Theoretical Model Studies of Intestinal Drug Absorption IV: Bile Acid Transport at Premicellar Concentrations across Diffusion Layer–Membrane Barrier

N. F. H. HO[x] and W. I. HIGUCHI

Abstract □ A general physical model is described for the simultaneous active and passive transport of conjugated and unconjugated bile acids from nonmicellar solutions in the ileum. It reduces to the passive absorption mechanism in the duodenum and jejunum. The model provides the basis for the experimental design of *in situ* studies and the quantification of physically meaningful and experimentally accessible transport parameters and of the effect of functional groups on bile acids. The interaction and factorization of *(a)* the permeability of the stagnant water layer, the lipoidal and aqueous channel pathway of the membrane according to the diffusion mechanisms, *(b)* the permeability of the membrane according to the active mechanism, *(c)* the bile acid concentration dependence, and *(d)* the pH and pKa are mathematically explicit. Theoretical computations indicated that the stagnant water layer may be the rate-determining barrier. A model is described for the first-pass absorption of bile acids from dilute solutions in the small intestine.

Keyphrases □ Drug absorption, theoretical models—bile acid transport at premicellar concentrations across diffusion layer-membrane □ Bile acids—general physical model described for active and passive transport of conjugated and unconjugated bile acids from nonmicellar solutions □ Absorption, intestinal drug—theoretical model described, simultaneous active and passive transport of conjugated and unconjugated bile acids, premicellar concentrations, diffusion layer-membrane barrier □ Diffusion layer-membrane—physical model described for bile acid transport, equations □ Membranes, diffusion layer—physical model described for bile acid transport, equations

According to recent reviews (1, 2), bile acids are absorbed passively *in vivo* in the duodenum and jejunum but are absorbed both passively and actively in the ileum. Because the nondissociated species are transported by simple diffusion across the lipoidal pathway of the intestinal membrane and the anionic species are transported passively across the aqueous channels of the intestinal membrane and actively through the ileal membrane, the total transport rate across any segment (*i.e.*, duodenum, jejunum, and ileum) depends effectively on the pKa of the acid and the pH of the solution. For this reason, the taurine-conjugated bile acids (pKa ~ 2.0) are absorbed principally within the ileal segment of the small intestine. For the glycine-conjugated bile acids (pKa 4–5) and the unconjugated bile acids (pKa 5–6), there will be a more significant contribution of the passive mechanism to the total transport rate in the ileum.

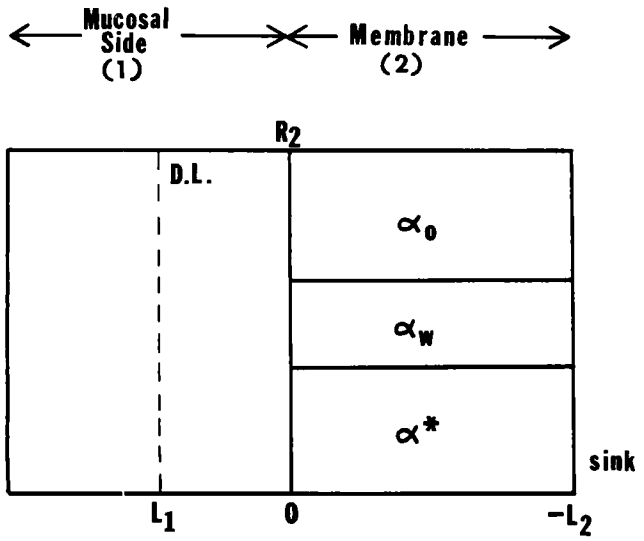
The circumstances of the concentration dependence of the total transport rate are recognized. Since the active transport rate *per se* in the ileum increases with the increasing concentration of anionic species until a maximum rate is reached, the total concentration of bile acid and the pKa and pH are important considerations. However, in the limit where the activity of the bile acid has drastically changed beyond a critical concentration, one must now also consider the transport of bile acids from micellar solutions. Here, the total transport rate decreases since micelles are not absorbed.

