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Research Article

An Equation for the Systemic Availability of Drugs Undergoing Simultaneous Enterohepatic Cycling, First-Pass Metabolism, and Intestinal Elimination

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A relationship between systemic availability and its determinants has been derived for a physiologically realistic model of drug disposition that includes enterohepatic cycling (EHC), gallbladder emptying (with an arbitrary time course), first-pass metabolism to noncycling metabolites, and fecal excretion. Systemic availability (F) has been shown to be determined by the fraction of the dose initially absorbed (f_a^*), the fraction of the drug excreted into the GI tract that is reabsorbed with each cycle (f_a), the hepatic extraction ratio (E), and the fraction of extracted drug that is transported to the gallbladder for EHC (f_g) according to the relationship

$$F = f_a^*(1 - E)/(1 - f_a f_g E)$$

The implications of the above relationship are that (1) systemic availability is dependent on EHC, (2) values of F calculated to be greater than unity cannot be explained simply by the presence of EHC, (3) calculations of E based on the usual expression $F = f_a^*(1 - E)$ are erroneous for drugs subject to EHC, and (4) a compound that has a high systemic availability and is subject to EHC is not necessarily inefficiently metabolized. The quantitative interrelationship of systemic availability and its determinants is illustrated using a contour plot. Slices through the surface are used to demonstrate that the presence of EHC changes the sensitivity of F to changes in E.

KEY WORDS: enterohepatic recirculation; pharmacokinetics; bioavailability; area under the curve; bile; hepatic extraction.

INTRODUCTION

A simplified model of enterohepatic cycling (1) was used in a recent communication (2) to demonstrate that the area under the plasma concentration–time curve (AUC) is independent of the time and time course of gallbladder emptying. Two important assumptions of the model were that (1) drug and/or drug conjugate released by the gallbladder into the gut is quantitatively reabsorbed as unchanged drug (complete hydrolysis of conjugates in the gut and no fecal elimination of drug and/or metabolite) and (2) all drug extracted by the liver is cycled (no metabolism to noncycling species).

The purposes of the investigation reported herein were (1) to derive an expression for the systemic availability (F) of a drug for a model of enterohepatic cycling (EHC) that includes metabolism by the liver to noncycling metabolites and elimination of drug in the feces, (2) to illustrate the quantitative interrelationships of systemic availability and its determinants, and (3) to determine the influence of the time and time course of gallbladder emptying on AUC for this more complex and more physiologically realistic model of EHC.

RESULTS AND DISCUSSION

The model of EHC appears in Scheme I. For this model, 1 represents the sampling compartment, 4 the liver, 3 the storage compartment (or gallbladder), 5 the compartment from which absorption from the dosage form takes place, and 2 the compartment from which reabsorption from bile takes place. Two absorption compartments were included in the model to allow for different absorption kinetics from the dosage form and bile. Different absorption kinetics would be expected (1) when absorption from a solid dosage form is dissolution rate-limited since drug excreted in bile will be in solution or (2) when deconjugation by intestinal bacteria of conjugated drug originating from the liver is rate-limiting. All transfer processes except gallbladder emptying are represented as first order and are denoted by k_{10} for nonbiliary elimination from the sampling compartment, k_{20} for fecal elimination, k_a^* and k_a for absorption of drug from the administered dosage form and bile, respectively, into the hepatoportal blood supply, k_{14} for transport of drug to the liver via the hepatic arterial blood supply, k_{41} for transport of drug out of the liver, k_{43} for transport of drug to the storage com-

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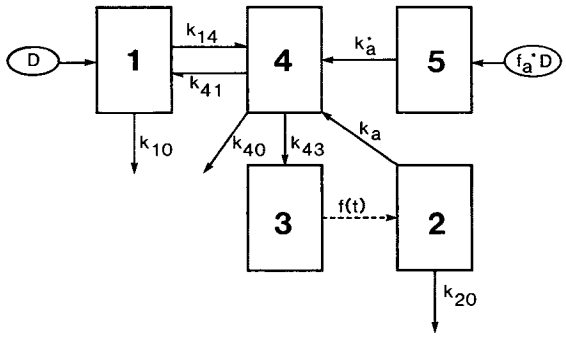


