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THEORETICAL MODEL STUDIES OF INTESTINAL DRUG ABSORPTION V. NON-STEADY-STATE FLUID FLOW AND ABSORPTION

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SUMMARY

A reasonably realistic physical model has been described for the simultaneous longitudinal spreading, fluid flow and absorption of drugs in solution under non-steady-state conditions in the small intestinal tract. Various input cases included first-order and zero-order stomach emptying and input from an infinite drug reservoir at constant infusion rate. The mathematical solutions were unique and rigorous. Theoretical simulations using reasonable physical parameter values illustrated the interrelationships of the longitudinal spreading diffusion coefficient, flow rate, apparent permeability coefficient and intestinal length on the change in concentration–distance profiles with time and the kinetics of appearance of unabsorbed drug at the end of the intestinal segment. The model is accessible to the design of intestinal absorption experiments and data interpretation on a quantitative mechanistic basis and also provides the way for studying intestinal absorption under more realistic situations.

INTRODUCTION

In advancing systematic studies of simultaneous bulk fluid flow and absorption in the intestinal tract and the concept of the anatomical reserve length for absorption, a physical model embodying reasonably realistic phenomenological events under non-steady-state conditions is needed.

Furthermore, there is a gap in our understanding of the flow pattern of drugs in solution and dispersed systems and the factors affecting the flow patterns on a quantitative and mechanistic basis. The flow pattern is believed to have a significant influence on absorption as the drug courses its way in a liquid flowing along the intestinal tract. When a non-

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absorbable marker in solution is introduced into the intestinal lumen either from an infinite reservoir or as a bolus, longitudinal zonal spreading will very likely occur. This spreading will be due to non-plug flow regimes, turbulence, surface irregularities, peristaltic and villous activities, S-shaped course of the intestines, binding to mucoidal substances on the membrane surface and possibly, the presence of the aqueous boundary layer. In situ rat intestinal segments and in vitro silicone rubber tubes appropriately designed as model intestines can be used. The longitudinal spreading of the non-absorbable solute determined by following the outflow concentration of an intestinal segment of a given length with time will mirror the hydrodynamic events in the lumen and, in turn, the spreading characteristics of absorbable solutes, when compared with that of the non-absorbable marker solute, will then mirror the absorption event.

This paper emphasizes the description of a comprehensive physical model, rigorous solution of the mathematics and ensuing theoretical predictions which provide the basic framework whereupon experiments can be designed, carried out and quantified on a mechanistic basis.

THEORY

General description of the model

The physical model for the simultaneous turbulent diffusion, fluid flow and absorption of a drug in solution in the intestinal tract taken as a hollow cylinder is depicted in Fig. 1. Mass balance within a cylindrical element at non-steady-state is described by

$$\pi r^2 \Delta x \cdot \frac{\Delta C}{\Delta t} = \left(QC - \pi r^2 D_e \cdot \frac{\Delta C}{\Delta x}\right)\Big|_x - \left(QC - \pi r^2 D_e \cdot \frac{\Delta C}{\Delta x}\right)\Big|_{x+\Delta x} - 2\pi r\, \Delta x P_e C \qquad (1)$$

where $C = C(x, t)$, the drug concentration at any distance, x, along the intestine and time, t; D_e = effective diffusion coefficient for longitudinal spreading, cm^2/sec; Q = bulk fluid flow rate, cm^3/sec; P_e = apparent permeability coefficient, cm/sec, for the absorption process (Ho et al., 1979); and r = radius of the intestinal lumen, cm. In the limit of Δx approaching zero,

$$\frac{\partial C}{\partial t} = \alpha \frac{\partial^2 C}{\partial x^2} - \beta \frac{\partial C}{\partial x} - \gamma C \qquad (2)$$

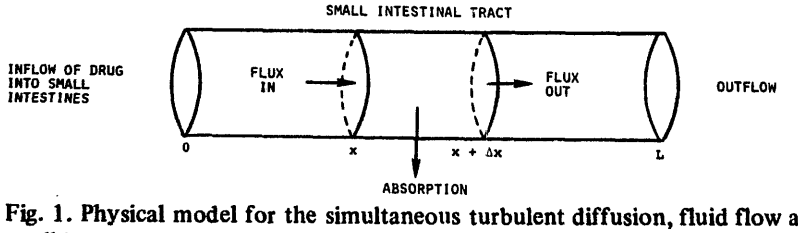

Fig. 1. Physical model for the simultaneous turbulent diffusion, fluid flow and drug absorption in the small intestines at non-steady-state.

where

$$\alpha = D_e \tag{3a}$$

$$\beta = Q/\pi r^2 \text{ (cm/sec)} \tag{3b}$$

$$\gamma = 2P_e/r \text{ (sec}^{-1}\text{)} \tag{3c}$$

The parameter β is then the linear flow velocity. In the event where a non-absorbable marker is used, the partial differential equation becomes

$$\frac{\partial C}{\partial t} = \alpha \frac{\partial^2 C}{\partial x^2} - \beta \frac{\partial C}{\partial x} \tag{4}$$

In Eqns. 2 and 4, the diffusion coefficient for longitudinal zonal spreading for the absorbable solute is assumed to be the same as that for the non-absorbable solute.

