4	1.36
Average pooled	203	65		7	0.78[a]
Intersubject standard deviation (min)		31			

[a] Subject 4 was excluded. Otherwise, the average dispersion coefficient would be 1.43 cm^2/s.

ment is only conducted once in each individual, no intrasubject variance would be expected from their results. The intradose mean and variance were used to estimate the optimum number of compartments and the dispersion coefficient to characterize the transit time distribution in the human small intestine.

4. Results and discussion

4.1. Means and variances of small intestinal transit time

Table 1 shows the intradose means and their standard deviations for the six individuals based on the liquid results of Malagelada et al. (1984). The intradose mean transit time is relatively consistent and varies from 154 to 238 min. The mean transit time for the population is 203 min, in agreement with our previous finding (199 min; Yu et al., 1996b).

There are remarkable differences in the intradose variances among individuals. The standard deviation varies from 45 to 114 min and the mean standard deviation was 65 min, which is in agreement with the population standard deviation (78 min) from our previous publication (Yu et al., 1996b).

The intersubject standard deviation was calculated to be 31, substantially smaller than the mean intradose variation. Coupe et al. (1991) and Argenyi et al. (1995) studied intrasubject variation using γ-scintigraphy. It was found that the intrasubject variability was generally lower than the intersubject variability based on the difference in time between 50% of the drug arriving in the colon and 50% of the drug leaving the stomach. Despite the confounding effect of the intradose variation in their analysis (the intradose variance was not separated from the intrasubject and intersubject variances), the conclusion would be expected to remain valid. Considering the analysis of intersubject variance, we also conclude that the intrasubject variance was substantially smaller than the intradose variance.

4.2. Estimation of the number of compartments

The slope at the mean transit time of the small intestinal transit time distribution was calculated to determine the optimum number of compartments and the dispersion coefficient. Table 1 shows the slopes calculated for each individual. The optimum number of compartments was estimated based on Eq. (6) for $N > 5$ and the real values for $N < 5$. The optimum number of compartments varies from one to 14 (Table 1) for the six individuals studied, suggesting the complexity and difficulty in developing a 'universal' model to describe the 'spreading' in humans. The average optimum number of compartments was found to be seven, which is the same as the number obtained in our previous publication (Yu et al., 1996b).

