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Theoretical Model Studies of Drug Absorption and Transport in the GI Tract III

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Abstract □ The diffusional transport of drugs across a membrane under the influence of hydrostatic (or osmotic) flow is described. The physical model consists of a bulk aqueous phase with a diffusion layer followed by a heterogeneous (lipid/aqueous) compartment and a perfect sink. The steady-state rate of change of the total drug concentration in the bulk aqueous phase is in the general form of a first-order equation useful for the evaluation of experiments. Computations are made for different cases in simulation of the *in situ* absorption of drugs in animals when the tonicity of the drug solution is varied. Several limiting models are mathematically deduced from the more general approach.

Keyphrases □ Drug transport—effect of hydrostatic (or osmotic) flow and surface pH in the GI tract, theoretical □ Membrane diffusion—effect of hydrostatic (or osmotic) flow and surface pH on GI drug absorption, theoretical □ Absorption, GI, theoretical—effect of hydrostatic (or osmotic) flow and surface pH on drug transport

Previous theoretical studies of drug absorption and transport in the GI tract have been involved with diffusion models (1, 2). The correlation of the intestinal, gastric, and rectal absorption of sulfonamides and barbituric acid derivatives with the models were found to be generally satisfactory and encouraging. More recently, the application of one of the models for the quantitative interpretation of the *in vivo* buccal absorption of a homologous series of *n*-alkanoic acids was highly successful (3).

This paper is an extension of the previous theoretical studies. It is also a description of a physical model for the transport of neutral, acidic, basic, and amphoteric drugs applicable to situations in which the diffusional flux of the drug is influenced by bulk fluid flow. The surface pH is also considered in a manner not previously treated. The general nature of the drugs, the ionic equilibria, and the distribution of drug species in a compartment were already described. Thus, Eqs. 1–9 of *Reference 2* are also appropriate here. To be consistent, the notations and definitions used in the previous papers will be generally followed[1].

The aqueous channel (or pore) is an important pathway of drug transport across biological membranes. In this connection, the permeation of solute as well as solvent should be simultaneously considered. The concepts of the aqueous pore route of mass transport in *in vitro* and biological membrane systems and the results of some experimental studies with biological membranes such as the gastric mucosa of animals, cell and capillary membranes, and tissues are found in the reviews of Pappenheimer (4), Solomon (5), and others (6–9). The well-known work of Renkin (10) provided the present physicochemical basis for the effective restriction on the diffusion of small solute molecules through pores. This was rigorously tested by Beck and Schultz (11). The meaning of pores in biological membranes was reviewed

[1] In this paper, K (instead of P) is used for the intrinsic partition coefficient and K_e (instead of P_e) is used for the effective partition coefficient.

by Smyth and Whittam (12). The implication is that pores, which have not been seen with an electron microscope, represent regions of the membrane that are more aqueous than the lipoidal part. Therefore, from an operational point of view, these pores can be regarded as simple tubes.

THEORY

General Description of Model—The model is schematically shown in Scheme I. The first compartment (mucosal side) consists of the bulk aqueous phase and a diffusion layer of thickness L_1. The second compartment, of thickness L_2, provides for a heterogeneous phase to simulate a membrane consisting of a lipoidal phase of volume fraction α and aqueous pores or channels ($1 - \alpha$). Thereafter, sink conditions on the serosal side are assumed to prevail.

In this model, all molecular species (cationic, anionic, and nonionic) existing in the aqueous diffusion layer are able to permeate through the heterogeneous compartment. The aqueous pathway is accessible to all molecular species by diffusion under the influence of osmotic or hydrostatic flow. It is assumed that only the nonionized species can partition into and diffuse through the lipid phase. The existence of a hydrostatic flow in the diffusion layer is also accounted for.

Diffusion of a Single Drug Species under Influence of Hydrostatic (or Osmotic) Flow—The steady-state flux for the diffusion of the kth drug species (cationic, nonionic, or anionic) under the influence of hydrostatic flow (13) is expressed by:

$$G_k = D_w \frac{d(R_w^k)}{dx} + v \cdot (R_w^k) \qquad \text{(Eq. 1)}$$

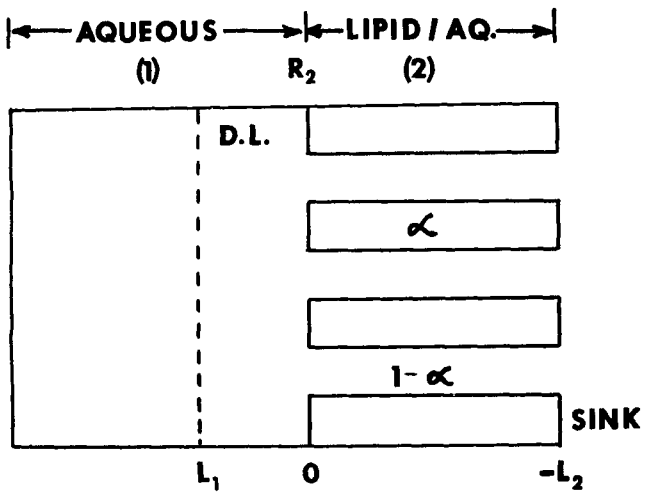
where G_k is the flux of the kth species, D_w is the aqueous diffusion coefficient, (R_w^k) is the aqueous concentration of the kth species, and v is the velocity of fluid flow in centimeters second^{-1}. As shown in the *Appendix*, the flux in the aqueous diffusion layer is:

$$G_{1,k} = \frac{D_{w,1}}{L_1} [(R_w^k)_1 - (R_w^k)_{+0}] + v(R_w^k)_1 \qquad \text{(Eq. 2)}$$

and the flux in the aqueous channels ($1 - \alpha$) is:

$$G_{(1-\alpha),k} = \frac{(1 - \alpha)(D_{w,2} + v'L_2)}{L_2} (R_w^k)_{-0} \qquad \text{(Eq. 3)}$$

where $G_{1,k}$ and $G_{(1-\alpha),k}$ are the fluxes of the kth species in the diffusion layer and aqueous channels, respectively; the subscripts 1, +0, and −0 denote the bulk aqueous phase and the interfaces of the membrane on the first- and second-compartment sides, respectively; and v' is the velocity of water flow in the channels and is different in magnitude from the flow velocity, v, in the diffusion layer.



Scheme I—Schematic model of the transport of drugs across the GI tract. The bulk aqueous solution with an aqueous diffusion layer on the mucosal side is followed by a heterogeneous membrane consisting of lipoidal and aqueous channel pathways and thereafter by a sink on the serosal side.

Total Flux Equations—The total flux in the aqueous diffusion layer, G_1, is the sum of the fluxes of the individual drug species:

$$G_1 = A \cdot \Sigma G_{1,k} \qquad \text{(Eq. 4)}$$

Substituting Eq. 2 into Eq. 4 and letting the aqueous diffusion coefficients be equal ($D_{w,1}^+ = D_{w,1}^0 = D_{w,1}^- = D_{w,1}$), one gets:

$$G_1 = \frac{AD_{w,1}}{L_1} [(TR)_{w,1} - (TR)_{w,+0}] + Av(TR)_{w,1} \qquad \text{(Eq. 5)}$$

Here, $(TR)_{w,1}$ and $(TR)_{w,+0}$ are the total drug concentrations in the bulk and at the interface, respectively, and A is the geometric surface area.

Likewise, the total flux in the second compartment is the sum of the fluxes in the lipid phase and the aqueous channels; thus:

$$G_2 = AR_2 \left\{ \frac{\alpha D_0 (R_0^0)_{-0}}{L_2} + \frac{(1 - \alpha)}{L_2} [(D_{w,2}^+ + v'L_2)(R_w^+)_{-0} + (D_{w,2}^0 + v'L_2)(R_w^0)_{-0} + (D_{w,2}^- + v'L_2)(R_w^-)_{-0}] \right\} \qquad \text{(Eq. 6)}$$

where R_2 is the ratio of the interfacial area to the geometrical area such that $A \cdot R_2$ is the true surface area, and D_0 is the lipid diffusion coefficient of the nonionized species whose lipid concentration at the interface is $(R_0^0)_{-0}$. The superscripts (+, 0, and −) denote the cationic, nonionic, and anionic species.

By noting that the ratios of the concentrations of the various drug species in the lipid and aqueous phases with respect to the total concentration at the interface, $(TR)_{-0}$, are:

$$C_{0,-0}^0 = (R_0^0)_{-0}/(TR)_{-0} \qquad \text{(Eq. 7a)}$$

$$C_{w,-0}^0 = (R_w^0)_{-0}/(TR)_{-0} \qquad \text{(Eq. 7b)}$$

$$C_{w,-0}^+ = (R_w^+)_{-0}/(TR)_{-0} \qquad \text{(Eq. 7c)}$$

$$C_{w,-0}^- = (R_w^-)_{-0}/(TR)_{-0} \qquad \text{(Eq. 7d)}$$

and that the effective diffusion coefficient, D_e, is:

$$D_e = \alpha D_0 C_{0,-0}^0 + (1 - \alpha)[(D_{w,2}^+ + v'L_2)C_{w,-0}^+ + (D_{w,2}^0 + v'L_2)C_{w,-0}^0 + (D_{w,2}^- + v'L_2)C_{w,-0}^-] \qquad \text{(Eq. 8)}$$

and that the effective partition coefficient, K_e, is:

$$K_e = \frac{(TR)_{-0}}{(TR)_{w,+0}} \qquad \text{(Eq. 9)}$$

Eq. 6 may be rewritten as:

$$G_2 = \frac{AR_2 D_e K_e}{L_2} (TR)_{w,+0} \qquad \text{(Eq. 10)}$$

The continuity of flow through the interface is given by $G_1 = G_2$, from which, with Eqs. 5 and 10, one readily finds:

$$(TR)_{w,+0} = \frac{[(D_{w,1}/L_1) + v](TR)_{w,1}}{[(D_{w,1}/L_1) + v] + (R_2 D_e K_e/L_2)} \qquad \text{(Eq. 11)}$$