Many investigations on bile acid absorption have been cited in the reviews (1, 2). However, some recent studies (3–7) involve the application of physical models to the quantitation of various mechanistic transport parameters (active and passive) and the assessment of functional groups on bile acids affecting the transport across the intestinal brush border of rats. While the importance of the unstirred water layer on the mucosal side to the total transport rate of bile acids from micellar and nonmicellar solutions has been recognized (5, 6), this transport barrier admittedly has not been accounted for in determining the intrinsic active and passive flux of the bile acid across the intestinal membrane (3, 4). Although the intrinsic permeability coefficients of the membrane according to the active and passive mechanism, after factoring out the effect of the unstirred water layer and the pH of the solution relative to the pKa of the acid, have not been determined, a knowledge of these parameters would appear to be extremely useful. It has been the authors' experience, both theoretically (8, 9) and experimentally[1,2], that the unstirred water layer can significantly affect the total transport rate of solute molecules and the proper quantification of the factors involved in intestinal absorption.

The purpose of this paper is to derive a general physical model for the intestinal transport of bile acids from nonmicellar solutions. The model is based on the first principles of transport, thermodynamics, and various biological and physicochemical relationships known about the transport of bile acids in dilute solutions. As will be seen, the mathematical expressions are explicit in describing the interaction of the permeabilities of the physically relevant transport barriers, the pH of the solution at the membrane surface, and the characteristic pKa of the bile acid. Furthermore, the physical model and the accompanying mathematics are presented in a manner accessible to experimental evaluation and determi-

[1] N. F. H. Ho, J. T. Doluisio, and W. I. Higuchi, "*In Vivo* Drug Absorption I: Preliminary Studies of the Rat Intestinal Absorption of *n*-Alkanoic Acids by the Static Method," *J. Lipid Res.*, submitted for publication.

[2] K. J. Desai, N. F. H. Ho, and W. I. Higuchi, "*In Vivo* Drug Absorption II: Aqueous Diffusion Layer in the Rat Intestinal Tract," *J. Lipid Res.*, submitted for publication.



Scheme I—Physical model for the simultaneous active and passive transport of bile acids from nonmicellar solutions in the intestinal tract. The bulk aqueous solution with an aqueous diffusion layer on the mucosal side is in series with a heterogeneous membrane consisting of parallel lipoidal (α_o) and aqueous channel (α_w) pathways for passive transport and an active transport pathway (α^*). Thereafter, a sink on the serosal side follows.

nation whereby the permeability of the stagnant water layer, the permeability of the lipoidal pathway and the aqueous channels of the membrane according to the passive diffusional mechanism, the active transport kinetic parameters, and the effects of the molecular structure of the bile acids to active and passive transport can be quantified.

THEORY

General Description of Model—The first compartment of the model (Scheme I) (mucosal side) consists of the bulk aqueous phase and a stagnant water layer, *i.e.*, an aqueous diffusion layer, of thickness L_1. The second compartment of thickness L_2 provides for a heterogeneous phase to simulate the ideal membrane consisting of a lipoidal phase of volume fraction α_o and a hydrophilic phase α_w. Thereafter, sink conditions on the serosal side are assumed to prevail.

In this model, the concentration of the conjugated or nonconjugated bile acid solution is below the critical micelle concentration (CMC). All molecular species (anionic and undissociated) existing in the aqueous diffusion layer are able to permeate through the heterogeneous compartment. The aqueous pathway is accessible to all molecular species. It is assumed that only the nondissociated species can partition into and diffuse through the lipid phase. The anionic species are transported passively across the aqueous channels of the membrane, α_w, as well as actively across the α^* part of the membrane. The terms for the volume fractions of the membrane (α_w, α_o, and α^*) denote the distinct parallel pathways for transport and their relative quantitative importance.

Total Steady-State Flux Equations—The total steady-state flux in the aqueous diffusion layer, J_1, is the sum of the fluxes of the individual bile acid species. Assuming that the diffusion coefficients are nearly the same, the total flux is:

$$J_1 = \frac{AD_{w,1}}{L_1}(C_b - C_s) \qquad \text{(Eq. 1)}$$

where C_b and C_s are the total bile acid concentrations in the bulk solution and at the interface of the membrane, respectively; A is the geometric surface area; and $D_{w,1}$ is the diffusion coefficient in the stagnant water layer.