Scheme I

partment, and k_{40} for metabolism of the drug to noncycling species. No assumptions regarding the nature of the transfer of drug between compartment 3 and compartment 2 are necessary to derive an expression for F. The time course of drug transfer from 3 to 2 is represented by an arbitrary function, $f(t)$, that describes gallbladder emptying. An intravenous dose, D, is administered into compartment 1, whereas an oral dose, $f_a^* D$ (where f_a^* is the fraction of the dose which reaches the hepatoportal blood supply), is administered into compartment 2. The derivations will be carried out with respect to unchanged drug, but the common EHC events of first-order conjugation by the liver, excretion of conjugates into the intestine via the bile, and subsequent hydrolysis of conjugates in the intestine can be viewed as being included in the rate processes for unchanged drug represented as k_{43}, $f(t)$, and k_a, respectively. Use of this model does assume, however, that all of the drug metabolized to cycling species is transferred to the gallbladder for subsequent release into the gut (i.e., there is no provision for renal elimination of the cycling metabolite).

Bioavailability (F) can be defined as $(1/D)\int_0^\infty g(t)dt$, where $g(t)$ is the rate of drug input into the systemic circulation. The full derivation of F appears in Appendix A. The resultant expression is

$$F = f_a^*(1 - E)/(1 - f_a f_g E) \qquad (1)$$

where f_a is the fraction of the dose reabsorbed, E is the hepatic extraction ratio, and f_g is the fraction of extracted drug which is transported to the gallbladder for EHC.

To understand the effect of the presence of EHC on systemic availability, Eq. (1) should be compared to that for F in the absence of EHC ($f_g = 0$), that is, $F = f_a^*(1 - E)$. The term $1/(1 - f_a f_g E)$ in Eq. (1) may be viewed as a factor which quantifies the influence of enterohepatic cycling on systemic availability. Since the term $(1 - f_a f_g E)$ will always be less than 1 in the presence of EHC, F will be greater than $f_a^*(1 - E)$. Thus, for two compounds with the same hepatic extraction ratio and fraction absorbed across the gut wall, the compound subject to EHC will have the greater systemic availability. Conversely, interpretation of bioavailability data is complicated in the presence of EHC. A compound which has a high systemic availability is not necessarily inefficiently metabolized (low E value) if it is subject to EHC.

It is difficult simply to look at Eq. (1) and decide how F will be affected by changes in f_a, f_g, or E. Thus, in an attempt to visualize the interrelationships of the determinants of F, a contour plot was constructed for F/f_a^* as a function of E and $f_a f_g$ (Fig. 1). Each line represents a constant value of F/f_a^*. The lines are shown at intervals of 0.1. It is evident that many combinations of E and $f_a f_g$ yield the same value for F/f_a^*. Systemic availability increases as a function of increasing $f_a f_g$ at fixed values of E and f_a^*. As expected, the systemic availability decreases as the hepatic extraction ratio increases at fixed values of $f_a f_g$ and f_a^*.

The maximum bioavailability occurs when $E = 0$. Substituting $E = 0$ into Eq. (1), $F_{max} = f_a^*$. Thus, when $E \neq 0$ and EHC does occur, F cannot be greater than unity even though a larger percentage of the dose is cycled after oral dosing than after intravenous administration. Therefore, values of F greater than 1 cannot be explained simply by the presence of EHC.