The form of the solution sought is

$$C(x, t) = C^*(x, t) \cdot e^{\beta x/2\alpha - \beta^2 t/4\alpha - \gamma t} \tag{5}$$

whereupon the use of this expression transforms Eqn. 2 to a simpler one:

$$\frac{\partial C^*(x, t)}{\partial t} = \alpha \frac{\partial^2 C^*(x, t)}{\partial x^2} \tag{6}$$

The initial boundary condition is

$$C(x, 0) = 0 \tag{7a}$$

and, correspondingly,

$$C^*(x, 0) = 0 \tag{7b}$$

Since $C(x, t)$ is bounded as x approaches infinity, i.e.

$$C(\infty, t) = 0 \tag{8a}$$

it follows that

$$C^*(\infty, t) = 0 \tag{8b}$$

There are several drug-input conditions at $x = 0$ which are of general interest.

(a) Infinite drug reservoir at constant infusion rate:

$$C(0, t) = C_0 \tag{9a}$$

or

$$C^*(0,t) = C_0\, e^{(\beta^2/4\alpha+\gamma)t} \tag{9b}$$

(b) Zero-order infusion rate of finite mass of drug:

$$C(0,t) = C_0 - k_0 t \tag{10a}$$

or

$$C^*(0,t) = (C_0 - k_0 t)\, e^{(\beta^2/4\alpha+\gamma)t} \tag{10b}$$

(c) First-order infusion rate of finite mass of drug:

$$C(0,t) = C_0\, e^{-k_1 t} \tag{11a}$$

or

$$C^*(0,t) = C_0\, e^{(\beta^2/4\alpha+\gamma-k_1)t} \tag{11b}$$

(d) Pulse input:

$$C(0,t) = C_0\, e^{-kt} \quad (k = \infty) \tag{12}$$

where C_0 = drug concentration at the entrance of the intestinal lumen; and k_0, k_1 and k = drug input rate constant for the zero-order, first-order and pulse situations, respectively.

Approach to the mathematical solution

Various approaches to the solution of Eqn. 6 and accompanying boundary conditions are available. The Laplace transformation method is the easiest since many of the inverses of the transform pertinent here are already tabulated (Carslaw and Jaeger, 1959a). An alternative method leading to the same analytical solution is the classical approach employing Duhamel's theorem (Carslaw and Jaeger, 1959b; Churchill, 1958).

Taking the Laplace transform of Eqn. 6, one gets

$$sU^* - C^*(x,0) = \alpha \frac{d^2U^*}{ds^2} \tag{13}$$

where $U^* = U^*(x,s)$ = Laplace transform of $C^*(x,t)$; and s = a variable in time, t.
The solution is

$$U^*(x,s) = A_1\, e^{x\sqrt{s/\alpha}} + A_2\, e^{-x\sqrt{s/\alpha}} \tag{14}$$

Since $U^*(x, s)$ is bounded as $x \to \infty$, it follows that the integration constant A_1 must be zero. Therefore,

$$U^*(x, s) = A_2 e^{-x\sqrt{s/\alpha}} \tag{15}$$

where A_2 is to be determined next from the various drug input conditions.

Case A: Infinite drug reservoir at constant infusion rate.

From Eqns. 9b and 15,

$$U^*(0, s) = A_2 = \frac{C_0}{s - \xi} \tag{16}$$

where

$$\xi = \beta^2/4\alpha + \gamma \tag{17}$$

Thus,

$$U^*(x, s) = \frac{C_0 e^{-x\sqrt{s/\alpha}}}{s - \xi} \tag{18}$$

whereupon the inverse is

$$C^*(x, t) = \frac{C_0 e^{\xi t}}{2}\left\{e^{-x\sqrt{\xi/\alpha}}\,\mathrm{erfc}\left[\frac{x}{2\sqrt{\alpha t}} - \sqrt{\xi t}\right] + e^{x\sqrt{\xi/\alpha}}\,\mathrm{erfc}\left[\frac{x}{2\sqrt{\alpha t}} + \sqrt{\xi t}\right]\right\} \tag{19}$$

Consequently, with Eqn. 5, the fraction of drug remaining at any distance, x, and time, t, is

$$\frac{C(x, t)}{C_0} = \frac{e^{\beta x/2\alpha}}{2}\left\{e^{-x\sqrt{\xi/\alpha}}\,\mathrm{erfc}\left[\frac{x}{2\sqrt{\alpha t}} - \sqrt{\xi t}\right] + e^{x\sqrt{\xi/\alpha}}\,\mathrm{erfc}\left[\frac{x}{2\sqrt{\alpha t}} + \sqrt{\xi t}\right]\right\} \tag{20}$$

It can be readily shown that Eqn. 20 satisfies all boundary conditions.

