An *in Vitro/in Vivo* Correlation for the Disintegration and Onset of Drug Release from Enteric-Coated Pellets

James P. Ebel,[1,4] Michael Jay,[2] and Robert M. Beihn[3]

Received August 23, 1991; accepted July 10, 1992

An empirical mass-transfer model for enteric-coating dissolution that uses *in vitro* dissolution data to characterize the pH-dependent solubility properties of the polymer film and a mass-transfer coefficient determined from *in vivo* dissolution or disintegration studies is developed. Once the *in vivo* mass-transfer coefficient has been evaluated, it can be used in conjunction with *in vitro* dissolution data from other formulations to predict the *in vivo* time to disintegration and onset of drug release. Results of *in vitro* dissolution experiments using the USP basket dissolution apparatus and *in vivo* disintegration experiments using gamma scintigraphy with four enteric-coated pellet formulations are presented. The good agreement among the *in vivo* mass-transfer coefficients that were determined supports the validity of the model.

KEY WORDS: enteric coated; *in vitro/in vivo* correlation; targeted release; pellet formulation.

INTRODUCTION

Attempts to compare *in vitro* dissolution or disintegration and *in vivo* onset of absorption or bioavailability of enteric-coated preparations have resulted in poor correlations (1–3) or are limited to qualitative results (4). A physicochemical model for polymer dissolution and drug release from enteric-coated tablets has been presented that adequately describes *in vitro* dissolution data (5). The model should be applicable to *in vivo* dissolution given the appropriate mass transfer parameters. Until now, however, a quantitative model utilizing parameters derived from *in vitro* and *in vivo* dissolution experiments to predict enteric-coated dosage form performance has not been reported.

THEORETICAL

Film Dissolution and Drug Release in the Gastrointestinal Tract

Drug release from enteric-coated dosage forms can be modeled as the result of two parallel processes. The first process is dissolution of the film, which, when the film thickness is reduced to zero, results in drug release by convection and diffusion. The second process is penetration of water into the film, which, when the degree of hydration renders the film sufficiently permeable, results in drug release by diffusion. Figure 1 is a diagram of the changes in the film as a result of these processes. The diagram defines three thicknesses; the initial physical film thickness, l_0, the instantaneous physical film thickness, l_f, and the drug impermeable film thickness, l_i. The rate of change of the impermeable film thickness is given by the sum of the rates of these two parallel processes

$$\frac{dl_i}{dt} = -(r_d + r_w) \tag{1}$$

where r_d is the rate of film dissolution, and r_w is the rate of penetration of the aqueous front into the film.

As an approximation we assume that the rate of penetration of the aqueous front, r_w, is independent of the solution properties and the hydrodynamics of the gastrointestinal tract. Thus, r_w is assumed constant and, in practice, can be determined from the onset of drug release at low pH values as measured *in vitro*.

By mass balance, the molar flux of polymer away from the interface is equal to the molar loss of polymer film,

$$C_p \frac{dl_f}{dt} = -km\,(x_0 - x_b) \tag{2}$$

where C_p is the molar density of the polymer, x_0 is the mole fraction of polymer at the interface, k_m is the mass-transfer coefficient, and x_b is the mole fraction of polymer in the bulk of the gastrointestinal milieu.

The dependence of k_m on the hydrodynamics of the small intestinal tract can be modeled empirically by

$$k_m = n\left(\frac{1}{t_I}\right)^r \tag{3}$$

where t_I is the small intestinal transit time, the exponent r is a constant, and the constant n is a function of dosage form and dissolution medium properties (6).

Combining Eqs. (2) and (3) and setting x_b equal to zero for sink conditions gives

$$\frac{dl_f}{dt} = -\frac{n}{C_p}\left(\frac{1}{t_I}\right)^r x_0 \tag{4}$$

which is the negative of r_d, the dissolution rate of the film.