The dependence of F on E is greatest when $f_a f_g$ is large (Fig. 1). Interpretation of this steep gradient is made easier if a slice is taken through the surface at a high value of $f_a f_g$ (large fraction of extracted drug is transported to bile and subsequently reabsorbed) and compared to a slice taken at a low value of $f_a f_g$. Figure 2 contains two-dimensional slices through the surface for $f_a f_g = 0.1$ and 0.9. It can be concluded by comparing the two curves that the presence of EHC changes the dependence of F on E. When $f_a f_g = 0.1$, F/f_a^* is nearly equally dependent on E over the range of E values. For $f_a f_g = 0.9$, F/f_a^* is relatively insensitive to changes in E at low values of E. At high values of E, a small change in E results in a marked change in F/f_a^*. The degree of deviation of the curves in Fig. 2 from the linear relationship $F = f_a^*(1 - E)$ is indicative of the error involved in using this simpler relationship when EHC does occur.

It can also be demonstrated that Eq. (1) is valid when there is distribution of drug into other compartments (Appendix B). For this derivation a more general model of EHC

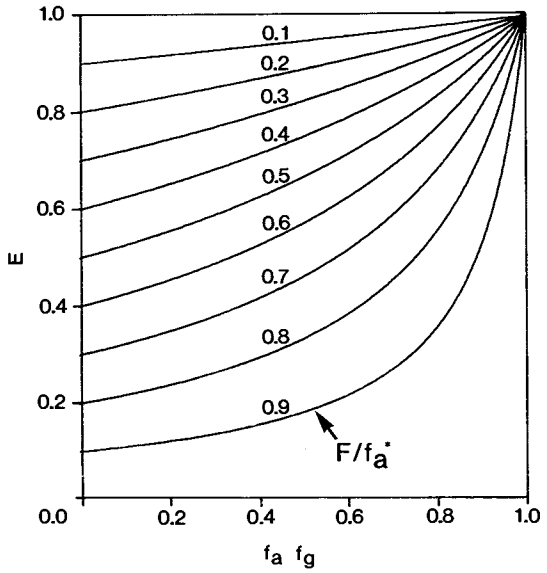


Fig. 1. Contour plot of the ratio of systemic availability to the fraction of the dose initially absorbed (F/f_a^*) as a function of the hepatic extraction ratio (E) and the product of the fraction of extracted drug which is transported to the gallbladder for cycling and the fraction of drug excreted in bile that is reabsorbed ($f_a f_g$). The contour lines for F/f_a^* are shown at intervals of 0.1.

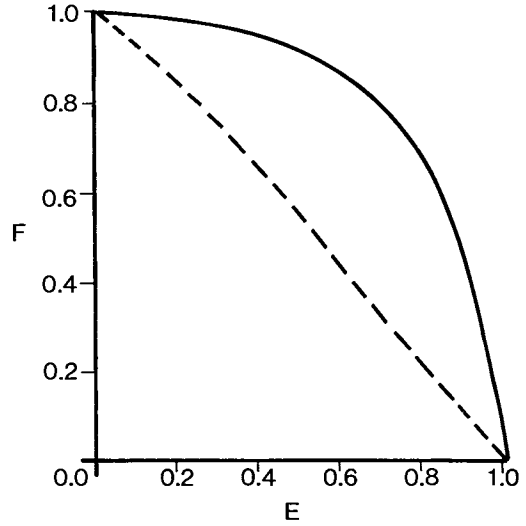


Fig. 2. The ratio of systemic availability to the fraction of the dose initially absorbed (F/f_a^*) as a function of the hepatic extraction ratio (E) when a large fraction of the extracted drug is transported to bile and subsequently reabsorbed ($f_a f_g = 0.9$; ——) or a small fraction is transported to bile and subsequently reabsorbed ($f_a f_g = 0.1$; --).

which included distribution into an arbitrary number of compartments reversibly connected to compartment 1 (Scheme II) was used.