The total flux across the membrane, J_2, is expressed by:

$$J_2 = \frac{AR_2}{L_2}\{\alpha_o D_o (R_o^0)_{-o} + \alpha_w D_{w,2}[(R_w^0)_{-o} + (R_w^-)_{+o}]\} + \frac{AR_2\alpha^* J_{max}(R_w^-)_{+o}}{K_m^* + (R_w^-)_{+o}} \qquad \text{(Eq. 2)}$$

The first term on the right side of the equation represents the passive flux of all species in the membrane, where R_2 is the ratio of the interfacial area to the geometrical surface area such that $(A)(R_2)$ is the true surface area, D_o is the lipid diffusion coefficient of the nondissociated species whose concentration at the interface on the membrane side is $(R_o^0)_{-o}$, and $D_{w,2}$ is the aqueous diffusion coefficient of both the anionic and nondissociated species whose concentrations on the membrane side are $(R_w^-)_{-o}$ and $(R_w^0)_{-o}$, respectively. The superscripts (0 and −) denote the nondissociated and anionic species. The second term on the right side of the equation has the same form as the Michaelis-Menten expression for enzymatic reactions and represents the flux for the active membrane transport of the anionic species at the interface on the aqueous diffusion layer side, *i.e.*, $(R_w^-)_{+o}$. Here, J_{max} is the intrinsic maximum flux for active transport in units of moles centimeters^{-2} seconds^{-1} and K_m^* is the Michaelis constant for active transport in units of moles centimeters^{-3}.

The intrinsic lipid-aqueous partition coefficient, K, is defined as:

$$K = \frac{(R_o^0)_{-o}}{(R_w^0)_{-o}} = \frac{(R_o^0)_{-o}}{(R_w^0)_{-o}} \qquad \text{(Eq. 3)}$$

When the pH's at the interface of the membrane on the aqueous diffusion layer side and the aqueous pore side are assumed to be the same, it follows that:

$$(R_w^0)_{+o} = (R_w^0)_{-o} \qquad \text{(Eq. 4a)}$$

$$(R_w^-)_{+o} = (R_w^-)_{-o} \qquad \text{(Eq. 4b)}$$

The mole fraction of nondissociated species at the membrane interface, X_s^0, is:

$$X_s^0 = \frac{(R_w^0)_{+o}}{(R_w^0)_{+o} + (R_w^-)_{+o}} = \frac{(R_w^0)_{+o}}{C_s} \qquad \text{(Eq. 5)}$$

and, correspondingly, the mole fraction of anionic species, X_s^-, is:

$$X_s^- = \frac{(R_w^-)_{+o}}{(R_w^0)_{+o} + (R_w^-)_{+o}} = \frac{(R_w^-)_{+o}}{C_s} \qquad \text{(Eq. 6)}$$

With Eqs. 3–6 and $J_{max}^* = \alpha^* R_2 J_{max}$, the total flux in the membrane becomes:

$$J_2 = \frac{AR_2}{L_2}(\alpha_o D_o K X_s^0 + \alpha_w D_{w,2})C_s + \frac{AJ_{max}^* X_s^- C_s}{K_m^* + X_s^- C_s} \qquad \text{(Eq. 7)}$$

Furthermore, defining the permeability coefficient of the nondissociated species for the passive diffusion across the lipoidal membrane as:

$$P_o = \frac{\alpha_o R_2 D_o K}{L_2} \qquad \text{(Eq. 8)}$$

and the permeability coefficient of the anionic and nondissociated species for the passive diffusion across the aqueous channels or pores as:

$$P_p = \frac{\alpha_w R_2 D_{w,2}}{L_2} \qquad \text{(Eq. 9)}$$

and the permeability of the aqueous diffusion layer as:

$$P_{aq} = \frac{D_{w,1}}{L_1} \qquad \text{(Eq. 10)}$$

Equations 1 and 7 are rewritten accordingly:

$$J_1 = AP_{aq}(C_b - C_s) \qquad \text{(Eq. 11)}$$

$$J_2 = A(P_o X_s^0 + P_p)C_s + \frac{AJ_{max}^* X_s^- C_s}{K_m^* + X_s^- C_s} \qquad \text{(Eq. 12)}$$

Equations 11 and 12 comprise the primary set of equations that describe the rate of change in the concentration of bile acid in the