From Eqn. 20, the steady-state concentration ratio of absorbable drug at the end of an intestinal segment of length, ℓ, and incoming concentration arrives expectedly at an asymptotic value as expressed by

$$\frac{C(\ell, \infty)}{C_0} = \exp\left[\frac{\beta\ell}{2\alpha}(1 - \sqrt{1 + 4\alpha\gamma/\beta^2})\right] < 1.0 \tag{21}$$

In the case of a non-absorbable solute ($\gamma = 0$) at steady-state, $C(\ell, \infty) = C_0$. The binomial expansion of the square-root term, neglect of insignificant high order expansion terms and algebraic arrangement will reduce Eqn. 21 to

$$\frac{C(\ell, \infty)}{C_0} = \exp\left(-\frac{2\pi r\ell P_e}{Q}\right) \qquad (4\alpha\gamma/\beta^2 < 1.0) \tag{22}$$

This final expression has been used in studies involving the simultaneous bulk fluid flow and intestinal absorption of *n*-alkanoic acids and steroids (Ho et al., 1979; Komiya et al., 1980) and also in developing the concept of the anatomical reserve length for absorption.

Case B: Zero-order infusion of finite amount of drug

With the input boundary condition expressed in Eqn. 10b, the constant of integration A_2 in Eqn. 15 is

$$U^*(0, s) = A_2 = \frac{C_0}{(s - \xi)} - \frac{k_0}{(s - \xi)^2} \tag{23}$$

and, therefore,

$$U^*(x, s) = \left[\frac{C_0}{s - \xi} - \frac{k_0}{(s - \xi)^2}\right] e^{-x\sqrt{s/\alpha}} \tag{24}$$

After taking the inverse of the Laplace transform to obtain $C^*(x, t)$ and substituting into Eqn. 5, one arrives at

$$\frac{C(x, t)}{C_0} = \frac{e^{\beta x/2\alpha}}{2}\left\{e^{-x\sqrt{\xi/\alpha}}\,\mathrm{erfc}\left[\frac{x}{2\sqrt{\alpha t}} - \sqrt{\xi t}\right] + e^{x\sqrt{\xi/\alpha}}\,\mathrm{erfc}\left[\frac{x}{2\sqrt{\alpha t}} + \sqrt{\xi t}\right]\right\}$$

$$- \frac{k_0\, e^{\beta x/2\alpha}}{2C_0}\left\{\left(t - \frac{x}{2\sqrt{\alpha\xi}}\right)e^{-x\sqrt{\xi/\alpha}}\,\mathrm{erfc}\left[\frac{x}{2\sqrt{\alpha t}} - \sqrt{\xi t}\right]\right.$$

$$\left. + \left(t + \frac{x}{2\sqrt{\alpha\xi}}\right) e^{x\sqrt{\xi/\alpha}}\,\mathrm{erfc}\left[\frac{x}{2\sqrt{\alpha t}} + \sqrt{\xi t}\right]\right\} \tag{25}$$

Case C: First-order infusion of finite amount of drug

As can be seen, the first-order input condition in Eqn. 11b has the identical form as that for the infinite drug reservoir case in Eqn. 9b. Consequently, one can readily write the following expressions:

$$U^*(x, s) = \frac{C_0\, e^{-x\sqrt{s/\alpha}}}{s - (\xi - k_1)} \tag{26}$$

and finally,

$$C^*(x, t) = \frac{C_0\, e^{(\xi - k_1)t}}{2}\left\{e^{-x\sqrt{(\xi - k_1)/\alpha}}\,\mathrm{erfc}\left[\frac{x}{2\sqrt{\alpha t}} - \sqrt{(\xi - k_1)\,t}\right]\right.$$

$$\left. + e^{x\sqrt{(\xi - k_1)/\alpha}}\,\mathrm{erfc}\left[\frac{x}{2\sqrt{\alpha t}} + \sqrt{(\xi - k_1)\,t}\right]\right\} \tag{27}$$

$$\frac{C(x,t)}{C_0} = \frac{e^{(\beta x/2\alpha - k_1 t)}}{2}\left\{e^{-x\sqrt{(\xi - k_1)/\alpha}}\,\mathrm{erfc}\left[\frac{x}{2\sqrt{\alpha t}} - \sqrt{(\xi - k_1)\,t}\right]\right.$$

$$\left. + e^{x\sqrt{(\xi - k_1)/\alpha}}\,\mathrm{erfc}\left[\frac{x}{2\sqrt{\alpha t}} + \sqrt{(\xi - k_1)\,t}\right]\right\} \qquad (28)$$

There are no constraints on the value of the first-order input constant k_1 placed on Eqn. 28. However, the case of $k_1 > \xi$ is not particularly relatistic, since in physiological situations the disappearance rate of the drug in solution from the stomach is less than the combined effects of flow and spreading within the intestines. Consequently, $k_1 \leqslant \xi$ is the usual situation.

In examining Eqn. 28 for the first-order input case and Eqn. 25 for the zero-order input case retrospectively, one observes that these equations are somewhat similar to Eqn. 20 for the infinite reservoir case, the important distinction being modifications that bring about the limiting situation at infinite time of

$$\frac{C(x,\infty)}{C_0} = 0 \qquad (29)$$

which is due to the finite amount of drug introduced into the intestinal lumen at first-order or zero-order rates.