The third aim of this paper was to determine the influence of the time and time course of gallbladder emptying on AUC for the model of EHC in Scheme I. The full derivations of AUC^{iv} and AUC^{po} appear in Appendix C. The resultant expressions for AUC^{iv} and AUC^{po} are

$$AUC_1^{iv} = D(k_2k_4 - k_ak_{43})/(k_1k_2k_4 - k_1k_ak_{43} - k_{14}k_2k_{41})V_1 \quad (2)$$

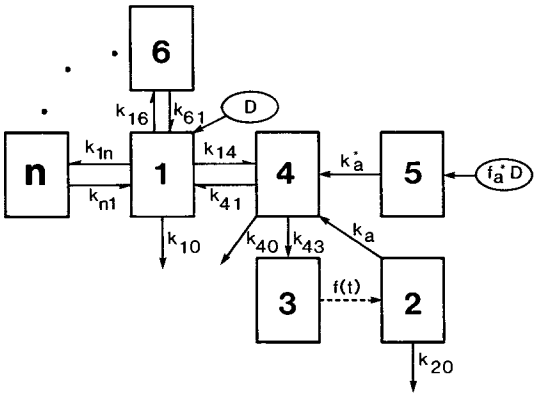
$$AUC_1^{po} = f_a^*Dk_2k_{41}/(k_1k_2k_4 - k_1k_ak_{43} - k_{14}k_2k_{41})V_1 \quad (3)$$

where $k_1 = k_{10} + k_{14}$, $k_2 = k_a + k_{20}$, and $k_4 = k_{40} + k_{41} + k_{43}$. Equations (2) and (3) demonstrate an important aspect of the effect of discontinuous drug transfer from the gallbladder to the gut on AUC(0 − ∞). Since $f(t)$ does not appear in either equation, it can be concluded that AUC(0 − ∞) is independent of the time and time course of gallbladder emptying. Equations (2) and (3) can be used to obtain an expression for the ratio AUC^{po}/AUC^{iv}:

$$AUC_1^{po}/AUC_1^{iv} = f_a^*(1 - E)/(1 - f_af_gE) \quad (4)$$

Since the expressions for the ratio AUC^{po}/AUC^{iv} [Eq. (4)] and F [Eq. (1)] are identical, it can be concluded that the ratio of AUC values (oral to intravenous) can be used as a measure of systemic availability even in the presence of enterohepatic cycling. The same conclusion is true for the more general model of EHC shown in Scheme II.

In conclusion, a fundamental relationship between systemic availability and its determinants has been derived for a physiologically realistic model of drug disposition that includes distribution into peripheral compartments, enterohepatic cycling, gallbladder emptying, first-pass metabolism to noncycling metabolites, and fecal excretion. Systemic availability is determined by the fraction of the dose initially absorbed, the fraction of the drug excreted into the GI tract that is reabsorbed with each cycle, the hepatic extraction ratio and the fraction of extracted drug which is transported to the gallbladder for EHC. Although it may be difficult to obtain experimental values for the constants f_a^*, f_a, and f_g that determine the relationship between F and E, the expression clearly shows the inaccuracy that occurs when simpler relationships are used in the presence of EHC.



Scheme II

APPENDIX A. DERIVATION OF AN EXPRESSION FOR BIOAVAILABILITY

Bioavailability (F) can be defined as $(1/D)\int_0^\infty g(t)dt$, where $g(t)$ is the rate of drug input into the systemic circulation. For the model in Scheme I, an expression for $g(t)$ can be derived indirectly. The amount of drug in the systemic circulation (compartment 1) changes due to input, irreversible elimination from any compartment to which it is reversibly connected (either directly or indirectly), and distribution between the systemic circulation and the liver. Thus, an expression for $g(t)$ for the model in Scheme I can be written

$$g(t) = dA_1/dt + \sum_{i=1}^{4} m_i(k)A_1 - d_{14}(k)A_1 + d_{41}(k)A_4 \quad (A1)$$