Recognizing that $G_1 = \{-V[d(TR)_{w,1}/dt]\}$, where V is the volume of the aqueous drug solution, and using Eq. 11, one can then write Eq. 5 as a first-order expression:

$$\frac{d(TR)_{w,1}}{dt} = -K_u(TR)_{w,1} \qquad \text{(Eq. 12)}$$

in which the rate constant is:

$$K_u = \frac{A}{V}\left(\frac{D_{w,1}}{L_1} \pm v\right) \left\{ \frac{1}{1 + [(D_{w,1} \pm vL_1)L_2/R_2 L_1 K_e D_e]} \right\} \qquad \text{(Eq. 13)}$$

Apparent First-Order Rate Constant K_u—According to the conventional form previously reported (1, 2), the rate constant may also be expressed by:

$$K_u = B_1 \cdot f(T) \qquad 0 < f(T) \leq 1 \qquad \text{(Eq. 14)}$$

where:

$$B_1 = \frac{A}{V}\left(\frac{D_{w,1}}{L_1} \pm v\right) \qquad \text{(Eq. 15)}$$

$$f(T) = \frac{1}{1 + [(D_{w,1} \pm vL_1)L_2/R_2L_1K_eD_e]} \qquad \text{(Eq. 16)}$$

The term B_1 has units of reciprocal seconds and is the maximum rate constant when the dimensionless $f(T) = 1$. In Eq. 13, if the current of the hydrostatic flow in the aqueous diffusion layer and channels is in the same direction of the diffusional flow, there will be a positive contribution of the hydrostatic flow beyond ordinary diffusion; otherwise, the contribution is negative.

Let one now expand the function K_eD_e. With Eqs. 7*a–d*, 8, 9, and:

$$K = \frac{(R_0^0)_{-0}}{R^0_{w,+0}} = \frac{(R_0^0)_{-0}}{R^0_{w,-0}} \qquad \text{(Eq. 17)}$$

$$X_{1,+0} = \frac{(R_w{}^0)_{+0}}{(R_w{}^0)_{+0} + (R_w{}^+)_{+0} + (R_w{}^-)_{+0}} \qquad \text{(Eq. 18)}$$

$$X_{2,-0} = \frac{(R_w{}^0)_{-0}}{(R_w{}^0)_{-0} + (R_w{}^+)_{-0} + (R_w{}^-)_{-0}} \qquad \text{(Eq. 19)}$$

where K is the intrinsic lipid/aqueous partition coefficient, and $X_{1,+0}$ and $X_{2,-0}$ are the mole fractions of the nonionized drug species in the aqueous phases at the interface, the function K_eD_e becomes:

$$K_eD_e = \alpha D_0KX_{1,+0} + (1 - \alpha)(D_{w,2} \pm v'L_2)\frac{X_{1,+0}}{X_{2,-0}} \qquad \text{(Eq. 20)}$$

One principal difficulty encountered here is the treatment of the boundary conditions for the pH at the surface. There are several possibilities, some being intuitively more reasonable than others.

Case 1—If the surface pH is the result of the simultaneous flux of acids (say, lactic and carbonic acids) from the cells to the surface of the gut wall and then across the aqueous diffusion layer and the flux of the buffer and drug species from the bulk aqueous solution to the surface and across the gut, then the boundary conditions require that $X_{1,+0} = X_{2,-0}$. Consequently, with Eqs. 14–16 and 20, the rate constant becomes:

$$K_u = B_1 \cdot \frac{1}{1 + \dfrac{(D_{w,1} \pm vL_1)L_2}{R_2L_1[\alpha D_0KX_{1,+0} + (1 - \alpha)(D_{w,2} \pm v'L_2)]}} \qquad \text{(Eq. 21)}$$

According to these circumstances, the surface pH should be influenced by the fluxes of the buffers and their buffer capacities. The expression for K_u may also be given in terms of permeability coefficients:

$$K_u = \frac{A}{V} \cdot P_{w,1} \cdot \frac{1}{1 + \dfrac{P_{w,1}}{R_2(P_{0,2}X_{1,+0} + P_{w,2})}} \qquad \text{(Eq. 22)}$$

where:

$$P_{w,1} = \frac{(D_{w,1} \pm vL_1)}{L_1} \qquad \text{(Eq. 23}a\text{)}$$

$$P_{w,2} = \frac{(1 - \alpha)(D_{w,2} \pm v'L_2)}{L_2} \qquad \text{(Eq. 23}b\text{)}$$

$$P_{0,2} = \frac{\alpha D_0K}{L_2} \qquad \text{(Eq. 23}c\text{)}$$

and $P_{w,1}$, $P_{w,2}$, and $P_{0,2}$ are the permeability coefficients of the aqueous diffusion layer, aqueous pores, and the lipoidal component of the membrane, respectively.