Substitution of Eq. (4) into Eq. (1), the rate of change of the impermeable film thickness, and integrating with the boundary conditions

$$\begin{aligned} t &= 0, \quad & l_i &= l_0 \\ t &= t_r, \quad & l_i &= 0 \end{aligned} \tag{5}$$

where l_0 is the initial film thickness and t_r is the time to drug release, and assuming that n and r_w are independent of film thickness, gives

$$l_0 = \frac{n}{C_p}\left(\frac{1}{t_I}\right)^r \int_0^{t_r} x_0\,dt + r_w\,t_r \tag{6}$$

which describes the relationship between the film thickness and the time to drug release.

The polymer solubility can be modeled empirically by

[1] The Procter & Gamble Company, Miami Valley Laboratories, P.O. Box 398707, Cincinnati, Ohio 45239-8707.
[2] College of Pharmacy, University of Kentucky, Lexington, Kentucky 40536-0082.
[3] VA Medical Center, Lexington, Kentucky 40536-0082.
[4] To whom correspondence should be addressed.

0724-8741/93/0200-0233$07.00/0

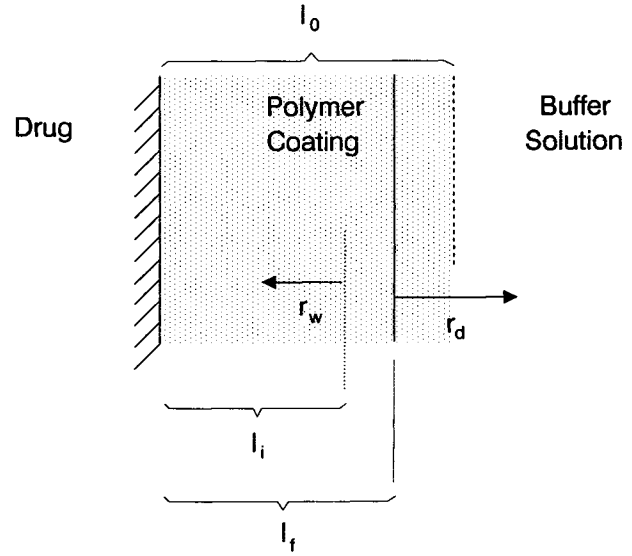


Fig. 1. Schematic defining the rate of film dissolution, r_d, the rate of penetration of water into the film, r_w, the initial physical film thickness, l_0, the instantaneous film thickness, l_f, and the drug impermeable film thickness, l_i.

$$x_0 = x_0^c \left\{ \frac{[1 - (x_0^u/x_0^c)]}{[1 + ([H^+]/K_p)^n]} + (x_0^u/x_0^c) \right\} \quad (7)$$

where K_p is a constant for the polymer, $[H^+]$ is the hydronium ion concentration, n is a constant characterizing the dependence of polymer solubility on $[H^+]$, x_0^c is the molar solubility of the completely ionized polymer, and x_0^u is the molar solubility of the completely nonionized polymer.

Substituting Eq. (7) into Eq. (6), and assuming that $x_0^u/x_0^c \ll 1$, gives

$$l_0 = \frac{n}{C_p} \left(\frac{1}{t_l}\right)^r x_0^c \int_0^{t_r} \left\{ \frac{1}{[1 + ([H^+]/K_p)^n]} \right\} dt + r_w t_r \quad (8)$$

which is the relationship between the film thickness and the time to onset of drug release for an enteric-coated dosage form in the gastrointestinal tract.

The relationship between the film thickness and the time to onset of disintegration is given by the first term on the right-hand side of Eq. (8), which describes dissolution of the film. The result can be written

$$l_0 = \frac{n}{C_p} \left(\frac{1}{t_l}\right)^r x_0^c \int_0^{t_d} \left\{ \frac{1}{[1 + ([H^+]/K_p)^n]} \right\} dt \quad (9)$$

where t_d is the time to the onset of disintegration. Disintegration occurs when the film thickness, l_f, is reduced to zero.