THEORETICAL RESULTS AND DISCUSSION

Computations were carried out using the following reasonable values of physical parameters:

Effective diffusion coefficient	$D_e = 10^{-5}$ and 10^{-2} cm^2/sec
Flow rate	$Q = 0.5$ and 2.0 ml/min
Intestinal length	$\ell = 25$ and 50 cm
Effective radius of rat intestines	$r = 0.18$ cm
Effective permeability coefficient	$P_e = 0, 3 \times 10^{-5}$ and 3×10^{-4} cm/sec
First-order infusion constant	$k_1 = 10^{-1}, 10^{-2}$ and 10^{-3} sec^{-1}

To demonstrate the predictions of the model the infinite drug reservoir and first-order infusion cases were employed.

Infinite drug reservoir at constant infusion rate

In Fig. 2 the large longitudinal zonal spreading of a non-absorbable solute has a marked influence on the character of the outflow to inflow concentration ratio vs time profile. The effective diffusion coefficient of 10^{-5} cm^2/sec corresponding to ordinary molecular diffusion has negligible effect on spreading, while the magnitude of D_e being 10^{-2} cm^2/sec is a reflection of strong eddy diffusion currents. At steady-state, the concentration ratios converge to unity.

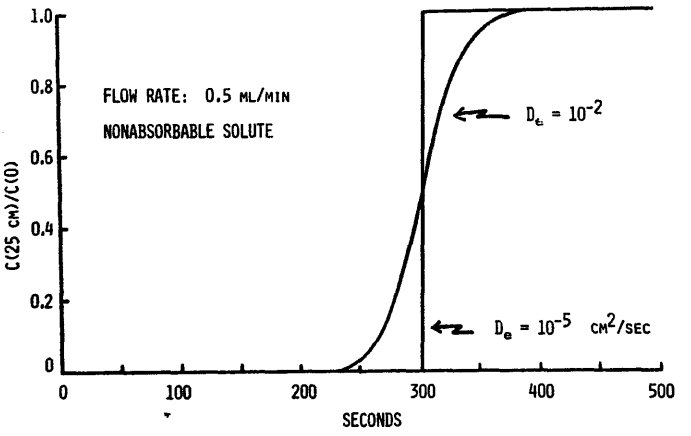

Fig. 2. Changes in outflow-to-inflow concentration ratio with time for a non-absorbable marker solute for effective spreading diffusion coefficients of 10^{-5} and 10^{-2} cm^2/sec. The flow rate is 0.5 ml/min.

Fig. 3 illustrates the changes in outflow to inflow concentration ratio with time for absorbable solutes with different permeability coefficients under the influence of longitudinal spreading. The profile of a non-absorbable marker solute ($P_e = 0$) is also shown. The sigmoidal-shaped curves in the non-steady-state region are separated from each other both vertically and horizontally. The concentration ratios at steady-state are 0.9 and 0.36 for P_e of 3×10^{-5} and 3×10^{-4} cm/sec, respectively.

In contrast to Fig. 3 where the flow rate is 0.5 ml/min, the concentration ratio–time plots at the flow rate of 2 ml/min in Fig. 4 are shifted down the time scale due to the shorter residence time. The residence time is the time it takes for a flowing liquid to displace a given volume of liquid within a tube and can be roughly estimated by dividing the

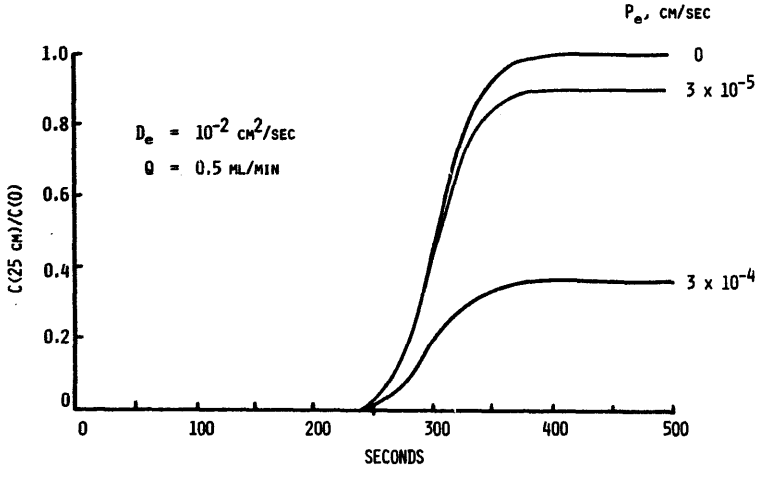

Fig. 3. Changes in outflow-to-inflow concentration ratio with time for absorbable solutes with effective permeability coefficients of 3×10^{-5} and 3×10^{-4} cm/sec under the influence of a zonal spreading diffusion coefficient of 10^{-2} cm^2/sec.