It is readily seen that at surface pH > pKa of an acidic drug, for example, the rate of absorption will approach an asymptotic minimum indicative of the passage of drug species through the aqueous channels. The magnitude of this minimum rate will be modified by the effects of adsorption in the aqueous channels, filtration of molecules of sizes in the same order of magnitude or larger than the average pore diameter, and the tortuosity of the channels. Therefore, the $P_{w,2}$ should be replaced by an effective permeability coefficient, $P_{w,\text{eff}(2)}$, such as:

$$P_{w,\text{eff}(2)} = \frac{(1 - \alpha)}{\tau L_2}\left(\frac{D_{w,2}}{1 + k_{ad}} \pm v'\tau L_2\right)F \qquad \text{(Eq. 24)}$$

where τ is the tortuosity factor, k_{ad} is the linear absorption constant, and F is the filtration factor describing the molecular exclusion on geometrical considerations and the hydrodynamic drag on the solute due to proximity of the wall of the channels (10, 14).

Case 2—Another possibility is that the surface pH is governed by the pH of the bulk aqueous solution in which the buffer capacity is high. To account for the situation of the simultaneous diffusion of buffer species from the bulk and the subsequent effect on the pH of the aqueous phase in the membrane compartment, it may be arbitrarily assumed that the $\text{pH}_{(1-\alpha)} = (\text{pH}_{\text{bulk}} + 7.4)/2$. Therefore, $X_{1,+0} \neq X_{2,-0}$, and K_u is:

$$K_u = B_1 \cdot \frac{1}{1 + \dfrac{(D_{w,1} \pm vL_1)L_2}{R_2L_1[\alpha D_0KX_{1,+0} + (1 - \alpha)(D_{w,2} \pm v'L_2)X_{1,+0}/X_{2,-0}]}} \qquad \text{(Eq. 25)}$$

In this, perhaps unrealistic, situation at surface pH > pKa of an acidic drug, the rate slowly approaches zero instead of a constant minimum rate, although aqueous channels are available for drug transport. Here, $X_{1,+0}$ approaches zero faster than $X_{2,-0}$. In effect, this is like having a thin lipid membrane behaving as a gate at the entrance of the aqueous channels in which the fraction of nonionized species at the surface is one of the rate-determining factors as to whether the drug will go through the pore. This second case was used in *Reference 2*.

Hydrostatic Flow Velocity of Water—If one assumes that the aqueous channels consist of uniform cylindrical pores, then a Poiseuille-type flow is applicable here. Thus:

$$U = \frac{n\pi d^4\,\Delta P}{128\eta L_2} \qquad \text{(Eq. 26)}$$

where U is the total bulk flow in cubic centimeters second^{-1}, n is the number of pores, d is the average pore diameter, ΔP is the pressure difference, η is the viscosity, and L_2 is the length of the cylinder. Also, the velocity flow in centimeters second^{-1} is related to the bulk flow by:

$$v' = \frac{U}{n} = \frac{U}{R_2A(1 - \alpha)} \qquad \text{(Eq. 27)}$$

where, as previously defined, R_2A is the true interfacial area and is modified by the porosity $(1 - \alpha)$. By knowing v' and ΔP, the average pore diameter can be approximated. An estimation of the hydrostatic flow in the aqueous diffusion layer is given by:

$$v = \frac{U}{R_2A} = (1 - \alpha)v' \qquad \text{(Eq. 28)}$$

Hence, $v < v'$ always unless there is no hydrostatic flow.

Special Cases of Eq. 21—A mathematical analysis of Eq. 21 points out various limiting cases or models of interest.