Film Dissolution and Drug Release in the Dissolution Apparatus

Modeling of the film dissolution and drug release in the USP Apparatus I is similar to that in the gastrointestinal tract. The resulting expression, analogous to Eq. (8), for the rate of change of the impermeable film thickness, l_0/t_r, at a constant pH and basket rotation rate, is

$$\frac{l_0}{t_r} = \frac{\mathcal{B}}{C_p} \omega^m x_0^c \left\{ \frac{1}{[1 + ([H^+]/K_p)^n]} \right\} + r_w \quad (10)$$

where ω is the basket rotation rate, the exponent m is a constant, and the constant $\mathcal{B}$ is a function of dosage form and dissolution medium properties.

In Vitro/in Vivo Correlation

Equations (8) and (9) can be used to determine the *in vivo* time to onset of drug release, t_r, and the time to onset of disintegration, t_d, respectively, given the polymer dissolution parameters and mass-transfer coefficient. The dissolution parameters K_p, n, and r_w, functions of polymer and formulation properties, can be evaluated from *in vitro* dissolution experiments and Eq. (10). The mass-transfer coefficient in the gastrointestinal tract, k_m, given by Eq. (3), can be determined from *in vivo* measurements of the time to onset of drug release, or the time to onset of disintegration as reported here.

Integration of Eqs. (8) and (9) requires a knowledge of the hydronium ion concentration, $[H^+]$, or pH of the intestinal milieu, at different locations in the gastrointestinal tract. Because these data were unavailable, we approximated the pH in the intestine with a constant function of location that is given by

$$pH = \alpha_3 + \left[\frac{\alpha_1 P}{(\alpha_2 P + 1)} \right] \quad (11)$$

where $\alpha_1 = 13.2$, $\alpha_2 = 5.6$, and $\alpha_3 = 5.5$ are constants, and $P = x/\mathcal{L}$ is the dimensionless position in the intestinal tract. The position, x, is equal to zero at the pylorus and to $\mathcal{L}$ at the ileocecal junction. Equation (11) results in a sigmoid pH profile. The shape and pH values for the curve were based on mean pH values in normal ambulant human subjects reported by Evans *et al.* (7).

Since location was determined at discrete time points, the transit data were cubic spline interpolated using the method of Akima (8) to express location in the gastrointestinal tract as a continuous function of time. The integral in Equations (8) and (9) was then evaluated numerically using univariate quadrature (9).

Experimentally determined values of k_m for different formulations were compared without independent measurements of x_0^c by normalizing Eq. (9) by x_0^c of a reference formulation. Using formulation A as a reference, and rearranging, Eq. (9) can be written

$$\frac{k_m}{C_p} x_{0A}^c = \frac{l_{0i}(x_{0A}^c/x_{0i}^c)}{\int_0^{t_d} \{1/[1 + ([H^+]/K_p)^n]\}\, dt} \quad (12)$$

where the subscripts A and i refer to the A formulation and the i formulation, respectively. We assume that the molar densities of the polymers, C_p, are approximately equal and that the relative values of the x_0^c are equivalent *in vitro* and *in vivo*.

As indicated by Eq. (3), the values for $k_m x_{0A}^c/C_p$ are a function of small intestinal transit time. To facilitate the comparison of the $k_m x_{0A}^c/C_p$ values among all subjects and

Table I. Specifications for Formulations Tested

Formulation	Eudragit polymer	Nominal dissolution pH	Coating thickness (μm)
A	L	6.0	29
B	50/50 (w/w) L and S	6.5	27
C	50/50 (w/w) L and S	6.5	48
D	S	7.0	25

formulations, however, we define a transit time corrected value that is given by

$$\frac{k_m^*}{C_p} x_{0A}^c = \frac{k_m}{C_p} x_{0A}^c \left(\frac{t_l}{t_l^*}\right)^r \tag{13}$$

where k_m^* is the transit time corrected mass-transfer coefficient and t_l^* is the reference small intestinal transit time. We define t_l^* such that the mean $k_m^* x_{0A}^c / C_p$ value equals the mean $k_m x_{0A}^c / C_p$ value. The reference transit time is given by

$$t_l^* = \left[\frac{\langle (k_m/C_p) x_{0A}^c \rangle}{\langle (k_m/C_p) x_{0A}^c (t_l)^r \rangle}\right]^{-(1/r)} \tag{14}$$

where the angle brackets designate the average for all subjects and formulations.