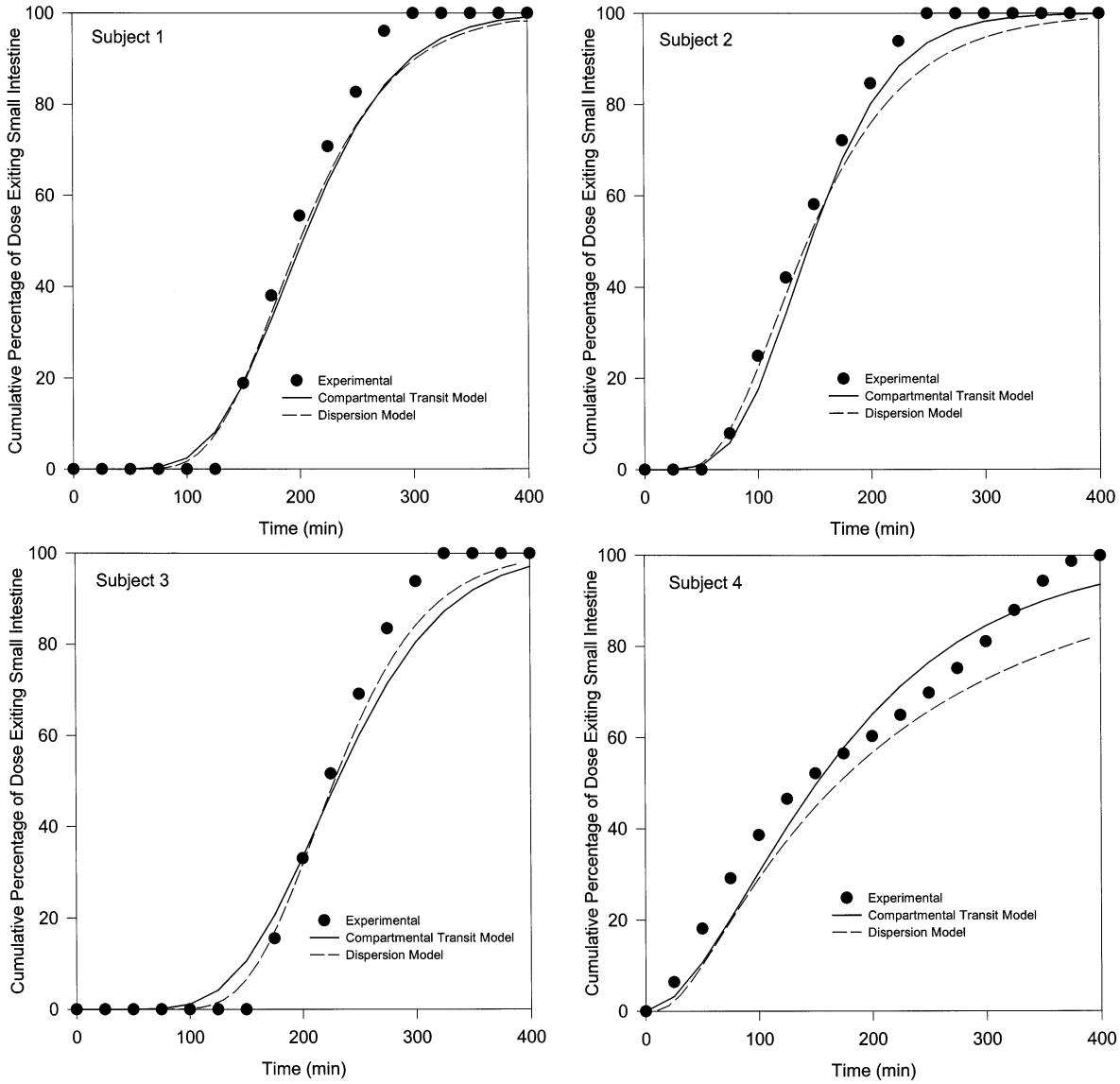

Fig. 2. Estimating individual small intestinal transit time distribution using compartmental transit and dispersion models, where experimental data points were from Malagelada et al. (1984).

Fig. 2 shows the experimental and theoretical small intestinal transit time distributions. The theoretical estimates are overall in agreement with the experimental distributions. The predicted values are generally too low at the high end or too high at the low end. This may be due to the fact that it allows only integer values of N and that it may not be possible to obtain a match of the transit time distribution at both high and low values of F with the same value of N.

Individuals 4 and 6 show double phase transit distribution curves characterized by a rapid output phase, followed by a slow, continuous output, and finally, a rapid output phase in which all drug solution was quickly emptied from the small intestine. The double phase phenomena contradict the

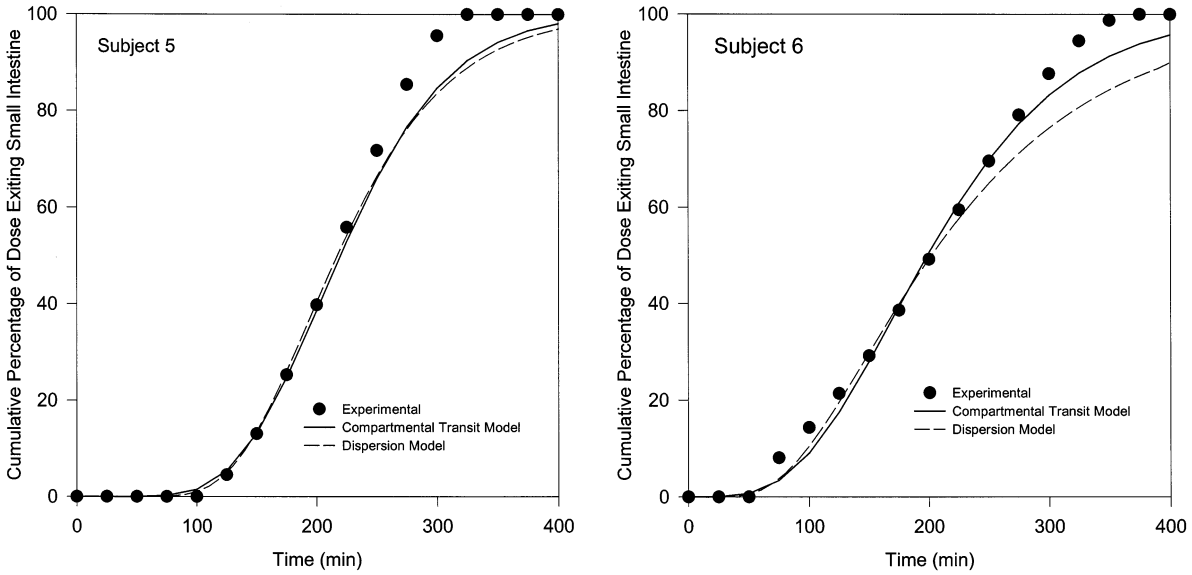

Fig. 2. (*Continued*)

model assumption that all compartments have the same time-independent transit time. It is possible to abandon the assumption and let each compartment have different time-dependent transit time. However, this requires hard experimental data that are currently unavailable.