Case 1—In the absence of hydrostatic pressure and when the aqueous channel pathway is negligible, *i.e.*, $(1 - \alpha) \sim 0$, the rate constant reduces to that of Model I described in *References 1* and *2*:

$$K_u = \frac{AD_{w,1}}{VL_1} \cdot \frac{1}{1 + (D_{w,1}L_2/L_1R_2D_0KX_{1,+0})} \qquad \text{(Eq. 29)}$$

Case 2—When the thickness of the aqueous diffusion layer is negligible as compared to the thickness of the gut wall and there is no bulk flow of water:

$$K_u = \frac{AR_2}{VL_2}[\alpha KD_0X_{1,+0} + (1 - \alpha)D_{w,2}] \qquad \text{(Eq. 30)}$$

whereby a plot of K_u *versus* $X_{1,+0}$ gives a straight line with a slope proportional to the permeability of the membrane and an intercept

Table I—Numerical Dimensions of Constants Used for Computation

A	= 100 cm.^{2}	$D_{w,1}$	= 10^{-5} cm.^{2} sec.$^{-1}$
V	= 25 cm.^{3}	$D_{w,2}$	= 10^{-7} cm.^{2} sec.$^{-1}$
R_2	= 1.0	D_0	= 10^{-10} cm.^{2} sec.$^{-1}$
L_1	= 2.5×10^{-3}; 10^{-2} cm.	α	= 0.99
L_2	= 2×10^{-6} cm.	$1 - \alpha$	= 10^{-2}
K	= 10; 10^2; 10^3	v'	= 0; $\pm 5 \times 10^{-2}$ cm. sec.$^{-1}$
pKa	= 5.0	$(TR)_{w,1}$	= 10^{-2} M at $t = 0$

proportional to the permeability of the aqueous pores. This is essentially the classical pH-partition theory of drug absorption (15). With $\alpha = 1$ in Eq. 30, the model reduces to the simple aqueous-lipid compartment model and the rate expression for the classical theory is:

$$K_u = \frac{AR_2KD_0X_{1,+0}}{VL_2} \qquad \text{(Eq. 31)}$$

However, it is recognized that the classical theory (Eq. 30 or 31) is not only a special case of the more general theory presented here or elsewhere (1, 2) but also is inadequate for explaining the *in situ* rat intestinal and gastric absorption of sulfonamides and barbiturates (2) and the *in vivo* buccal absorption of *n*-alkanoic acids (3).

CALCULATIONS

Computations were carried out for a range of parameters and situations using Eqs. 21 and 29–31. Table I gives the dimensions of the constants. The surface pH, thickness of the aqueous diffusion layer, partition coefficient, and hydrostatic flow velocity were varied.

RESULTS AND DISCUSSION

Comparison between Models—Figure 1 gives the results of the calculation for the absorption rate constant as a function of the surface pH in which four models, *i.e.*, aqueous plus diffusion layer/lipid-aqueous (Eq. 21), aqueous plus diffusion layer/lipid (Eq. 29), classical pH-partition with aqueous channels (Eq. 30), and classical pH-partition (Eq. 31) models, are compared under constant conditions. There are several points of general interest here.

The models containing an aqueous diffusion layer predict a lower maximum absorption rate than the classical pH-partition theoretical models which ignore the existence of a diffusion layer. This result is expected since the diffusion layer is an additional transport barrier in series with the membrane. The importance of this layer may be determined by varying the degree of agitation of the bulk aqueous solution on the mucosal side. Or one may carry out experiments with a homologous series of a drug. The model with a diffusion layer predicts that one will eventually arrive at a maximum asymptotic rate that is independent of higher order drugs within the homologous series (or partition coefficient), whereas the simple pH-partition models always predict an increasing rate.

When aqueous channels in the membrane are present, there is a predictable asymptotic minimum absorption rate at pH $\gg$ pKa of an acidic drug, provided the passage of the solute molecules through the channels is unrestricted. In the limit that the molecular size of the solute is comparable or greater than the size of the channels, then by Eq. 24 the permeability of the channels is negligible. Consequently, the rate eventually approaches zero with increasing pH_{+0} so that the membrane behaves essentially as a lipoidal barrier.

Upon comparing the two profiles of the pH-partition models with and without aqueous channels, one readily observes that the porous pathways give rise to higher rates and also a shift of the profile to the right of the dissociation curve of the acidic drug such that the absorption rate constant $K_u = {}^1/_2K_{u,max.}$ at $pH_{+0} >$ pKa. With regard to the other two models, the rightward shift of the profile is due to the presence of not only aqueous channels but also the aqueous diffusion layer.

Aqueous plus Diffusion Layer/Lipid-Aqueous Model—The absorption rate-surface pH profiles as a function of partition coefficients at various constant hydrostatic flow velocities in the aqueous channels are shown in Fig. 2. In the acid surface pH range, the absorption rate increases with increasing partition coefficients. Although it is not explicitly shown here, increasing the partition coefficient (*i.e.*, with higher order acidic drug molecules within a homologous series) beyond $K = 10^3$ at these conditions does not improve the absorption rate since the rate-determining factor is not the permeability of the membrane but the permeability of the aqueous diffusion layer. Also, as the partition coefficient is increased, the profiles shift to the right and $K_u = {}^1/_2K_{u,max.}$ of each drug at $pH_{+0} >$ pKa due to the increasing significance of the aqueous diffusion layer.