MATERIALS AND METHODS

Enteric-Coated Pellets

Pellets were labeled for the gamma scintigraphy study using stable, nonradioactive natural abundance samarium in the form of samarium oxide. Enteric-coated samarium oxide containing pellets were prepared by spray application of a samarium oxide suspension to 10- to 12-mesh (1.70–2.00 mm in diameter) sugar spheres using the Wurster configuration of a fluid-bed coater (UniGlatt, Glatt Air Techniques, Ramsey, NJ). Hydroxypropyl methylcellulose was used as a suspending agent and binder. The enteric coatings were subsequently applied to the samarium oxide cores using the Wurster column. The plasticizer used was tributyl citrate at a 16.7% level, and the solvent employed was a 20/80 (w/w) acetone/isopropyl alcohol mixture. Unlabeled enteric-coated pellets were prepared by spray application of the enteric coating to 10- to 12-mesh sugar spheres without the samarium oxide-containing undercoat.

The enteric polymers employed were the Eudragit L and Eudragit S methacrylic acid copolymers [Rohm Pharma, Weiterstadt, Germany, Prospectus (Info L/S-1/e)]. Four formulations having three different pH–solubility profiles were tested. The specifications of the formulations tested are summarized in Table I.

Dissolution Test

The dissolution experiments were carried out in a USP dissolution apparatus I (Vanderkamp 6000, Vankel Industries, Edison, NJ) using 300-mg samples of the samarium oxide-containing pellets added directly to the baskets. The media were 0.05 *M* potassium phosphate buffer solutions adjusted to the appropriate pH using NaOH. All of the experiments were conducted at 37°C using solutions that were deaerated under vacuum.

Since the samarium oxide is water insoluble, the release of sucrose from the sugar cores was monitored during the dissolution experiment and detection was by visible spectrophotometry. The assay was based on a double sequential enzyme-catalyzed reaction (10) and was initiated with the invertase-catalyzed hydrolysis of sucrose to D-glucose and D-fructose. By adding the enzymes and *o*-tolidine to the dissolution medium, the release of sucrose was monitored continuously *in situ*. The time to sucrose release, t_r, for the enteric film was defined as the x intercept of the tangent to the weight released-versus-time curve at the inflection point that occurred during the most rapid sucrose release.

Scintigraphy

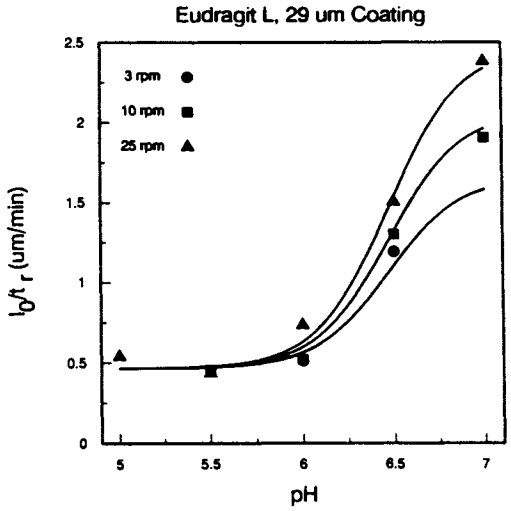
The protocol for the gamma scintigraphy study was approved by the Institutional Review Board of the University of Kentucky. The study was a single-blind, four-period crossover in eight normal, healthy male subjects, ages 20 to 50 years.