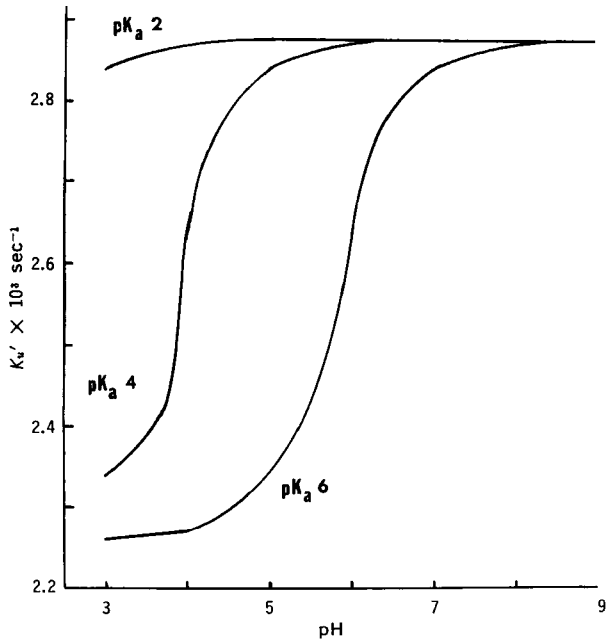


Figure 1—*Theoretical profiles of* K_u' versus *pH for bile acids with different pKa's based on Eq. 18 for the simultaneous passive and active transport in the ileum. Computations are based on Table I, and the permeability of the stagnant water layer equals* 4×10^{-4} *cm sec*$^{-1}$.

lumen of the ileum. Because Eq. 12 is nonlinear, the set of equations is more readily solved by numerical methods. To gain an explicit and helpful insight into the immediate treatment and interpretation of experimental data, approximate, but analytic, solutions to this primary set of equations are sought.

Case I: Linear Approximation of the Flux for Active Transport—In this case where $K_m^* \gg X_s^- C_s$ (concentration of bile acid anion at the mucosal surface), the total flux in the membrane is linearly related to the total concentration at the membrane surface:

$$J_2 = A(P_o X_s^0 + P_m^* X_s^- + P_p)C_s \qquad \text{(Eq. 13)}$$

where the permeability coefficient for active transport in centimeters seconds^{-1} is:

$$P_m^* = \frac{J_{max}^*}{K_m^*} \qquad \text{(Eq. 14)}$$

The continuity of flow through the interface is given by $J_1 = J_2$ from which, with Eqs. 11 and 13, one readily finds:

$$C_s = \frac{P_{aq} C_b}{P_o X_s^0 + P_m^* X_s^- + P_p + P_{aq}} \qquad \text{(Eq. 15)}$$

Combining Eqs. 11 and 15 and recognizing that:

$$J_1 = -V \frac{dC_b}{dt} \qquad \text{(Eq. 16)}$$

where V is the volume of the aqueous solution, one can then write the first-order expression:

$$\frac{dC_b}{dt} = -K_u' C_b \qquad \text{(Eq. 17)}$$

where:

$$K_u' = \left(\frac{A}{V}\right)(P_{aq})\left(\frac{1}{1 + \dfrac{P_{aq}}{P_o X_s^0 + P_m^* X_s^- + P_p}}\right) \qquad \text{(Eq. 18)}$$

Integrating between the limits of $C_b = C_b(0)$ and $C_b(t)$, one gets:

$$\ln C_b = \ln C_b(0) - K_u' t \qquad \text{(Eq. 19)}$$

Table I—Numerical Dimensions of Constants[a] Used for Computations

Constant	Value Used
Surface area to volume	$A/V = 10$
pKa	2.0, 4.0, and 6.0
Permeability coefficients:	
Aqueous diffusion layer	$P_{aq} = 2 \times 10^{-4}$; 4×10^{-4} cm sec^{-1}
Lipoidal pathway	$P_o = 5 \times 10^{-4}$ cm sec^{-1}
Aqueous pores	$P_p = 2 \times 10^{-5}$ cm sec^{-1}
Active transport	$P_m^* = 1 \times 10^{-3}$ cm sec^{-1}
Active transport parameters	$J_{max}^* = 5 \times 10^{-10}$ mole cm^{-2} sec^{-1}
	$K_m^* = 5 \times 10^{-7}$ mole cm^{-3}

[a] The values of the constants represent reasonable estimates from some studies in this laboratory and various literature sources.