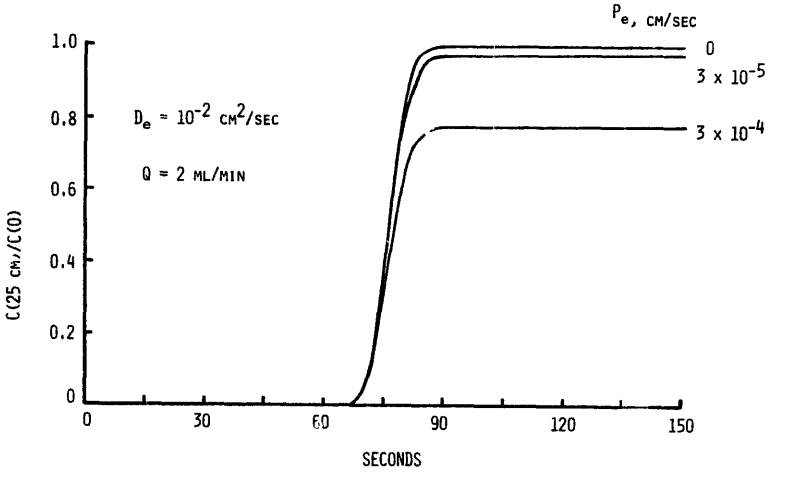

Fig. 4. Changes in outflow-to-inflow concentration ratio with time for absorbable solutes with effective permeability coefficients of 3×10^{-5} and 3×10^{-4} cm/sec under the influence of a zonal spreading diffusion coefficient of 10^{-2} cm^2/sec.

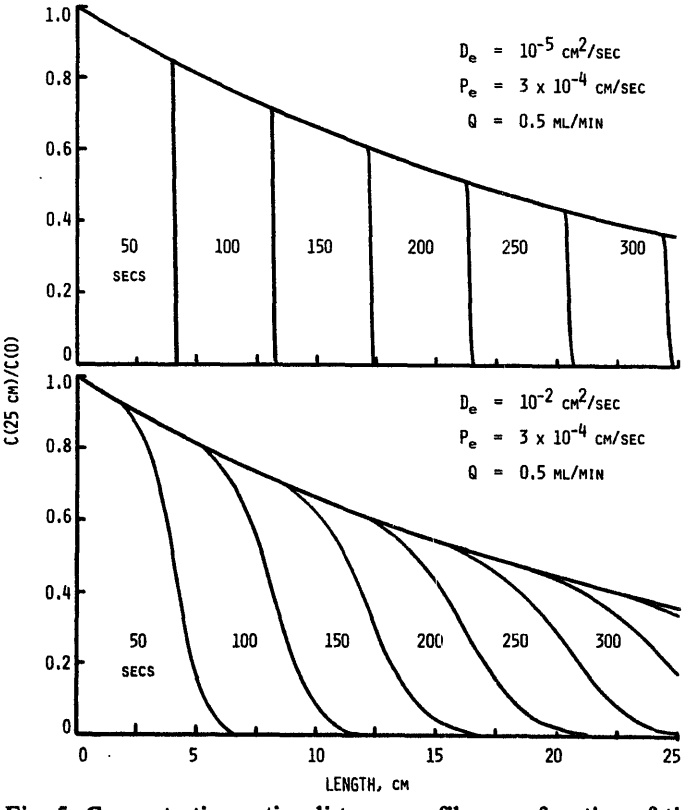

Fig. 5. Concentration ratio–distance profiles as a function of time for an absorbable solute for two longitudinal spreading situations.

lumenal volume of the tube by the flow rate. As can be seen, there are smaller differences in shifts in the horizontal and vertical directions in the non-steady-state region of the profiles. Because of the shorter residence time, the steady-state concentration ratios at 2 ml/min are 0.98 and 0.78 for P_e equal to 3×10^{-5} and 3×10^{-4} cm/sec, respectively, as compared to 0.90 and 0.36 at 0.5 ml/min.

Lastly, Fig. 5 shows typical examples of zonal spreading profiles for absorbable solutes within the length of the tube at various time intervals. The spreading is expectedly less when eddy diffusion currents are small.

In Figs. 2–4, the fraction of solute remaining in the intestinal segment of length ℓ at steady-state is $C(\ell, \infty)/C_0$. It follows that the steady-state fraction absorbed is

$$\text{F.A.} = 1 - \frac{C(\ell, \infty)}{C_0} \tag{30}$$

and, with Eqn. 22,

$$\text{F.A.} = 1 - \exp\left(-\frac{2\pi r \ell P_e}{Q}\right) \tag{31}$$

First-order infusion of finite amount of drug

Fig. 6 shows the $C(\ell, t)/C_0$ (i.e. ratio of outflow concentration at intestinal length ℓ at time t to the initial concentration at the entrance of the intestines) vs time profiles as a function of permeability coefficients representing a non-absorbable solute ($P_e = 0$), membrane-controlled solute ($P_e = 3 \times 10^{-5}$ cm/sec) and aqueous boundary layer-controlled solute ($P_e = 3 \times 10^{-4}$ cm/sec). The conditions of flow rate, infusion rate, intestinal length and effective diffusion coefficient are constant. The area under the curve becomes progressively smaller as the permeability of the intestines increases.