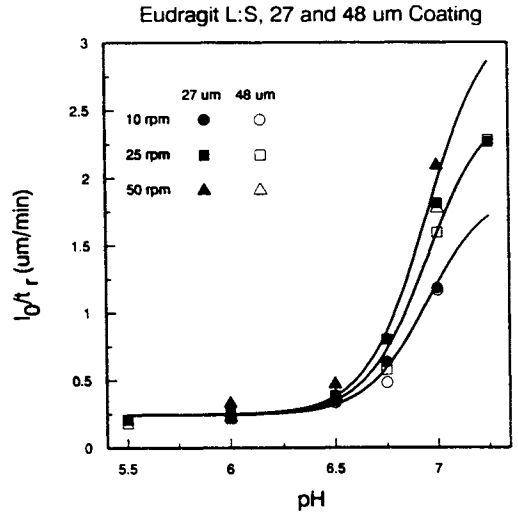
Subjects were fasted overnight. Prior to dosing, the samarium oxide-containing pellets were activated by neutron bombardment (11,12). For each dose, five activated pellets were added to a hard gelatin capsule that had been volume filled with unlabeled pellets. Immediately after ingesting the test dose, the subjects were placed beneath a gamma scintillation camera, and gamma radiation count data were collected continuously in the dynamic mode until gastric emptying had occurred. For the remainder of the test period, scintigraphs were taken at 0.5-hr intervals up to 8 hr, and 2-hr intervals thereafter, up to 12 hr. The number and location of the five radiolabeled pellets were recorded at each time point and disintegration of a pellet was marked by the dispersal of the radiomarker.

Table II. Parameters Determined from Nonlinear Least-Squares Fit of Dissolution Data to Eq. (15)

Formulation	m	n	K_p (M)	$x_0^c \mathcal{B}/C_p$ [μm/min$^{(1-m)}$]	r_w (μm/min)
Eudragit L, A	0.24	2.2	3.4×10^{-7}	0.92	0.46
	(0.04)[a]	(0.4)	(0.5×10^{-7})	(0.14)	(0.04)
Eudragit L:S, B and C	0.36	2.9	1.1×10^{-7}	0.74	0.24
	(0.04)	(0.3)	(0.1×10^{-7})	(0.10)	(0.03)
Eudragit S, D	0.33	2.7	4.3×10^{-8}	0.64	0.15
	(0.06)	(0.8)	(1.0×10^{-8})	(0.25)	(0.04)

[a] Asymptotic estimated standard error in parentheses.





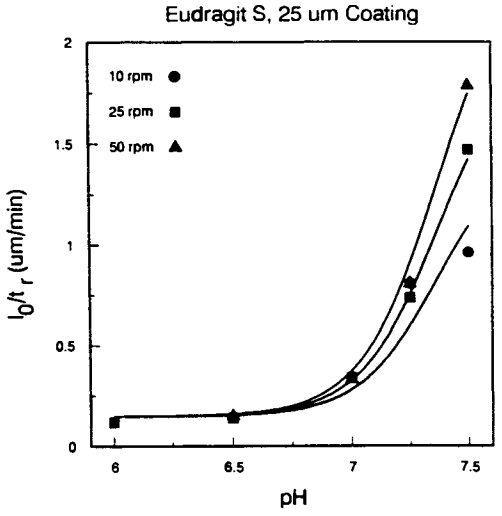


Table III. Transit and Disintegration Data from Gamma Scintigraphy: Mean (±SD) of Eight Subjects

Formulation	Hours		
	Gastric residence time	Transit time to disintegration[a]	Small intestinal transit time
A	0.83 (0.93)[b]	1.97 (0.55)	4.05 (1.32)
B	0.44 (0.83)	3.12 (0.76)	4.88 (1.73)
C	1.19 (0.93)	3.58 (0.73)	4.25 (1.48)
D	0.75 (1.01)	3.76 (0.85)	3.88 (1.35)

[a] After gastric emptying.
[b] Standard deviation in parentheses.

RESULTS AND DISCUSSION

Dissolution Test

The times to onset of sucrose release, t_r, were determined for an array of pH values and basket rotation rates for each of the formulations. The data for the rate of change of the impermeable film thickness, l_0/t_r, as a function of pH and rotation rate, were fit to Eq. (10) using Gauss–Newton nonlinear least-squares regression and the values for the parameters m, n, K_p, $\mathcal{B}x_0^c/C_p$, and r_w were determined for each of the formulations. The data for formulations B and C were pooled since they were the same polymer composition. The values for the parameters are presented in Table II.