There are several interesting limiting situations of Case I. Taking, for example, the absorption of taurocholic acid (pKa = 2.0) in the ileum at pH ~ 6–7, Eq. 18 reduces to:

$$K_u' = \left(\frac{A}{V}\right)(P_{aq})\left(\frac{1}{1 + \dfrac{P_{aq}}{P_m^* + P_p}}\right) \qquad \text{(Eq. 20)}$$

since the fraction of nondissociated acid is negligible at pH $\gg$ pKa. This will not apply to the other bile acids whose pKa ~ 5–6. However, in the duodenum and jejunum where all the bile acids undergo only passive transport, Eq. 18 reduces to an already familiar expression (9):

$$K_u' = \left(\frac{A}{V}\right)(P_{aq})\left(\frac{1}{1 + \dfrac{P_{aq}}{P_o X_s^0 + P_p}}\right) \qquad \text{(Eq. 21)}$$

From an experimental viewpoint, the permeability coefficients, P_o, P_m^*, and P_p can be determined simultaneously by applying Eq. 18 to the first-order rate constants obtained under three pH conditions, for example, pH $\ll$ pKa, pH = 6.0, and pH $\gg$ pKa. This is readily feasible for bile acids with pKa ~ 5–6. The permeability coefficient of the stagnant aqueous layer, P_{aq}, can be found from independent experiments using the *n*-alkanoic acid homologous series[1,2] and Eq. 21. The contribution of functional groups on the different bile acids to membrane transport can be evaluated by comparing the permeability coefficients of the bile acids to that of a reference bile acid. Thus, for the passive transport across the lipoidal pathway:

$$n = \frac{P_{o(\text{bile acid})}}{P_{o(\text{reference bile acid})}} \qquad \text{(Eq. 22)}$$

and for active transport:

$$n^* = \frac{P_{m\,(\text{bile acid})}^*}{P_{m\,(\text{reference bile acid})}^*} \qquad \text{(Eq. 23)}$$

Figure 1 shows a plot of the apparent first-order rate constant K_u' *versus* pH for bile acids with pKa 2.0, 4.0, and 6.0. The numerical dimensions of the constants used for the calculations are found in Table I. The intrinsic permeability coefficient of the membrane for active transport is taken to be larger than the permeability coefficient for passive transport. The curves are indicative of the kind of data that might be expected from the *in situ* rat intestinal absorption in the ileum of conjugated and nonconjugated bile acids in solution much below their CMC's. While it is assumed in these sample calculations that the permeability coefficients of the membrane for active and passive transport are the same among the bile acids, it may not necessarily be true (3, 4). In the pH $\ll$ pKa region, the transport across the membrane is primarily passive. As the pH becomes increasingly greater than the pKa, the passive transport becomes effectively less significant while the active transport mechanism becomes more significant;

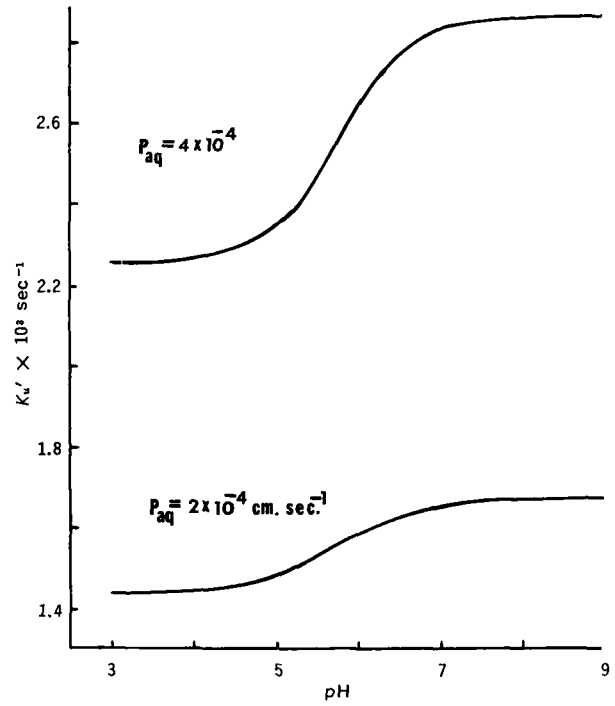


Figure 2—*Effect of the thickness of the stagnant water layer on the transport of a bile acid of pKa 6.0 in the ileum.*