All other factors being constant, the influence of longitudinal spreading on absorption is seen by comparing the corresponding curves in Fig. 6. The upward part of the curve is almost perpendicular when the effective diffusion coefficient is in the order of molecular diffusivity ($D_e = 10^{-5}$ cm^2/sec) and has more curvature when the effective diffusion coefficient is 1000-fold larger. The appearance of unabsorbed drug at the end of the 25 cm length occurs sooner when spreading is larger. However,the extent of drug unabsorbed, as indicated by the respective areas under the curves for similar permeability coefficients, is not significantly affected even by the large differences in longitudinal spreading diffusion coefficients used within the simulated conditions. Generally, large spreading coefficients tend not only to bring about the early appearance of unabsorbed drug at the end of the small intestines beyond that expected for simple plug-flow, but also to decrease the extent of absorption by effectively decreasing the residence time of the drug in the intestines beyond that determined by plug-flow alone. Examples of the effect of longitudinal spreading on concentration–distance curves with time are shown in Fig. 7.

Before proceeding further with the results of other situations, i.e. the effect of flow rate, infusion rate and intestinal length on absorption, the interpretation of the areas

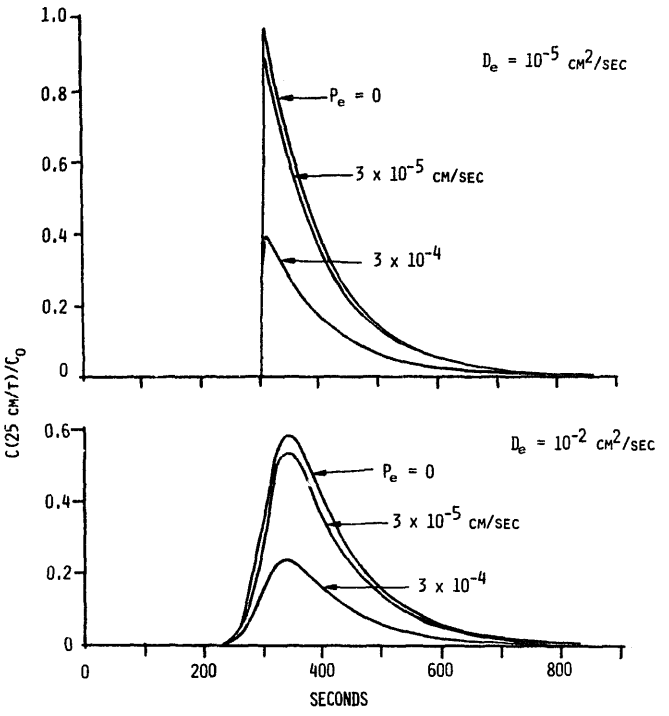

Fig. 6. Effect of longitudinal spreading diffusion coefficient on the outflow to initial inflow concentration ratio as a function of permeability coefficients for a 25 cm intestinal length. The flow rate is 0.5 ml/min and infusion rate constant is 10^{-2} sec^{-1}.

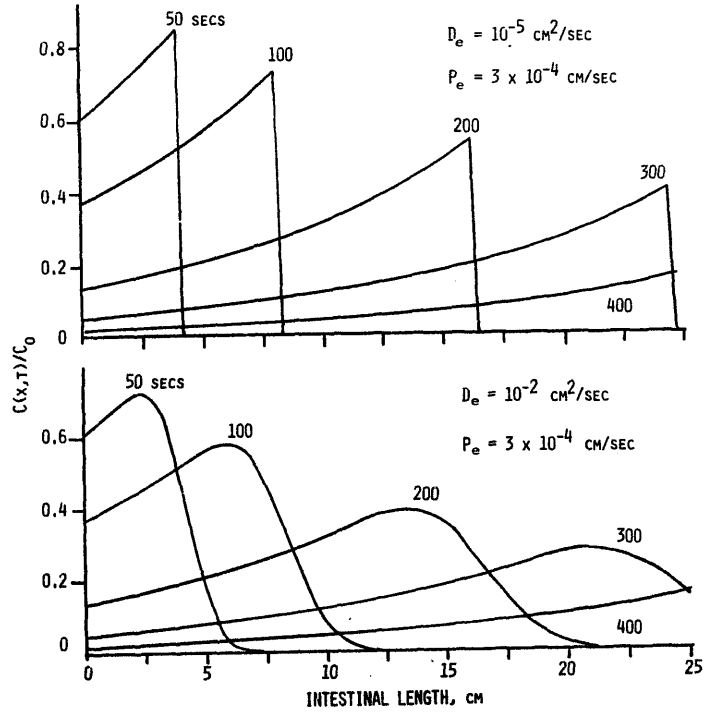

Fig. 7. Effect of spreading diffusion coefficient on concentration–distance curves with time. The flow rate is 0.5 ml/min; infusion rate constant is 10^{-2} sec^{-1} and maximum length is 25 cm.