Figure 2 shows plots of l_0/t_r versus pH for the Eudragit L, 29-μm coating, Eudragit L:S, 27-μm coating, Eudragit L:S, 48-μm coating, and Eudragit S, 25-μm coating. The solid lines in the plots were calculated using the least squares-determined parameters and Eq. (10). We obtained good correlations for each of the formulations, with r^2 values of 0.995 for Eudragit L, 0.993 for Eudragit L:S, and 0.988 for Eudragit S.

Scintigraphy

Table III lists mean gastric residence times, transit times to disintegration after gastric emptying, and small intestinal transit times for each of the formulations. Gastric emptying was considered to have occurred at the time point when a pellet was last observed in the stomach. Small intestinal transit time was determined as the time from gastric

Fig. 2. Rate of change of the impermeable film thickness, l_0/t_r, as a function of pH at basket rotation rates of 3, 10, 25, and 50 rpm. The solid curves were calculated using the least squares-determined parameters in Table II and Eq. (10). The plots are for (top) Eudragit L, 27-μm coating; (middle) Eudragit L:S, 29- and 48-μm coating; and (bottom) Eudragit S, 25-μm coating.

emptying to the time when the radiolabeled milieu or pellets first reached the ileocecal junction. The gastrointestinal transit data are consistent with published results (13).

In Vitro/in Vivo Correlation

The values for $k_m x^c_{0A}/C_p$ were calculated for each subject and formulation. The values for the ratio x^c_{0A}/x^c_{0i}, given by Eq. (12), and derived from the *in vitro* dissolution data, were $x^c_{0A}/x^c_{0B} = 1.24$, $x^c_{0A}/x^c_{0C} = 1.24$, and $x^c_{0A}/x^c_{0D} = 1.43$.

We found a weak correlation between the mass-transfer coefficient, $k_m x^c_{0A}/C_p$, and the intestinal transit time, t_I. For the least-squares fit to the linearized form of Eq. (3), an r^2 value of 0.235 was obtained and the values for n and r were 3.63 and 0.515, respectively.

The values for $k_m x^c_{0A}/C_p$ for each subject were corrected for small intestinal transit time using Eq. (13). The means for $k^*_m x^c_{0A}/C_p$, which are in good agreement, were 19.0 (±8.8), 15.7 (±2.9), 21.5 (±4.2), and 22.6 (±6.3) μm/hr for formulations A, B, C, and D, respectively. The mean value of $k^*_m x^c_{0A}/C_p$ for all subjects and formulations was 19.8 (±6.6) μm/hr.

CONCLUSION

The agreement among the *in vivo* mass-transfer coefficients supports the validity of using this model to predict the time to onset of drug release *in vivo* using *in vitro* dissolution measurements. Since the variation in intestinal transit rate is accounted for in Eq. (9), the deviations in the $k^*_m x^c_{0A}/C_p$ values are likely the result of deviations from the assumed intestinal pH profile given by Eq. (11). This hypothesis could be tested by simultaneous measurement of the intestinal milieu pH and gastrointestinal transit.

When determining the mass-transfer coefficient, the *in vivo* measurement is not necessarily restricted to the measurement of disintegration using gamma scintigraphy. In situations where drug release from the dosage form is the rate-limiting step to the onset of absorption, the time to drug release, t_r, in Eq. (8) can be approximated as the time of appearance of drug or metabolite in blood. In this case the values of $k^*_m x^c_{0A}/C_p$ can be derived from pharmacokinetic data.

The focus of this work has been the dissolution of an enteric film; however, the above approach can also be applied to the dissolution of drug particles or drug-containing matrices where drug dissolution is the rate-limiting step to oral absorption. The use of *in vivo* mass-transfer coefficients derived from pharmacokinetic data could be a useful way to predict dissolution rate-limited drug absorption using *in vitro* solubility data.

ACKNOWLEDGMENTS

The authors would like to thank Ms. Connie Rudolph for conducting the *in vitro* dissolution experiments, Ms. Susan Yonts for assisting in the gamma camera acquisitions, Dr. Brad Keck and Dr. Kurt Zinn for performing the pellet irradiations, and Dr. Rose Marie Deibel for leading the clinical effort.