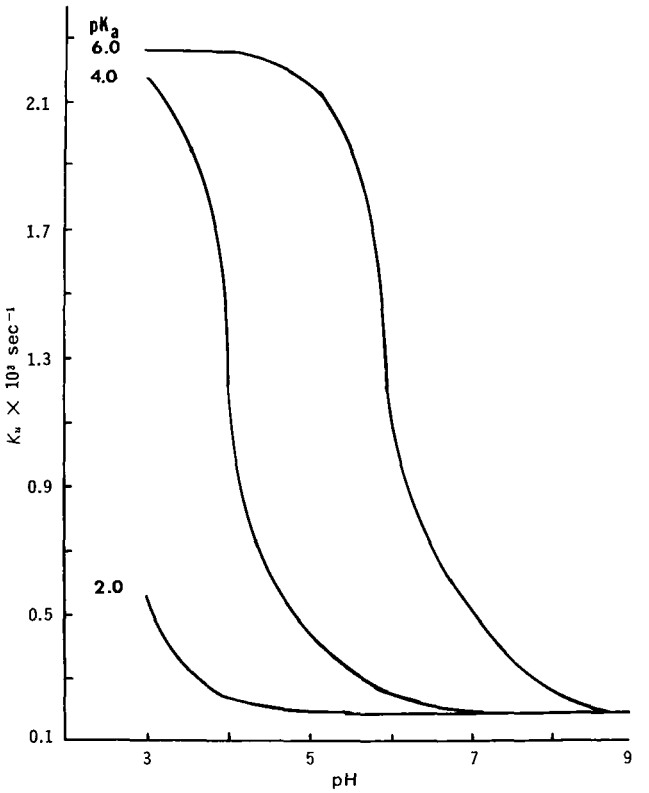


Figure 3—*Theoretical profiles of* K_u *versus pH for bile acids with different pKa based on Eq. 21 for passive transport in the duodenum and jejunum. The permeability of the stagnant water layer is* 4×10^{-4} *cm sec*$^{-1}$.

thus, the rate constant increases until it reaches a maximum. In the ileum where the pH is normally about 7.0, the active transport of the bile acids with pKa of 2.0-5.0 is dominant.

It is worthwhile to point out an important observation of the maximum rate constant of 2.87×10^{-3} sec^{-1} at pH $\gg$ pKa in Fig. 1. When the rate is aqueous diffusion controlled (Eq. 20), *i.e.*, the permeability of the stagnant aqueous layer is rate controlling, $K_u' = AP_{aq}/V = 4 \times 10^{-3}$ sec^{-1}. Here, the effective thickness of the aqueous diffusion layer is about 125 μm. Consequently, the maximum rate in Fig. 1 is about 75% aqueous diffusion controlled. At pH $\ll$ pKa, it is about 60% aqueous diffusion controlled.

Figure 2 shows a typical plot of K_u' *versus* pH at different permeability coefficients of the aqueous diffusion layer, *i.e.*, different thicknesses of the stagnant water layer, for a bile acid with pKa 6.0. By increasing P_{aq}, the rate constant increases. At $P_{aq} = 2 \times 10^{-4}$ cm sec^{-1}, corresponding to a diffusion layer of 250 μm when a diffusion coefficient of 5×10^{-6} cm^2 sec^{-1} is chosen, the maximum rate constant is then about 85% aqueous diffusion controlled.

Theoretical plots on the pH-passive transport profiles of the bile acids in the duodenum and jejunum are found in Fig. 3. The bile acid with pKa 6.0 is better absorbed at physiological pH 5-7 than is an acid with a smaller pKa. At higher pH, the rate constants converge since this is indicative of the transport across the aqueous channels of the membrane.