under the curves, such as those found in Fig. 6, should be discussed with respect to the extent of absorption. In general, the total area under the $C(\ell, t)/C_0$ vs t curve (AUC) is proportional to the total amount of drug unabsorbed [1]. When there is no absorption as in the situation of an unabsorbable marker,

$$\text{AUC}\,(P_e = 0) \propto \text{Total amount of unabsorbed marker} = \text{Total dose infused into the intestines} \tag{32}$$

The fraction of total drug absorbed within intestinal length ℓ relative to the total dose infused into the intestines via the stomach becomes:

$$\text{F.A.} = \frac{\text{AUC}(P_e = 0) - \text{AUC}(P_e > 0)}{\text{AUC}(P_e = 0)} \tag{33}$$

where F.A. = fraction of total drug absorbed within intestinal length ℓ relative to the total dose infused into the small intestines and

$$\frac{\text{AUC}(P_e > 0)}{\text{AUC}(P_e = 0)} = \text{fraction of unabsorbed drug}$$

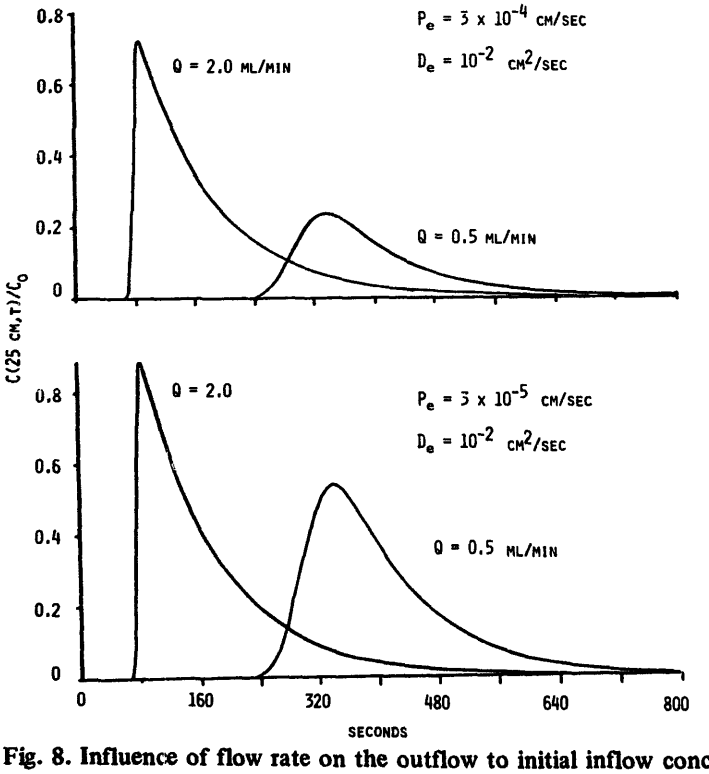

Fig. 8. Influence of flow rate on the outflow to initial inflow concentration ratio for various permeability coefficients in a 25 cm intestinal length. The infusion rate constant is 10^{-2} sec^{-1}.

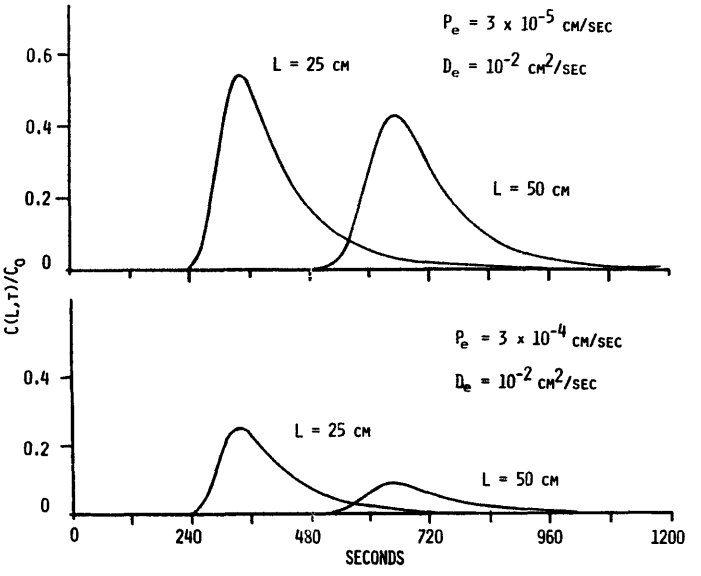

Fig. 9. Influence of intestinal length on the outflow to initial inflow concentration ratio with time for various permeability coefficient cases. The effective diffusion coefficient is 10^{-2} cm^2/sec, flow rate is 0.5 ml/min, infusion rate constant is 10^{-2} sec^{-1}.