NOMENCLATURE

$\mathcal{B}$, n	Constants in *in vitro* and *in vivo* mass-transfer equation
C	Molar concentration
k_m	Mass-transfer coefficient
K_p	Constant for polymer solubility relationship
l_f	Polymer film thickness
$\mathcal{L}$	Small intestinal length
m	Constant exponent of rotation rate
n	Constant exponent of hydronium ion concentration
N	Molar flux
P	Dimensionless position in intestinal tract
r	Constant exponent of intestinal transit time
r_d	Rate of film dissolution
r_w	Rate of penetration of water into film
t_d	Time to onset of disintegration
t_I	Small intestinal transit time
t_r	Time to onset of drug release
x	Mole fraction
α	Constants in pH profile expression
ω	Basket rotation rate

Superscripts

c	Ionized
u	Nonionized
*	Transit time corrected, reference transit time

Subscripts

f	Film
i	Impermeable
p	Polymer
0	Initial, interfacial

REFERENCES

1. T. Eckert, G. Cordes, and R. Seidel. Release of active substance from enteric-coated gelatine capsules *in vivo* and *in vitro*. 4. Studies with the pH endo-radio transmitter in man. *Arzneim-Forsch.* 21:1403–1406 (1971).
2. S. Rasmussen. A comparison between the *in vitro* and the *in vivo* disintegration times of enteric-coated tablets. *Deut. Apoth-Ztg.* 107:1321–1323 (1967).
3. N. Kanima, H. Ogata, N. Aoyagi, M. Koibuchi, T. Shibazaki, A. Ejima, S. Takanashi, H. Kamiyana, H. Suzuki, Y. Hinohara, H. Nakano, A. Okazaki, T. Fugikura, K. Igusa, and S. Bessho. Bioavailability of pyridoxal phosphate from enteric-coated tablets. III. Correlations between bioavailability in humans and beagel dogs and between bioavailability in humans and *in vitro* dissolution rates. *Chem. Pharm. Bull.* 33:3906–3914 (1985).
4. L. Borgstrom, B. Ekman, H. Larsson, I. Leden, A. Lindahl, A. Melander, and E. Wahlin-Boll. *In vitro* and *in vivo* evaluation of controlled-release and enteric-coated formulations of sodium salicylate. *Biopharm. Drug Dispos.* 5:261–272 (1984).
5. S. S. Ozturk, B. O. Palsson, B. Donohoe, and J. B. Dressman. Kinetics of release from enteric-coated tablets. *Pharm. Res.* 5:550–565 (1988).
6. R. B. Bird, W. E. Stewart, and E. N. Lightfoot. *Transport Phenomena,* John Wiley & Sons, New York, 1960, pp. 642–652.
7. D. F. Evans, G. Pye, R. Bramley, A. G. Clark, T. J. Dyson,

and J. D. Hardcastle. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. *Gut* **29**:1035–1041 (1988).
8. H. Akima. A new method of interpolation and smooth curve fitting based on local procedures. *J. ACM* **17**:589–602 (1970).
9. R. Piessens, E. deDoncker-Kapenga, C. W. Uberhuber, and D. K. Kahaner. *Quadpack*, Springer-Verlag, New York, 1983.
10. A. H. Free, E. C. Adams, M. L. Kercher, H. M. Free, and M. H. Cook. Simple specific test for urine glucose. *Clin. Chem.* **3**:163–168 (1957).
11. A. Parr, M. Jay, G. A. Digenis, and R. M. Beihn. Radiolabeling of intact tablets by neutron activation for in vivo scintigraphic studies. *J. Pharm. Sci.* **74**:590–591 (1985).
12. G. A. Digenis, E. P. Sandefer, A. F. Parr, R. M. Beihn, C. McClain, B. M. Scheinthal, I. Ghebre-Sellassie, U. Iyer, R. U. Nesbitt, and E. Randinitis. Gastrointestinal behavior of orally administered radiolabeled erythromycin pellets in man as determined by gamma scintigraphy. *J. Clin. Pharmacol.* **30**:621–631 (1990).
13. S. S. Davis, J. G. Hardy, and J. W. Fara. Transit of pharmaceutical dosage forms through the small intestine. *Gut* **27**:886–892 (1986).