where $m_i(k)$ is the function which quantitates the effect of loss of drug from compartment i on the rate of change of drug in compartment 1 and $d_{14}(k)$ and $d_{41}(k)$ are the functions which quantitate the distribution of the drug which has been input to compartment 1 between compartment 1 and compartment 4. The terms $m_i(k)$, $d_{14}(k)$, and $d_{41}(k)$ are functions of the vector of rate constants, k. An expression for F can be obtained by integration and dose normalization of Eq. (A1):

$$F = (1/D)\int_0^\infty(dA_1/dt)dt + \sum_{i=1}^{4}[m_i(k)/D]\int_0^\infty A_1dt - [d_{14}(k)/D]\int_0^\infty A_1dt + [d_{41}(k)/D]\int_0^\infty A_4dt \quad (A2)$$

If the rate of drug transfer from 3 to 2 is represented by an arbitrary function, $f(t)$, that describes gallbladder emptying, then the following differential equations for the amount of drug in compartments 1, 2, 3, 4, and 5 can be written:

$$dA_1/dt = -(k_{10} + k_{14})A_1 + k_{41}A_4 \quad (A3)$$

$$dA_2/dt = -(k_a + k_{20})A_2 + f(t)A_3 \quad (A4)$$

$$dA_3/dt = -f(t)A_3 + k_{43}A_4 \quad (A5)$$

$$dA_4/dt = k_{14}A_1 + k_aA_2 - (k_{40} + k_{41} + k_{43})A_4 + k_a^*A_5 \quad (A6)$$
$$dA_5/dt = -k_a^*A_5 \quad (A7)$$

There is irreversible elimination of drug from compartments 1, 2, and 4. Thus, $m_3(k) = 0$. The term $m_1(k)$ is simply equal to k_{10}. The expressions for $m_2(k)$ and $m_4(k)$ are less straightforward. They are derived by considering the fraction of the original dose irreversibly eliminated with each emptying of the gallbladder.

In the following derivation, f_a^* refers to the fraction absorbed from the dosage form, E is the hepatic extraction ratio (includes metabolism to noncycling species as well as transport to the gallbladder for EHC), f_g is the fraction of drug extracted by the liver which is transported to the gallbladder for EHC, f_a is the fraction absorbed from secreted bile during recycling [refer to Eq. (A23) for definition of these fractions in terms of the rate constants in Scheme I] and n is the number of passes through the hepatoportal–duodenal system (starting in compartment 5). After oral administration of the drug Df_a^* reaches the portal circulation and $Df_a^*E(1 - f_g)$ is irreversibly eliminated by metabolism to noncycling species, while $Df_a^*f_gE$ is secreted into the gallbladder and subsequently released into the intestine. On the second pass through the hepatoportal–duodenal system, a fraction of the drug released into the intestine is irreversibly lost by fecal elimination $[Df_a^*f_gE(1 - f_a)]$, while the remainder of the fraction $(Df_a^*f_af_gE)$ is then absorbed into the portal circulation. In the liver $Df_a^*f_af_gE^2(1 - f_g)$ is irreversibly eliminated by metabolism to noncycling species, while $Df_a^*f_af_g^2E^2$ is secreted into the gallbladder and subsequently released into the intestine. On the third pass through the hepatoportal–duodenal system, a fraction of the drug released into the intestine $[Df_a^*f_af_g^2E^2(1 - f_a)]$ is irreversibly lost by fecal elimination, while the remainder of the fraction $(Df_a^*f_a^2f_g^2E^2)$ reaches the portal circulation. On the nth pass through the hepatoportal–duodenal system, $Df_a^*f_a^{n-1}f_g^{n-1}E^n(1 - f_g)$ is irreversibly eliminated from compartment 4 by metabolism to noncycling species, while $Df_a^*f_a^{n-2}f_g^{n-1}E^{n-1}(1 - f_a)$ is irreversibly lost from compartment 2 by fecal elimination. The terms $m_2(k)$ and $m_4(k)$ are derived as the products of the rate constant for transport of drug to the liver via the hepatic arterial supply, k_{14}, and the sum of the fractions of the original dose (f_a^*D) which are irreversibly eliminated from compartments 2 and 4, respectively, with each pass through the hepatoportal–duodenal system.