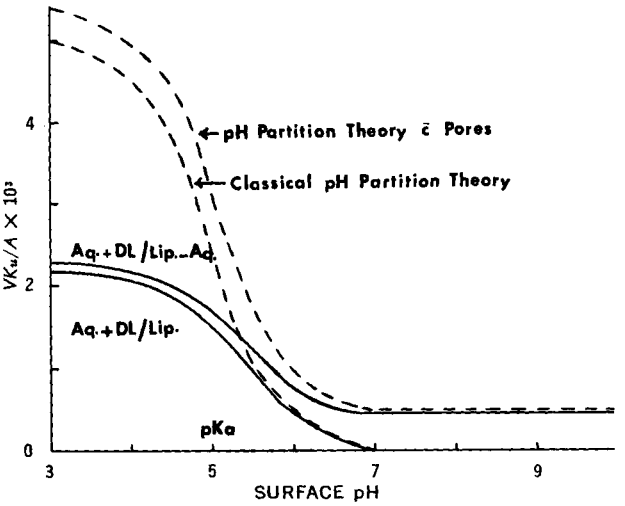


Figure 1—*Absorption rate-surface pH profiles distinguishing four physical models. Partition coefficient* K = *100; aqueous diffusion layer* $L_1 = 2.5 \times 10^{-3}$; *hydrostatic flow velocities in the diffusion layer and aqueous channels* v = v′ = *0.*

At the surface pH $\gg$ pKa, the rate is finite and becomes independent of the partition coefficient, providing the passage of the drug in the ionized form through the aqueous channels is unhindered.

In the situation where the bulk fluid flow is in the same direction as the diffusional flux, as designated by the hydrostatic flow velocity in the aqueous channels, $v' = 5 \times 10^{-2}$ cm. sec.$^{-1}$, the rate of absorption at any pH condition is faster than that for the no bulk fluid flow case, *i.e.*, $v' = 0$, and, in turn, is faster than the situation

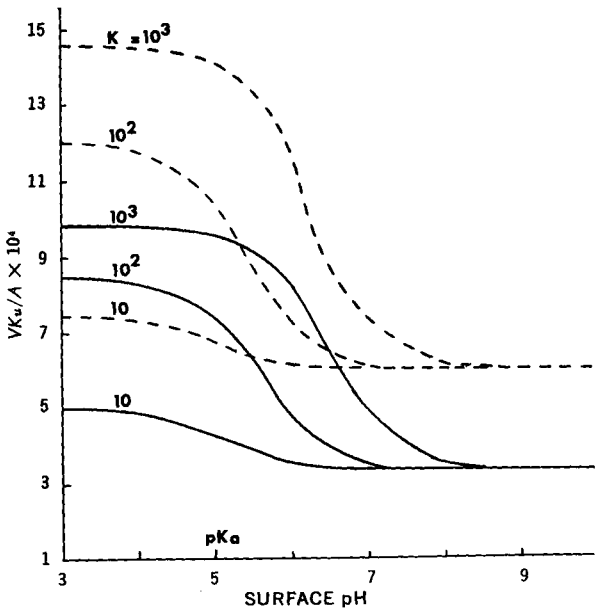


Figure 2—*Absorption rate-surface pH profiles as a function of partition coefficients at various constant hydrostatic flow velocities in the aqueous channels;* $L_1 = 10^{-2}$ *cm. Key:* - - -, v′ = 5×10^{-2}; *and* ——, v′ = *0.*

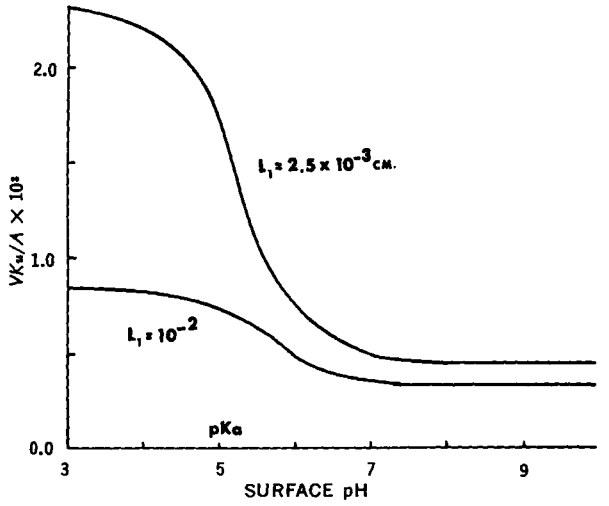


Figure 3—*Absorption rate–surface pH profiles for various aqueous diffusion layer thicknesses;* K = 10^2 *and* v = v′ = 0.

in which the bulk flow opposes the diffusional flux. As one example of some practical situations, the cases of positive, negative, or negligible bulk fluid flow with respect to the diffusional flux may apply to the transport of drugs from hypotonic, hypertonic, or isotonic solutions, respectively. The hydrostatic flow velocity of $v' = 5 \times 10^{-2}$ cm. sec.$^{-1}$ used in the calculations corresponds to a bulk flow of 3 ml. water/hr. In the event that the opposing hydrostatic flow velocity of water is greater than the diffusional velocity of the solutes, Eq. 21 predicts that there should be no transport of drug across the membrane. Instead, there will be secretion of fluid from the serosal side to the mucosal side.

