Pharmaceutical Research, Vol. 7, No. 5, 1990

Report

Estimate of Volume/Flow Ratio of Gastrointestinal (GI) Fluids in Humans Using Pharmacokinetic Data

Panayotis Macheras,[1,3] Christos Reppas,[1] and Jennifer B. Dressman[2]

Received June 22, 1989; accepted November 21, 1989

Based on the mixing tank and tube models for drug absorption, the apparent absorption rate constant is shown to be related to the fraction of dose absorbed as a function of the volume/flow ratio of GI fluids. This analysis applies to drugs that are absorbed according to first-order kinetics, without limitation by dissolution rate, lumenal decomposition, or first-pass metabolism. Analysis of pharmacokinetic data of drugs that fit these criteria and are absorbed to varying extents enabled the estimation of the volume/flow ratio of GI fluids in humans; it was found to be 1.6 ± 0.3 (SE) hr using a mixing tank model and 0.32 ± 0.05 hr using a tube model. These findings are discussed with respect to volume and flow parameters used in the design of various types of drug absorption studies.

KEY WORDS: gastrointestinal absorption; volume/flow ratio; drug absorption; absorption studies.

INTRODUCTION

The importance of assessing absorption of compounds via the oral route has led to the development of *in vitro* systems (1,2) to simulate absorption. Another alternative to simulate absorption is based on the application of models. Two kinds of strategies are employed in these models. First, the rate and extent of absorption are simulated for various physicochemical drug properties, e.g., solubility, lipophilicity, and pK_a, using physiologically realistic estimates for parameters such as flow rate, volume of lumenal contents, GI pH, etc. (3–9). Second, mass transfer models with a variety of convection and diffusion assumptions are utilized to determine and interpret the permeability of the intestinal wall from *in situ* perfusion experiments (10–13).

Two important parameters that are inherent to both types of model simulating absorption are the volume of the lumenal contents, V, and the flow rate of GI fluids, Q. Studies of the volume–flow relationship of GI fluids in humans are limited (14); reported values for the flow rate in humans vary from 0.33 to 8 ml/min (Table I), while a value equal to 250 ml was assigned to volume for the purpose of simulating drug absorption (4). In the present study the value of the volume/flow (V/Q) ratio is estimated utilizing a pharmacokinetic approach. It is shown that under certain conditions the V/Q ratio can be related to the absorption rate constant and the fraction of dose absorbed, thereby making it possible to estimate the usual value of V/Q in human subjects without resorting to invasive techniques.

[1] Department of Pharmacy, University of Athens, Athens 10680, Greece.

[2] College of Pharmacy, The University of Michigan, Ann Arbor, Michigan 48109.

[3] To whom correspondence should be addressed.

THEORETICAL

Two known models, the perfect mixing tank model and the tube model, are considered. The following assumptions are incorporated into the models.

(1) Absorption proceeds uniformly throughout the tank or tube representing the GI tract.
(2) The drug dose is administered as a bolus and its dissolution rate is considered rapid compared to the absorption and transit rates. Drugs with dissolution rate-limited absorption therefore are excluded from the analysis.
(3) Uptake by the intestinal wall is a first-order process.
(4) Transit is a first-order process.

The following symbols are used: X_t, the amount of drug in the tube or tank; X_{abs}, the amount of drug absorbed; V, the volume of the tube or rank; Q, the flow or transit rate; k_i, the intrinsic absorption rate constant; k_a, the apparent absorption rate constant; X_0, the dose administered; and F, the fraction of dose absorbed.

Mixing Tank Model

This model assumes complete mixing throughout the tank, as illustrated in Fig. 1. If it is also assumed that absorption is fast compared with diffusion of drug to the intestinal wall, the mass transported across the absorbing surface per unit time is given by Eq. (1)

$$\frac{dX_{abs}}{dt} = k_i \cdot X_t \tag{1}$$

whereas the rate of loss from the tank is given by Eq. (2):

$$-\frac{dX_t}{dt} = [k_i + (Q/V)] \cdot X_t \tag{2}$$

0724-8741/90/0500-0518$06.00/0

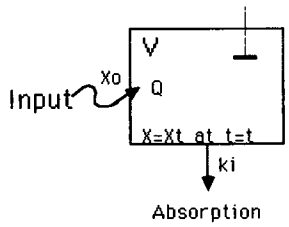

Fig. 1. Schematic of a one-tank perfect mixing tank model for oral drug absorption.