4.3. Estimation of dispersion coefficient

The dispersion coefficient was calculated based on the slope of the transit time distribution curve. Table 1 shows the calculated results. Again, large intradose variability causes large variations in the dispersion coefficient among six individuals. Subject 4 has a dispersion coefficient of 4.66 cm^2/s that is far above the dispersion coefficients of the other subjects. If we excluded subject 4, the average dispersion was 0.78 cm^2/s, which is in agreement with literature values ranging from 0.33 to 0.61 cm^2/s (Ho et al., 1983) and 0.78 cm^2/s (Yu et al., 1996b).

The calculated transit time distributions by the dispersion model are also shown in Fig. 2. The theoretical curves for both compartmental transit and dispersion models are similar. For individuals 4 and 6, fitting by both models largely deviates at the high end, indicating the limitations of the model.

5. Conclusions

The intradose, intrasubject, and intersubject means and variances were defined to examine small intestinal transit time. It was shown that the intra- or intersubject variance was significantly smaller than the intradose variance. The slope-based method was presented to estimate the optimum number of compartments and the dispersion coefficient. The estimated results are in agreement with the literature data. The slope-based method has the advantages of simplicity and intuition over the least square of errors method used in our previous publication (Yu et al., 1996b). The compartmental transit and dispersion models are in essence single parameter models. Such models are still relatively simple compared to the enormous complexity of the GI tract, e.g. villi, microvilli, motility, and various dosing conditions, despite the fact that they represent advances over the commonly used single compartmental model. Consideration of these factors will be necessary to develop a robust transit flow model. The information gained about small intestinal transit time can be used to better understand its effect on oral drug absorption.

Acknowledgements

The authors would like to thank Dr Robert Leipold for helpful discussions and Dr Mark Sacchetti for reviewing the manuscript.

References

Argenyi, E.E., Soffer, E.E., Madsen, M.T., Berbaum, K.S., Walkner, W.O., 1995. Scintigraphic evaluation of small bowel transit in healthy subjects: inter- and intrasubject variability. Am. J. Gastroenterol. 90, 938–942.

Coupe, A.J., Davis, S.S., Wilding, I.R., 1991. Variation in gastrointestinal transit of pharmaceutical dosage forms in healthy subjects. Pharm. Res. 8, 360–364.

Davis, S.S., 1989. Small intestinal transit. In: Hardy, J.G., Davis, S.S., Wilson, C.G. (Eds.), Drug Delivery to the Gastrointestinal Tract. Wiley, New York, pp. 49–62.

Davis, S.S., Hardy, J.G., Fara, J.W., 1986. Transit of pharmaceutical dosage forms through the small intestine. Gut 27, 886–892.

Ho, N.F.H., Park, J.Y., Ni, P.F., Higuchi, W.I., 1983. Advanced quantitative and mechanistic approaches in interfacing gastrointestinal drug absorption studies in animals and humans. In: Crouthanel, W., Sarapu, A.C. (Eds.), Animal Models for Oral Drug Delivery in Man: In Situ and In Vivo Approaches. American Pharmaceutical Association, Washington, DC, pp. 27–106.

Malagelada, J.-R., Robertson, J.S., Brown, M.L., Remington, M., Duenes, J.A., Thomforde, G.M., Carryer, P.W., 1984. Intestinal transit of solid and liquid components of a meal in health. Gastroenterology 87, 1255–1263.

Mayersohn, M., 1990. Principles of drug absorption. In: Banker, G.S., Rhodes, C.T. (Eds.), Modern Pharmaceutics, 2nd ed. Marcel Dekker, New York, pp. 23–90.

Stirling, 1998. Stirling's Formula for N!. http://www.lassp.cornel.edu/sethna/Cracks/Stirling.htm1

Yu, L.X., Lipka, E., Crison, J.R., Amidon, G.L., 1996a. Transport approaches to the biopharmaceutical design of oral drug delivery systems: prediction of intestinal absorption. Adv. Drug Del. Rev. 19, 359–376.

Yu, L.X., Crison, J.R., Amidon, G.L., 1996b. Compartmental transit and dispersion model analysis of small intestinal transit flow in humans. Int. J. Pharm. 140, 111–118.

von der Ohe, M.R., Camilleri, M., 1992. Subspecialty clinics: gastroenterology. Mayo Clin. Proc. 67, 1167–1179.