The curves in Fig. 3 show the effect of the diffusion layer thickness on the rate at various pH.

Figure 4 gives the first-order plots of the change in the total drug concentration in the bulk aqueous phase with time at different bulk flow situations when $pH_{+0} = 5.0$ and $K = 100$. For comparison, the curves for the model of the pH-partition theory with

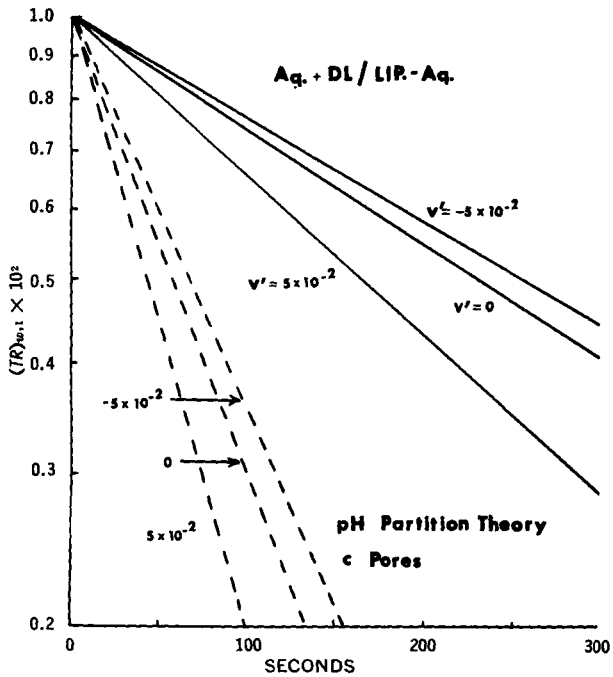
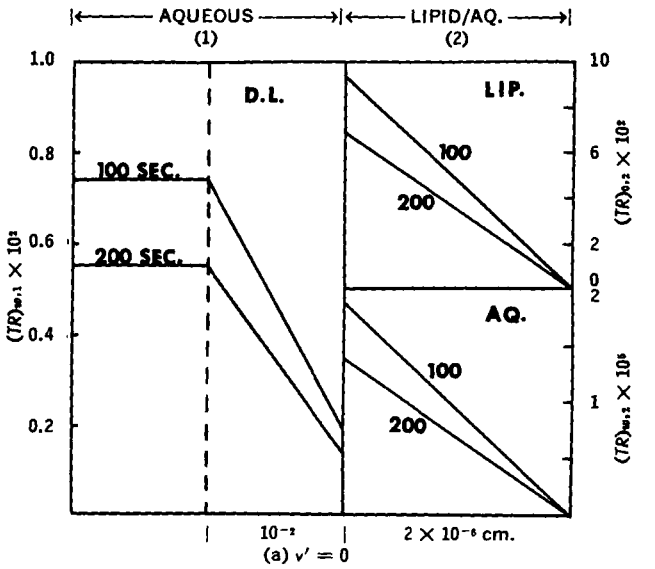


Figure 4—*First-order plots comparing the aqueous plus diffusion layer/lipid–aqueous model with the classical pH-partition with aqueous channels model at different hydrostatic flow velocities;* L_1 = 10^{-2} *cm.;* K = 10^2*; surface* $pH_{+0} = pKa = 5.0$.