Solution of Eq. (2) yields

$$X_t = X_0 \exp\{-[k_i + (Q/V)]t\} \tag{3}$$

Substituting X_t in Eq. (1) from Eq. (3) and integrating,

$$X_{abs} = \frac{k_i X_0}{k_i + Q/V}\{1 - e^{-[k_i (Q/V)t]}\} \tag{4}$$

From the last equation it can be concluded that as $t \rightarrow \infty$,

$$X_{abs_\infty} = \frac{k_i X_0}{k_i + Q/V} \tag{5}$$

Since $X_{abs_\infty} = F \cdot X_0$, the intrinsic absorption rate constant k_i is given by

$$k_i = \frac{Q}{V} \cdot \frac{F}{1 - F} \tag{6}$$

The last equation reveals that for drugs obeying the assumptions listed above, a linear relationship exists between k_i and $F/(1 - F)$, and an estimate for Q/V can be obtained from the slope of k_i versus $F/(1 - F)$.

Tube Model

Assuming that absorption is fast compared with diffusion to the gut wall, the rate of change of mass in a tube of radius r (Fig. 2) is given by the following equation:

$$V\frac{dX}{dt} = QX_l - QX_{l+dl} - Ak_L X \tag{7}$$

where $A = 2\pi rdl$ and k_L is the mass transfer coefficient. As $dl \rightarrow 0$, Eq. (7) can be rewritten as

Table I. Flow Rate (ml min^{-1}; Mean ± SE) of Intestinal Contents

Locus	Fasting[a]	Fed	Ref. No.
Jejunum	≤2	<20	15
	0.73 ± 0.11	3.00 ± 0.67	16
		8.3 ± 0.9	17
Ileum	1.8 ± 0.4	3.4 ± 0.7	18
	0.33 ± 0.09	3.3 ± 0.3	16, 18
		2.35 ± 0.28	16
Terminal ileum	0.43 ± 0.06	2.09 ± 0.16	16

[a] Means for all phases of fasting.

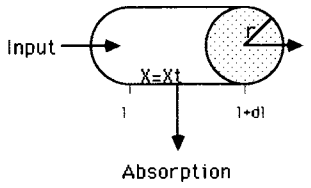

Fig. 2. Schematic of a tube model for oral drug absorption.

$$\frac{dX}{dt} = -\frac{QdX}{A_0 dl} - \frac{Ak_L}{V}X \tag{8}$$

where $V = A_0 dl$.

Under steady-state conditions, Eq. (8) becomes

$$\frac{dX}{dl} = -\frac{A_0}{Q}k_i X \tag{9}$$

where $k_i = Ak_L/V$

Integrating Eq. (9) and using $L = V/A_0$, where L is the total length of the tube, one obtains

$$X_l = X_0 \exp\left(-\frac{k_i A_0}{Q}1\right) \quad \text{and}$$

$$\frac{X_t(l = L)}{X_0} = \exp\left(-\frac{k_i A_0}{Q}\frac{V}{A_0}\right) \quad \text{or}$$

$$\frac{X_t}{X_0} = \exp\left(-\frac{k_i}{Q/V}\right) \tag{10}$$

The fraction absorbed is also given by

$$F = 1 - \frac{X_i}{X_0} \tag{11}$$

Combining Eqs. (10) and (11),

$$F = 1 - \exp\left(-\frac{k_i}{Q/V}\right)$$

which can be rearranged to

$$k_i = -\frac{Q}{V}\ln(1 - F) \tag{12}$$

Utilization of the apparent Absorption Rate Constant k_a *to Estimate* Q/V. According to Eqs. (6) and (12), the slope of the regression line corresponds to the reciprocal of transit time (Q/V) when k_i is plotted versus either $F/(1 - F)$ [Eq. (6)] or $-\ln(1 - F)$ [Eq. (12)]. Although the fraction of dose absorbed F is frequently estimated experimentally, the intrinsic absorption rate constant k_i is not derived from the pharmacokinetic studies. Instead, an apparent absorption rate constant, k_a, is usually calculated. It has been shown (19), however, that the value of the latter parameter is equal to the sum of all individual rate constants for simultaneous first-order loss of drug from the absorption site. According to Notari *et al.* (19) a simple relationship exists between k_a and k_i:

$$k_i = Fk_a \tag{13}$$

provided that all processes leading to nonabsorption follow first-order kinetics. For the mixing tank model, Eq. (6) becomes

$$k_a = \left(\frac{Q}{V}\right)\frac{1}{1-F} \quad (14)$$

and for the tube model, the equivalent expression is

$$k_a = -\left(\frac{Q}{V}\right)\frac{\ln(1-F)}{F} \quad (15)$$

These equations indicate that a plot of k_a versus $1/(1-F)$ or $-\ln(1-F)/F$ for various drugs conforming to the constraints postulated above should give straight lines with a slope corresponding to Q/V estimated according to each model.

RESULTS AND DISCUSSION

Although values for F and k_a are commonly reported, one has to be cautious in their use for estimating Q/V. Because of the individual variability of pharmacokinetic data, it would be desirable to analyze results from more than one reference study for every drug substance. However, only data for drugs that have no dissolution rate limitation to absorption, have no saturable first-pass effect, and are stable under fasting GI tract conditions can be employed for such an estimate. These restrictions limit the number of studies available. Further, it is desirable to refer to data from investigations with identical volunteer groups under controlled experimental conditions, but such data are lacking. To this end, only studies with similar dosing conditions (volume and type of administered fluid in fasted subjects) were considered. The data utilized for the plots in Fig. 3 are listed in Table II. As can be seen, a variety of drugs with a wide range of chemical structures and fraction of dose absorbed was analyzed. A reasonably good correlation ($R = 0.876$, $P < 0.001$, $n = 11$) was established using linear regression analysis for the mixing tank model

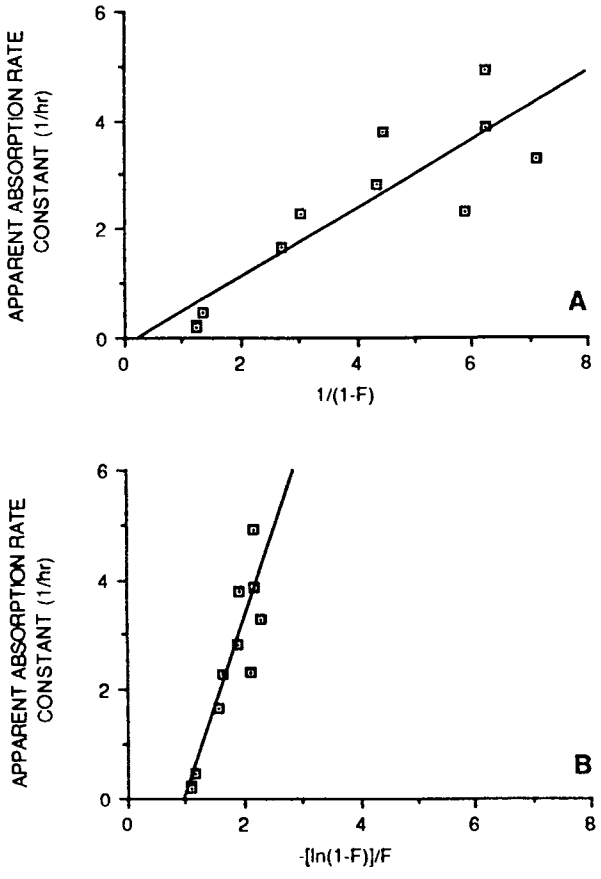

Fig. 3. Apparent absorption rate constant, k_a, versus $1/(1-F)$ (A) or $-\ln(1-F)/F$ (B) for drugs absorbed by a first-order process with no dissolution or first-pass metabolism limitations. Data are taken from Table II.