Thus,

$$m_2(k) = k_{14}(1 - f_a)\sum_{n=2}^{\infty} f_a^{n-2}f_g^{n-1}E^{n-1} \quad (A8)$$

$$m_4(k) = k_{14}(1 - f_g)\sum_{n=1}^{\infty} f_a^{n-1}f_g^{n-1}E^n \quad (A9)$$

Equations (A8) and (A9) can be simplified.

$$m_2(k) = k_{14}(1 - f_a)/f_a^2f_g^2E\sum_{n=2}^{\infty}(f_af_gE)^n \quad (A10)$$

$$m_4(k) = k_{14}(1 - f_g)/f_af_g\sum_{n=1}^{\infty}(f_af_gE)^n \quad (A11)$$

When $x < 1$,

$$x + x^2 + x^3 + \cdots = x/(1 - x)$$

and

$$x^2 + x^3 + x^4 + \cdots = x^2/(1 - x)$$

Since $0 < f_af_gE < 1$, Eqs. (A10) and (A11) can be rewritten as

$$m_2(k) = k_{14}f_gE(1 - f_a)/(1 - f_af_gE) \quad (A12)$$
$$m_4(k) = k_{14}E(1 - f_g)/(1 - f_af_gE) \quad (A13)$$

The distribution function $d_{14}(k)$ is simply k_{14}. The distribution function $d_{41}(k)$ is less straightforward, since it should include only drug which has first appeared in compartment 1 (i.e., to distinguish between input and redistribution). The term $d_{41}(k)$ is equal to the product of k_{41} and the fraction of drug in compartment 1 which is distributed back to compartment 4, $k_{14}/(k_{10} + k_{14})$.

If $AUAC_i$ is defined as $\int_0^\infty A_i dt$, Eq. (A2) can be rewritten using Eqs. (A3), (A12), and (A13), the expressions for $m_1(k)$ and $m_3(k)$ found in the text following Eq. (A7), and the expressions for $d_{14}(k)$ and $d_{41}(k)$ found in the text following Eq. (A13).

$$\begin{aligned} F = {} & -k_{14}AUAC_1/D + k_{41}AUAC_4/D \\ & + k_{14}f_gE(1 - f_a)AUAC_1/(1 - f_af_gE)D \\ & + k_{14}E(1 - f_g)AUAC_1/(1 - f_af_gE)D \\ & - k_{14}AUAC_1/D + k_{14}k_{41}AUAC_4/(k_{10} + k_{14})D \end{aligned} \quad (A14)$$

To derive $AUAC_1$ and $AUAC_4$, both sides of Eqs. (A3) through (A7) are multiplied by dt and integrated from time 0 to ∞. If we define

$$\int_{A_i(0)}^{A_i(\infty)} dA_i = A_i(\infty) - A_i(0) \quad (A15)$$

the resultant integrated equations are

$$A_1(\infty) - A_1(0) = -(k_{10} + k_{14})AUAC_1 + k_{41}AUAC_4 \quad (A16)$$
$$A_2(\infty) - A_2(0) = -(k_a + k_{20})AUAC_2 + \int_0^\infty f(t)A_3dt \quad (A17)$$
$$A_3(\infty) - A_3(0) = -\int_0^\infty f(t)A_3dt + k_{43}AUAC_4 \quad (A18)$$
$$A_4(\infty) - A_4(0) = k_{14}AUAC_1 + k_aAUAC_2 - (k_{40} + k_{41} + k_{43})AUAC_4 + k_a^*AUAC_5 \quad (A19)$$
$$A_5(\infty) - A_5(0) = -k_a^*AUAC_5 \quad (A20)$$