Case II: Maximum Flux for Active Transport—In this special case where $K_m^* \ll X_s^- C_s$, the flux for active transport is maximum and the total flux across the membrane is:

$$J_2 = A(P_o X_s^0 + P_p)C_s + AJ_{max}^* \qquad \text{(Eq. 24)}$$

In a similar procedure of derivation as in Case I, it can be shown that:

$$\frac{dC_b}{dt} = -K_u(B + C_b) \qquad \text{(Eq. 25)}$$

where:

$$K_u = \left(\frac{A}{V}\right)(P_{aq})\left(\frac{1}{1 + \dfrac{P_{aq}}{P_o X_s^0 + P_p}}\right) \qquad \text{(Eq. 26)}$$

$$B = \frac{J_{max}^*}{P_o X_s^0 + P_p} \qquad \text{(Eq. 27)}$$

The solution is:

$$\ln \frac{B + C_b}{B + C_b(0)} = -K_u t \qquad \text{(Eq. 28)}$$

The rate constant K_u is descriptive of the effective permeability coefficient for diffusional transport across the aqueous diffusion layer and the membrane. The specific permeability coefficients in Eq. 26 are readily determined by appropriate experiments based on Eq. 18. In turn, this permits the calculation of K_u for Case II. It also follows that an estimate of the constant B can be obtained from the experimental data by taking the initial slope of a log C_b *versus* t plot. Thus:

$$\left.\frac{d \log C_b}{dt}\right|_{t=0} = \frac{-K_u[B + C_b(0)]}{2.303 C_b(0)} \qquad \text{(Eq. 29)}$$

or:

$$B = -C_b(0)\left[1 + \left(\frac{2.303}{K_u}\right)\left.\frac{d \log C_b}{dt}\right|_{t=0}\right] \qquad \text{(Eq. 30)}$$

whereupon J_{max}^* can be calculated. In turn, with Eq. 14, the K_m^* is found by:

$$K_m^* = \frac{J_{max}^*}{P_m^*} \qquad \text{(Eq. 31)}$$

Case III: General Treatment of Flux for Active Transport[3]—Let us assume that: *(a)* the pH is much greater than the pKa so that $X_s^0 \sim 0$ and $X_s^- \sim 1.0$, and *(b)* the flux for active transport is much greater than the flux across the aqueous channels of the membrane. Accordingly, Eq. 12 becomes:

[3] At the time of submitting this manuscript, the authors became aware of the recently published work of Winne (10) with respect to this particular section of the manuscript. The same conclusions are arrived. However, it is believed here that the mathematical description of this special case is experimentally more accessible.

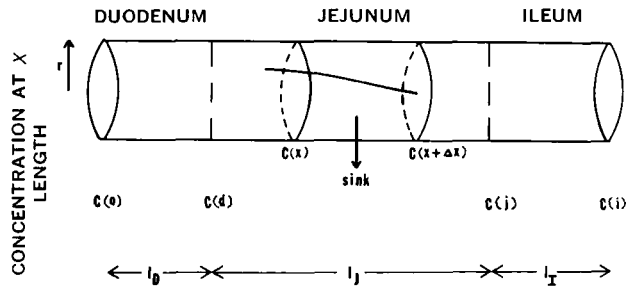


Figure 4—*Model for first-pass absorption of bile acid in the small intestine.*

$$J_2 = \frac{AJ_{max}{}^*C_s}{K_m{}^* + C_s} \qquad \text{(Eq. 32)}$$

or:

$$C_s = \frac{J_2K_m{}^*}{AJ_{max}{}^* - J_2} \qquad \text{(Eq. 33)}$$

The substitution of Eq. 33 and the expression for the continuity of flow through the membrane surface, $J_1 = J_2$, into Eq. 11 give:

$$J_1{}^2 - (\alpha + \beta C_b)J_1 + \delta C_b = 0 \qquad \text{(Eq. 34)}$$

where:

$$\alpha = A(J_{max}{}^* + K_m{}^*P_{aq}) \qquad \text{(Eq. 35)}$$

$$\beta = AP_{aq} \qquad \text{(Eq. 36)}$$

$$\delta = A^2P_{aq}J_{max}{}^* \qquad \text{(Eq. 37)}$$

The solution for J_1 by the quadratic formula is:

$$J_1 = \frac{\alpha + \beta C_b - \sqrt{(\alpha + \beta C_b)^2 - 4\delta C_b}}{2} \qquad \text{(Eq. 38)}$$

where the negative of the square root function is taken in relation to physical significance.