Table II. Drugs with No Significant First-Pass Effect, No Dissolution-Limited Bioavailability, and Stable at Fasting GI Conditions[a]

Drug	k_a (hr^{-1})	F	Ref. No.
Acyclovir	0.23	0.19	20, 21
Bretylium	0.18 (0.02)	0.19 (0.03)	22
	0.48 (0.07)	0.26 (0.05)	22
Bromazepam	3.87	0.84	23, 21
Bumetanide	4.9 (7.8)	0.84 (0.16)	24
	3.3 (7.4)	0.86 (0.13)	24
Captopril[b]	2.29	0.67 (0.03)	25, PCNONLIN
Furosemide	2.33 (0.93)	0.83 (0.14)	26
Lormetazepam	3.77	0.77	27, 21
Propylthiouracil	2.82 (1.74)	0.77 (0.13)	28
Xylose	1.68 (0.62)	0.63 (0.11)	29

[a] Standard deviations are given in parentheses when they were reported or could be calculated. All drugs were administered with 250 ml (or less) of water or orange juice. None of these compounds are listed as subject to significant first-pass metabolism in *Drug Information '84*, American Hospital Formulary Service, American Society of Hospital Pharmacists.

[b] The absorption rate constant was estimated using the program PCNONLIN [Statistical Consultants, Inc. *Am. Stat.* 40(1):52 (1986)].

Table III. Drugs that Have Demonstrated First-Pass Effect and Dissolution-Limited Absorption and/or Undergo Chemical Degradation in the Fasted GI Tract[a]

Drug	k_a (hr^{-1})	F	Ref. No.
Aspirin	4.0 (1.4)	0.17	30
	4.3 (2.2)	0.17	30
Betaxolol	0.50 (0.17)	0.87 (0.08)	31
	0.47 (0.24)	0.82 (0.06)	31
	0.51 (0.16)	0.84 (0.07)	31
Cimetidine[b]	0.46	0.62	32, PCNONLIN
	0.47	0.71	32, PCNONLIN
Erythromycin stearate	0.61 (0.25)	0.44 (0.14)	33
	0.57 (0.20)	0.26 (0.11)	33
Methylprednisolone	1.04 (0.51)	0.49 (0.29)	34
	0.71 (0.20)	0.58 (0.14)	34

[a] Standard deviations are given in parentheses when they were reported or could be calculated. All drugs were administered with 250 ml (or less) of water or cherry-flavored syrup.

[b] The absorption rate constant was estimated using the program PCNONLIN [Statistical Consultants, Inc. *Am. Stat.* 40(1):52 (1986)].

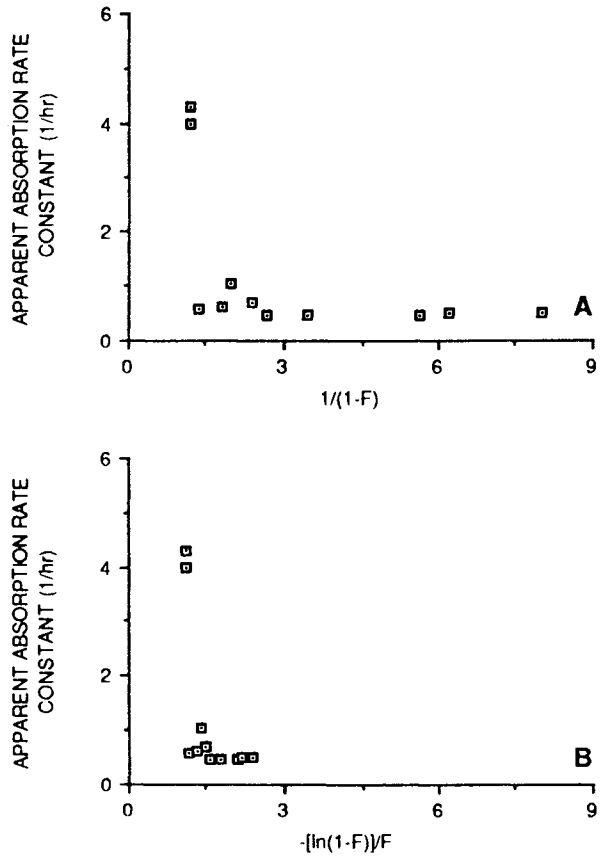

Fig. 4. Apparent absorption rate constant, k_a, versus $1/(1 - F)$ (A) or $-\ln(1 - F)/F$ (B) for compounds whose absorption is partly dissolution controlled and/or undergo first-pass metabolism. Data are taken from Table III.

$$k_a = -0.15 + 0.63\left[\frac{1}{1 - F}\right] \quad (16)$$

The standard errors of the intercept and slope were 0.52 and 0.11, respectively. For the tube model, the relationship was found to be

$$k_a = -3.18 - 3.16\left[\frac{\ln(1 - F)}{F}\right] \quad (17)$$

The correlation coefficient was 0.909 ($P < 0.001$) and the standard errors of the intercept and slope were 0.87 and 0.48, respectively.