After oral administration of drug, $A_5(0) = f_a^*D$ and all other initial and final conditions are 0. If the appropriate initial and final conditions are substituted, Eqs. (A16) through (A20) can be rewritten and the resultant series of equations solved for $AUAC_1$ and $AUAC_4$.

$$AUAC_1 = f_a^*Dk_2k_{41}/(k_1k_2k_4 - k_1k_ak_{43} - k_{14}k_2k_{41}) \quad (A21)$$
$$AUAC_4 = f_a^*Dk_1k_2/(k_1k_2k_4 - k_1k_ak_{43} - k_{14}k_2k_{41}) \quad (A22)$$

where $k_1 = k_{10} + k_{14}$, $k_2 = k_a + k_{20}$, and $k_4 = k_{40} + k_{41} + k_{43}$.

Using Eqs. (A14), (A21), and (A22) and the following definitions [Eq. (A23)], an expression for bioavailability [Eq. (A24)] can be written.

$$E = \frac{k_{40} + k_{43}}{k_{40} + k_{41} + k_{43}}, \quad f_g = \frac{k_{43}}{k_{40} + k_{43}}, \quad \text{and} \quad f_a = \frac{k_a}{k_a + k_{20}} \quad (A23)$$

$$F = f_a^*(1 - E)/(1 - f_af_gE) \quad (A24)$$

APPENDIX B. DERIVATION OF AN EXPRESSION FOR BIOAVAILABILITY FOR A MORE GENERAL MODEL OF ENTEROHEPATIC CYCLING

It can easily be demonstrated that the expression derived for F in Appendix A is independent of other potential compartments reversibly connected to compartment 1. This more general model is shown in Scheme II. The expression for $g(t)$ is similar for this more general model.

$$g(t) = dA_1/dt + \sum_{i=1}^{4} m_i(k)A_1 - d_{14}(k)A_1 + d_{41}(k)A_4 + \sum_{i=6}^{n} k_{1i}A_1 + \sum_{i=6}^{n} k_{i\ 1}A_i \quad \text{(B1)}$$

The differential equations for the amount of drug in each compartment for the model in Scheme II are

$$dA_1/dt = -(k_{10} + k_{14} + \sum_{i=6}^{n} k_{1i})A_1 + k_{41}A_4 + \sum_{i=6}^{n} k_{i1}A_i \quad \text{(B2)}$$

$$dA_2/dt = -(k_a + k_{20})A_2 + f(t)A_3 \quad \text{(B3)}$$

$$dA_3/dt = -f(t)A_3 + k_{43}A_4 \quad \text{(B4)}$$

$$dA_4/dt = k_{14}A_1 + k_aA_2 - (k_{40} + k_{41} + k_{43})A_4 + k_a^*A_5 \quad \text{(B5)}$$

$$dA_5/dt = -k_a^*A_5 \quad \text{(B6)}$$

$$dA_6/dt = k_{16}A_1 - k_{61}A_6 \quad \text{(B7)}$$

$$\vdots$$

$$dA_n/dt = k_{1n}A_1 - k_{n1}A_n \quad \text{(B8)}$$

An expression for F can be derived using Eqs. (B1), (B2), (A12), and (A13), the expressions for $m_1(k)$ and $m_3(k)$ found in the text following Eq. (A7), the expressions for $d_{14}(k)$ and $d_{41}(k)$ found in the text following Eq. (A13), and the definition of F in terms of $g(t)$. The resultant expression for F is the same as that for the less complicated model of EHC [Eq. (A14)].