Although an analytic solution for C_b as a function of time is available, it is quite complicated and is not explicitly useful in the quantitative assessment of the experimental data. A plot of the total flux, J_1 *versus* C_b, at initial concentrations will be more useful since it provides several limiting situations from which various transport parameters can be quantified. For example, utilizing Eq. 38:

$$\lim_{C_b \to 0} \frac{dJ_1}{dC_b} = \frac{\delta}{\alpha} = \frac{AP_{aq}P_m{}^*}{P_{aq} + P_m{}^*} \qquad \text{(Eq. 39)}$$

$$\lim_{C_b \to \infty} J_1 = \frac{\alpha}{2} = \frac{AK_m{}^*}{2}(P_{aq} + P_m{}^*) \qquad \text{(Eq. 40)}$$

As one can readily observe in Eq. 39, if $P_m{}^* \gg P_{aq}$, the initial slope will be determined by the permeability of the stagnant water layer. The opposite is also true.

Several points should be made about the special situation indicated by Eq. 40. First, the C_b should be sufficiently large but within the limit of the CMC. Second, this situation is probably never reached in *in situ* animal absorption experiments in the ileum.

Single-Pass Intestinal Absorption Model—An idealized model is shown in Fig. 4 for the simultaneous flow of a dilute nonmicellar solution of bile acid in the intestinal lumen, taken as a cylinder, and transport of the bile acid across the membrane into the sink on the serosal side. According to mass balance considerations, the difference in the concentration of solution entering into a cylindrical element at x and leaving at $x + \Delta x$ is equal to the transverse flux of the bile acid across the membrane within the element; thus:

$$Q[C_b(x) - C_b(x + \Delta x)] = (J_1')(2\pi r\,\Delta x) \qquad \text{(Eq. 41)}$$

where Q is the bulk fluid flow rate in cubic centimeters seconds^{-1}, r is the radius of the cylinder, and J_1' is the flux of the total bile acid per unit area. Taking the limit as $\Delta x \to 0$ and noting that:

$$J_1' = P_eC_b(x) \qquad \text{(Eq. 42)}$$

where P_e is the effective permeability coefficient, one gets:

$$\frac{dC_b}{dx} = -\frac{2\pi rP_eC_b}{Q} \qquad \text{(Eq. 43)}$$

After applying the boundary conditions to each section of the small intestine, that is, the duodenum *(d)*, the jejunum *(j)*, and the ileum *(i)*, the corresponding solutions to Eq. 43 become Eqs. 44–46:

$$C_b(d) = C_b(o)[\exp(-2\pi r_d l_d P_{e,d}/Q)] \qquad \text{(Eq. 44)}$$

$$C_b(j) = C_b(d)[\exp(-2\pi r_j l_j P_{e,j}/Q)] \qquad \text{(Eq. 45)}$$

$$C_b(i) = C_b(j)[\exp(-2\pi r_i l_i P_{e,i}/Q)] \qquad \text{(Eq. 46)}$$

The final concentration of bile acid appearing at the distal end of the ileum with respect to the initial concentration at the proximal end of the duodenum is:

$$C_b(i) = C_b(o)\left\{\sum_k \exp\left[-\frac{2\pi}{Q}(l_kr_kP_{e,k})\right]\right\} \qquad \text{(Eq. 47)}$$

where k = duodenum, jejunum, and ileum.

In general, the effective permeability coefficient for passive diffusion in the duodenum and jejunum may be expressed by:

$$P_e = (P_{aq})\left(\frac{1}{1 + \dfrac{P_{aq}}{P_oX_s{}^0 + P_p}}\right) \qquad \text{(Eq. 48)}$$

while that for both the passive and active transport of the bile acid in the ileum is:

$$P_e = (P_{aq})\left(\frac{1}{1 + \dfrac{P_{aq}}{P_oX_s{}^0 + P_m{}^*X_s{}^- + P_p}}\right) \qquad \text{(Eq. 49)}$$

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ACKNOWLEDGMENTS AND ADDRESSES

Received November 16, 1973, from the *College of Pharmacy, University of Michigan, Ann Arbor, MI 48104*

Accepted for publication December 21, 1973.

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