In contrast, an identical analysis for drugs (Table III) that exhibit either first-pass metabolism or dissolution rate-limited absorption and/or undergo degradation in the fasted GI tract gave a poor correlation ($R = 0.483$, $n = 11$) between k_a and $1/(1 - F)$ (Fig. 4A) or between k_a and $-[\ln(1 - F)]/F$ ($R = 0.583$; Fig. 4B).

The reciprocals of the slopes, V/Q, of the lines given by Eqs. (16) and (17) represent a characteristic residence time for the drug at the site of absorption, with an average value in fasted humans of approximately 1.6 ± 0.3 (SE) hr (mixing tank analysis) or 0.32 ± 0.05 hr (tube analysis).

To compare these values with physiological data requires knowledge of both flow rate and volume of GI contents. Whereas flow rate measurements were the subject of several studies, there have been few attempts to measure volume in the small intestine. Table I lists the results of several flow rate studies. Dillard *et al.* (14) showed that, as the volume in the small intestine increases, there is an associated increase in the flow rate, with flow becoming very rapid at large volumes. At flow rates typically observed under normal conditions (i.e., those listed in Table I), the corresponding volumes are small. For example, at a flow rate of 3 ml/min, the V/Q ratio is approximately 1.8 hr. This value is in reasonable agreement with the pharmacokinetically derived value using the mixing tank model, whereas the tube model underestimates the physiological data. The value calculated using the mixing tank model is also closer to residence times for fluids in the upper GI tract determined by Malagelada *et al.* (42). A potential source of error with both the tube and the mixing tank models is that the V/Q ratio may vary with location in the GI tract, with the phase of motility cycle for fasted state conditions, and between the fed and the fasted states.

Previous attempts to simulate rate and extent of drug absorption (4,5) utilized V/Q ratios of approximately 2 hr to obtain the majority of results. It was also predicted in these studies that the rate and extent of absorption would be sensitive to the flow and volume parameters, as expressed through changes in the mean residence time. There have been several studies of fluid effects on drug absorption (35–41). These indicate that the volume of coadministered fluid is likely to affect the rate and/or extent of drug absorption only if the drug is not freely water soluble. The most reasonable explanation of these findings lies in the tendency of the flow rate to offset any increase in volume ingested. Oberle (43), for example, showed that flow rate from the stomach was faster after ingestion of a 200- than a 50-ml volume of fluid [$t_{1/2}$ = 6.4 ± 2.7 (SD) and 13.0 ± 12.8 min, respectively].

In the fed-state studies, the mean residence time in the stomach (44,45), but not the intestine (42,46), appears to be prolonged. Since most drugs are absorbed much more quickly from the intestine, the extent of absorption is not expected to be dramatically improved in the fed state unless the drug is poorly soluble.

In contrast to fluid loading and fed-state studies, perfusion studies can be used to control the mean residence time of the drug in the absorptive region. Human studies typically employ flow rates between 5 and 15 ml/min over a perfused segment 30–45 cm in length. For example, Merfeld's study (47) of methyldopa absorption utilized a flow rate of 7 ml/min over a combined mixing and test segment of 45 cm. Assuming that the radius of human jejunum is approximately 1.5 cm, these values lead to a V/Q ratio of 0.75 hr. Similarly, the V/Q ratio used by Vidon *et al.* (48) in their study of metoprolol absorption was approximately 0.35 hr. These values for V/Q ratio are somewhat lower than the parameter derived from the pharmacokinetic data using the mixing tank model. Under perfusion conditions such as these, results may tend to result in underestimates of absorption following oral administration.

V/Q ratios used in rat perfusions are much higher than those used in humans. In the corresponding methyldopa study in rats, Amidon *et al.* (49) used a V/Q ratio of approximately 12 hr. More recently, Sinko *et al.* (50) used V/Q

ratios of 5–7.5 in their studies of cephalosporine absorption. These larger values are required to maintain appropriate values of Graetz number (i.e., the ratio of the radial diffusion rate to the axial convection rate) adjusted for the difference in lumenal radius between the two species. In addition to perfusion studies, whole-animal absorption studies are frequently conducted to predict oral absorption in humans. It would be of value to determine what the usual V/Q value is in rats and other commonly used animals, to determine whether the scaling methods used to extrapolate absorption data from animals to humans can be improved.