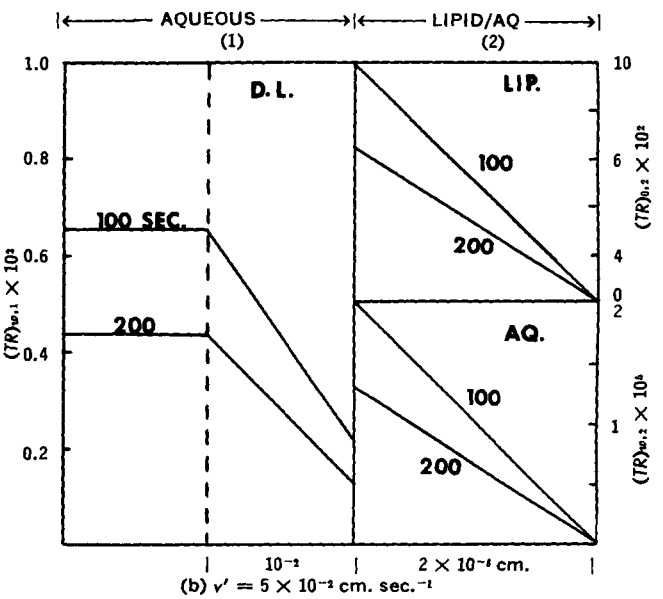


Figure 5—*Steady-state concentration distance profiles for two cases: (a)* v′ = 0*, and (b)* v′ = 5×10^{-2} *cm. sec.*$^{-1}$*. In each case,* K = 10^2 *and* $pH_{+0} = pKa = 5.0$.

aqueous channels are also included. The steady-state concentration distribution curves corresponding to the conditions of the calculations in Fig. 4 are found in Fig. 5. As compared to the no bulk fluid flow case, a positive bulk flow leads not only to a greater permeability of all drug species through the diffusion layer and aqueous channels of the membrane but also to an enriched concentration of lipid-transportable nonionized drug species at the membrane surface.

CONCLUSION

A physical model for the absorption of drugs applicable to situations in which the diffusional flux of the drug may be influenced by the bulk fluid flow and surface pH was described. This paper is not intended solely to be an exercise in mathematics, since the present investigators will use the models as guidelines to design *in vitro*, *in situ*, and *in vivo* experiments; to interpret data to obtain quantitative estimates of those physical parameters significant in transport phenomena; and to evaluate the applicability of the physical models. Systematic modifications of the models may become necessary as evidence accumulates. Experimental studies on the *in situ* rat intestinal absorption of *n*-alkanoic acids are presently being conducted and evaluated.

APPENDIX

The steady-state flux for the diffusion of the kth species (cationic, nonionic, or anionic) under the influence of hydrostatic flow in the x direction is given by:

$$G_k = D_w \frac{d(R_w^k)}{dx} + v(R_w^k) \qquad \text{(Eq. A1)}$$

The general solution is:

$$(R_w^k) = \frac{G_k}{v} + C \exp(-vx/D_w) \qquad \text{(Eq. A2)}$$

where C is a constant of integration.

In the aqueous diffusion layer of the first compartment (mucosal side), the particular solution to Eq. A2 is subject to the boundary conditions that:

$$(R_w^k) = (R_w^k)_1 \qquad \text{at } x = L_1 \qquad \text{(Eq. A3}a\text{)}$$

$$(R_w^k) = (R_w^k)_{+0} \qquad \text{at } x = +0 \qquad \text{(Eq. A3}b\text{)}$$

Consequently, one obtains:

$$G_{1,k} = \frac{v[(R_w^k)_1 \exp(vL_1/D_{w,1}) - (R_w^k)_{+0}]}{\exp(vL_1/D_{w,1}) - 1} \qquad \text{(Eq. A4)}$$

In the absence of hydrostatic flow, *i.e.*, $v = 0$, the form of Eq. A4 is indeterminant. Therefore, one performs the following expansion of the exponential terms and simplifies by assuming linearity; that is, when $vL_1/D_{w,1}$ is small:

$$\frac{v \cdot \exp(vL_1/D_{w,1})}{\exp(vL_1/D_{w,1}) - 1} = \frac{v(1 + vL_1/D_{w,1} + \ldots)}{1 + vL_1/D_{w,1} + \ldots - 1} \simeq \frac{D_{w,1} + vL_1}{L_1} \qquad \text{(Eq. A5)}$$

and, likewise:

$$\frac{v}{\exp(vL_1/D_{w,1}) - 1} \simeq \frac{D_{w,1}}{L_1} \qquad \text{(Eq. A6)}$$

so that, after introducing the approximations into Eq. A4, the flux becomes:

$$G_{1,k} = \frac{D_{w,1}}{L_1}[(R_w^k)_1 - (R_w^k)_{+0}] + v(R_w^k)_1 \qquad \text{(Eq. A7)}$$

The solution to Eq. A2 for the flux in the aqueous channels $(1 - \alpha)$ of the heterogeneous second compartment satisfying the conditions:

$$(R_w^k) = (R_w^k)_{-0} \qquad \text{at } x = -0 \qquad \text{(Eq. A8}a\text{)}$$

$$(R_w^k) = 0 \qquad \text{at } x = -L_2 \qquad \text{(Eq. A8}b\text{)}$$

is:

$$G_{(1-\alpha),k} = \frac{(1 - \alpha)(D_{w,2} + v'L_2)}{L_2}(R_w^k)_{-0} \qquad \text{(Eq. A9)}$$

The definitions of the terms used are given in the text.

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