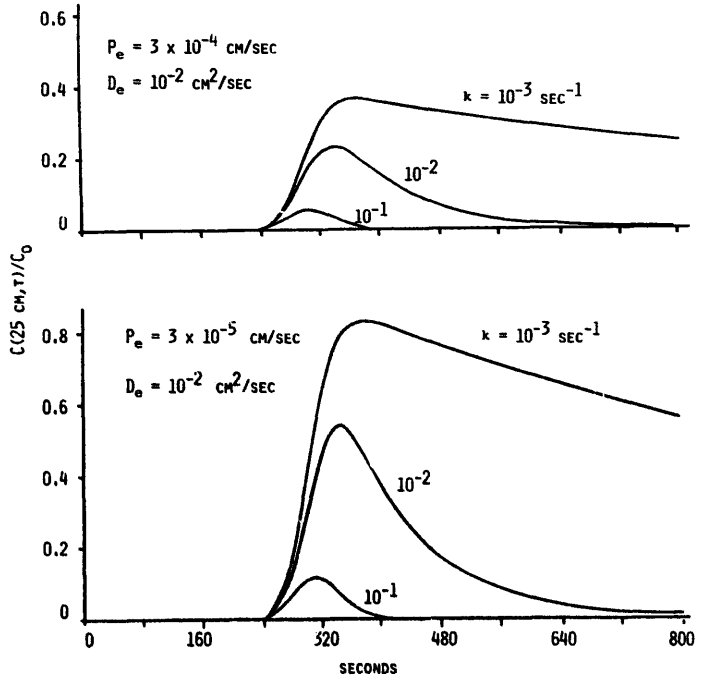

Fig. 10 Infusion rate effect on drug appearance at the end of 25 cm intestinal length for various permeability coefficients. The effective diffusion coefficient is 10^{-2} cm^2/sec and flow rate is 0.5 ml/min.

Fig. 8 illustrates the change in the concentration ratio of the appearance of solute to the initial reservoir with time as a function of flow rates. When the 2 ml/min rate is compared with the slower flow rate of 0.5 ml/min, the appearance of unabsorbed solute is faster by a factor of 4; however, the fraction of the dose absorbed is much less due to the smaller residence time in the 25 cm segment.

The effect of intestinal length on the extent of absorption can be seen in Fig. 9. By increasing the length from 25 to 50 cm, the total fraction unabsorbed in decreased about two-fold for the highly permeable solute (lower curves) and less significantly for the less permeable solute (upper set of curves).

Fig. 10 illustrates the effect of infusion rate constants. Bolus-like input into the intestines ($k = 10^{-1}$ sec^{-1}) exhibits a smaller AUC as, for example, compared to that for $k = 10^{-3}$ sec^{-1}. However, when the areas are compared to their respective AUC ($P_e = 0$), the fractions of drug absorbed are identical and, therefore, independent of the input rate constant.

RELEVANCE OF THE PHYSICAL MODEL

The partial differential equation and boundary conditions of the physical model are believed to be the most general, physically reasonable statements of what goes on within the small intestines representing comprehensively and concisely the mass balance relationships for solutes during flow and absorption. The mathematical solutions for various situations are rigorous and yield relationships useful in experimental design and data analysis in in vivo animal and human studies.

Employing a steady-state, in situ, single-pass perfusion technique in the small intestines of the rat and steroid solutes varying in lipophilicity, Komiya et al. (1980) found quantitative relationships between the flow rate and the apparent permeability coefficients, specifically the permeability of the aqueous boundary layer. Here, Eqns. 22 and 31 were used in the data analysis. The quantitative effect of hydrodynamics on absorption was discussed in the light of the S-shaped course of the intestines, rough surfaces due to villus projections, peristalsis and villus motility. To date, very little is known from the experimental standpoint as regards the influence of flow rate on the degree of longitudinal spreading in the intestines. This gap in knowledge should be breached before physically relevant parameters and their quantitative relationships can be applied to non-steady-state flow, spreading and absorption experiments to test the concepts of the model.

The physical model is founded on the existence of a time-dependent concentration gradient as the drug in the fluid flows down the small intestines, i.e. the intestine is longitudinally not a well-mixed compartment [1]. This premise, which intuitively makes physical sense, is supported by a host of human intubation studies. Soergel (1971) followed the appearance of a single bolus dose of a non-absorbable marker (phenol red) downstream in the jejunum and ileum (70 and 140 cm from the infusion tip positioned at the ligament of Treitz) to measure the average flow rates in fasted and non-fasted humans. Sharply

[1] Mathematical details of the amounts of drug leaving the intestines of length ℓ, amounts absorbed are forthcoming in the manuscript entitled 'Relating gastrointestinal absorption and blood levels by the physical model approach'.

defined parabolic concentration–time curves, similar to those shown in Fig. 9, were observed from aspirated samples in the jejunum and ileum. In a classical study Borgstrom et al. (1957) employed a liquid test meal of homogenized oil, protein and glucose mixture and found that glucose, protein and fat were completely absorbed within 100 cm of the jejunum which indicates an anatomical reserve length of about 250 cm for an average small intestinal length of 350 cm. The reserve length is the length of small intestines yet available for absorption (Ho et al., 1979).

In conclusion the proposed physical model provides a rigorously potential framework within which the bioavailability of orally administered drugs, the efficacy of pharmaceutical formulations and the effects of gastrointestinal physiological factors can be studied and mechanistically interpreted via in vivo perfusion techniques in the intubated human (Sladen, 1975).

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