In summary, the V/Q value estimated from analysis of pharmacokinetic data using the mixing tank model is in reasonable agreement with values obtained from physiological measurements which are used in simulations of GI absorption. V/Q ratios used in human perfusions tend to be lower, potentially resulting in an underestimate of GI absorption. In contrast to the mixing tank model, analysis using a tube model for the GI tract resulted in an underestimate of experimentally observed residence times and may, thus, represent a less useful hydrodynamic model for the upper GI tract in humans. Determination of V/Q values in other species by the pharmacokinetic method presented here, and using a mixing tank model analysis, may aid scaling of absorption studies from these species to man.

REFERENCES

1. H. Stricker. *Drugs Made Ger.* 13:35–42 (1970).
2. H. Stricker. *Drugs Made Ger.* 14:93–97 (1971).
3. J. B. Dressman, D. Fleisher, and G. L. Amidon. *J. Pharm. Sci.* 73:1274–1279 (1984).
4. J. B. Dressman, G. L. Amidon, and D. Fleisher. *J. Pharm. Sci.* 74:588–589 (1985).
5. J. B. Dressman and D. Fleisher. *J. Pharm. Sci.* 75:109–116 (1986).
6. B. C. Goodacre and R. J. Murray. *J. Clin. Hosp. Pharm.* 6:117–133 (1981).
7. N. F. H. Ho, H. P. Merkle, and W. I. Higuchi. *Drug Dev. Ind. Pharm.* 9:1111–1184 (1983).
8. P. Macheras and M. Symillides. *Biopharm. Drug Dispos.* 10:43–53 (1989).
9. D. Winne. *J. Pharmacokin. Biopharm.* 5:53–94 (1977).
10. R. L. Elliot, G. L. Amidon, and E. N. Lightfoot. *J. Theor. Biol.* 87:757–771 (1980).
11. G. L. Amidon, J. Kou, R. L. Elliot, and E. N. Lightfoot. *J. Pharm. Sci.* 69:1369–1373 (1980).
12. G. L. Amidon, P. J. Sinko, and D. Fleisher. *Pharm. Res.* 5:651–654 (1988).
13. P. J. Sinko, G. D. Leesman, and G. L. Amidon. Submitted for publication.
14. R. L. Dillard, H. Eastman, and J. S. Fordtran. *Gastroenterology* 49:58–66 (1965).
15. W. G. Karr and W. O. Abbott. *J.Clin. Invest.* 14:893–900 (1935).
16. P. Kerlin, A. Zinsmeister, and S. Phillips. *Gastroenterology* 82:701–706 (1982).
17. E. A. Mayer, J. B. Thompson, D. Jehn, T. Reedy, J. Elashoff, and J. H. Meyer. *Gastroenterology* 83:184–192 (1982).
18. A. M. Stephen, A. C. Haddad, and S. F. Phillips. *Gastroenterology* 85:589–595 (1983).
19. R. E. Notari, J. L. DeYoung, and R. Reuning. *J. Pharm. Sci.* 61:135–138 (1972).
20. P. Miranda and R. M. Blum. *J. Antimicrob. Chemother.* 12(Suppl. B):29–37 (1983).
21. M. Gibaldi and D. Perrier. *Pharmacokinetics,* Marcel Dekker, New York, 1975, p. 37.
22. E. R. Garrett, J. R. Green, and M. Bialer. *Biopharm. Drug Disp.* 3:129–164 (1982).
23. V. Ascalone, M. Cisternino, N. Sicolo, and E. Palo. *Arzneim. Forsch.* 34:96–98 (1984).
24. A. A. Holazo, W. A. Colburn, J. H. Gustafson, R. L. Young, and M. Parsonnet. *J. Pharm. Sci.* 73:1108–1113 (1984).