The method for obtaining the integrated equations is the same as that in Appendix A. As in the previous derivation, $A_5(0) = f_a^*D$ and all other initial and final conditions are 0. The resultant expressions are

$$0 = -(k_{10} + k_{14} + \sum_{i=6}^{n} k_{1i})\text{AUAC}_1 + k_{41}\text{AUAC}_4 + \sum_{i=6}^{n} k_{i1}\text{AUAC}_i \quad \text{(B9)}$$

$$0 = -(k_a + k_{20})\text{AUAC}_2 + \int_0^\infty f(t)A_3dt \quad \text{(B10)}$$

$$0 = -\int_0^\infty f(t)A_3dt + k_{43}\text{AUAC}_4 \quad \text{(B11)}$$

$$0 = k_{14}\text{AUAC}_1 + k_a\text{AUAC}_2 - (k_{40} + k_{41} + k_{43})\text{AUAC}_4 + k_a^*\text{AUAC}_5 \quad \text{(B12)}$$

$$-f_a^*D = -k_a^*\text{AUAC}_5 \quad \text{(B13)}$$

$$0 = k_{16}\text{AUAC}_1 - k_{61}\text{AUAC}_6 \quad \text{(B14)}$$

$$\vdots$$

$$0 = k_{1n}\text{AUAC}_1 - k_{n1}\text{AUAC}_n \quad \text{(B15)}$$

Equations (B9) through (B15) can be solved simultaneously to obtain expressions for AUAC_1 and AUAC_4. The resultant equations are also the same as those for the less complicated model of EHC [Eqs. (A21) and (A22)]. Thus, the final expression for F [Eq. (A24)] is independent of other potential compartments reversibly connected to compartment 1.

APPENDIX C. DERIVATION OF AN EXPRESSION FOR THE RATIO OF AUC VALUES

Expressions for AUC after oral and intravenous administration are obtained from the respective expressions for AUAC_1. AUAC_1^{po} has been derived in Appendix A and appears as Eq. (A21). AUAC_1^{iv} is derived by substitution of $A_1(0) = D$ and all other initial and final conditions = 0 into Eqs. (A16) through (A20). The area under the plasma concentration–time curve, $\text{AUC}(0 - \infty)$, is simply the quotient of AUAC_1 and the apparent volume of the sampling compartment, V_1:

$$\text{AUC}(0 - \infty) = \text{AUAC}_1/V_1 \quad \text{(C1)}$$

The resultant expressions for AUC_1^{iv} and AUC_1^{po} are

$$\text{AUC}^{iv} = D(k_2k_4 - k_ak_{43})/(k_1k_2k_4 - k_1k_ak_{43} - k_{14}k_2k_{41})V_1 \quad \text{(C2)}$$

$$\text{AUC}^{po} = f_a^*Dk_2k_{41}/(k_1k_2k_4 - k_1k_ak_{43} - k_{14}k_2k_{41})V_1 \quad \text{(C3)}$$

Equations (C2) and (C3) can be used to obtain an expression for the ratio $\text{AUC}^{po}/\text{AUC}^{iv}$:

$$\text{AUC}^{po}/\text{AUC}^{iv} = f_a^*(1 - E)/(1 - f_af_gE) \quad \text{(C4)}$$

APPENDIX D. NOMENCLATURE

F	the fraction of an orally administered dose which reaches the systemic circulation
f_a^*	the fraction of the administered dose initially absorbed
f_a	the fraction of the drug excreted in bile into the GI tract that is reabsorbed with each cycle
E	the hepatic extraction ratio (includes metabolism to noncycling species as well as transport into bile)
f_g	the fraction of drug extracted by the liver which is transported to the gallbladder for enterohepatic cycling
$g(t)$	the rate of drug input into the systemic circulation
A_i	the amount of drug in compartment i
$m_i(k)$	the function which quantitates the effect of loss of drug from compartment i on the rate of change of drug in compartment 1
$d_{ij}(k)$	the function which quantitates the effect of transfer of drug from compartment i to compartment j on the rate of change of drug in compartment 1
k	a vector of rate constants
AUAC_i	the area under the amount–time curve for drug in compartment i

REFERENCES

1. P. Veng-Pedersen and R. J. Miller. *J. Pharm. Sci.* **69**:394–398 (1980).
2. T. A. Shepard, R. H. Reuning, and L. J. Aarons. *J. Pharm. Sci.* **74**:227–228 (1985).