25. K. J. Kripalani, D. N. McKinstry, S. M. Singhvi, D. A. Willard, R. A. Vukovich, and B. H. Migdalof. *Clin. Pharmacol. Ther.* 27:636–641 (1980).
26. J. Zhu and T. Koizumi. *J. Pharmacobio-Dyn.* 10:370–376 (1987).
27. L. Zecca, L. Reina, F. Scaglione, P. Ferrario, R. Pirola, G. Ceccarelli, M. Ciampini, and F. Fraschini. *Arzneim. Forsch.* 35:1870–1872 (1985).
28. J. Kampmann and L. Skovsted. *Acta Pharmacol. Toxicol.* 35:361–369 (1974).
29. S. L. Johnson, M. Mayersohn, and K. A. Conrad. *Clin. Pharmacol. Ther.* 38:331–335 (1985).
30. P. A. Koch, C. A. Schultz, R. J. Wills, S. L. Hallquist, and P. G. Welling. *J. Pharm. Sci.* 67:1533–1535 (1978).
31. T. M. Ludden, D. A. Boyle, D. Gieseker, G. T. Kennedy, M. H. Crawford, L. K. Ludden, and W. A. Clementi. *J. Pharm. Sci.* 77:779–783 (1988).
32. S. S. Walkenstein, J. K. Dubb, W. C. Randolph, W. J. Westlake, R. M. Stote, and A. P. Intoccia. *Gastroenterology* 74:360–365 (1978).
33. P. G. Welling, H. Huang, P. F. Hewitt, and L. Lyons. *J. Pharm. Sci.* 67:764–766 (1978).
34. P. K. Narang, R. Wilder, D. C. Chatterji, R. L. Yeager, and J. F. Garelli. *Biopharm. Drug Disp.* 4:233–248 (1983).
35. P. G. Welling, L. L. Lyons, W. A. Craig, and G. Trochta. *Clin. Pharmacol. Ther.* 17:475–480 (1975).
36. P. G. Welling, L. L. Lyons, F. L. S. Tse, and W. A. Craig. *Clin. Pharmacol. Ther.* 19:559–565 (1976).
37. P. G. Welling, H. Huang, P. A. Koch, W. A. Craig, and P. O. Masden. *J. Pharm. Sci.* 66:549–552 (1977).
38. P. G. Welling, H. Huang, P. F. Hewitt, and L. L. Lyons. *J. Pharm. Sci.* 67:764–766 (1978).
39. P. G. Welling and R. H. Barbhaiya. *J. Pharm. Sci.* 71:32–35 (1982).
40. P. G. Welling, P. A. Koch, C. C. Lau, and W. A. Craig. *Antimicrob. Agents Chemother.* 11:462–469 (1977).
41. F. L. S. Tse, J. M. Jaffe, K. A. Mart, and H. Z. Schwartz. *J. Pharm. Pharmacol.* 36:56–58 (1984).
42. J. R. Malagelada, J. S. Robertson, M. L. Brown, M. Remington, J. A. Duenes, G. M. Thomforde, and P. W. Carryer. *Gastroenterology* 87:1255–1263 (1984).
43. R. Oberle. In *The Influence of the Inter-digestive Migrating Myoelectric Complex on the Gastric Emptying of Liquids and Oral Absorption of Cimetidine,* Ph.D. thesis, University of Michigan, Ann Arbor, 1988.
44. J.G. Moore, P. E. Christian, and R. E. Coleman. *Digest. Dis. Sci.* 26:16–22 (1981).
45. W. Brener, T. R. Hendrix, and P. R. McHugh. *Gastroenterology* 85:76–82 (1983).
46. S. S. Davis, R. Khosla, C. G. Wilson, and N. Washington. *Int. J. Pharm.* 35:253–258 (1987).
47. A.E. Merfeld, A. R. Mlodozeniec, M. A. Cortese, J. B. Rhodes, J. B. Dressman, and G. L. Amidon. *J. Pharm. Pharmacol.* 38:815–822 (1986).
48. N. Vidon, D. Evard, J. Godbillon, M. Rougier, M. Duval, J. P. Schoeller, J. J. Bernier, and J. Hirtz. *Br. J. Clin. Pharmacol.* 19:107S–112S (1985).
49. G. L. Amidon, A. E. Merfeld, and J. B. Dressman. *J. Pharm. Pharmacol.* 38:363–368 (1986).
50. P. J. Sinko and G. L. Amidon. *Pharm. Res.* 5:645–650 (1988).