solution of VII as the free base (1.96 g, 0.013 mole) in 50 ml of tetrahydrofuran was treated with triethylamine (1.27 g, 0.013 mole), followed by the dropwise addition of methanesulfonyl chloride (1.43 g, 0.013 mole). The reaction mixture was stirred at room temperature for 4 hr and filtered to remove the precipitated triethylamine hydrochloride. The filtrate was evaporated under reduced pressure to yield a light-yellow oil. Column chromatography of the oil using silica gel as the adsorbent and chloroform–methanol (9:1) as the solvent gave, after evaporation of the solvents, 0.77 g (26%) of a white crystalline solid. An analytical sample was obtained by recrystallization from chloroform–hexane to give white crystals, mp 82–83°; IR (KBr): 3300 (NH), 1785 (C=O, imide), 1710 (C=O, imide), and 1150 (SO_2) cm^{-1}; NMR: δ 0.90 (t, 3H, J = 6 Hz, $NCH_2CH_2CH_3$), 1.60 (m, 2H, $NCH_2CH_2CH_3$), 2.40–3.67 (m, including s at 3.13, 7H, SO_2CH_3), 4.47 (m, 1H, ring CH), and 5.77 (s, 1H, NH).

Anal.—Calc. for $C_8H_{14}N_2O_4S$: C, 41.01; H, 6.03; N, 11.96. Found: C, 41.19; H, 5.90; N, 12.22.

(*R,S*)-*N*-Benzyl-2-(methanesulfamido)succinimide (XI)—Compound XI was synthesized from VIII as the free base (1.00 g, 0.005 mole), triethylamine (0.496 g, 0.005 mole), and methanesulfonyl chloride (0.561 g, 0.005 mole) in 50 ml of tetrahydrofuran in the same manner as described for X. Recrystallization of the solid product from chloroform–hexane gave 0.729 g (57%) of analytically pure product, mp 118–121°; IR (KBr): 3300 (NH), 1785 (C=O, imide), 1710 (C=O, imide), and 1150 (SO_2) cm^{-1}; NMR ($CDCl_3$): δ 2.50 (m, including s at 3.10, 5H, SO_2CH_3), 4.10–4.77 (m, including s at 4.63, 3H, $NCH_2C_6H_5$), 5.77 (d, 1H, NH), and 7.33 (s, 5H, C_6H_5).

Anal.—Calc. for $C_{12}H_{14}N_2O_4S$: C, 51.04; H, 5.01; N, 9.92. Found: C, 50.97; H, 4.91; N, 10.08.

Pharmacological Testing[3]—Three tests were performed: the maximal electroshock seizure test (MES), the subcutaneous pentylenetetrazol seizure threshold test (sc Met), and the rotorod test to evaluate neurotoxicity[4].

All tests were performed on male Carworth Farms No. 1 mice. All compounds were tested at 30, 100, 300, and 600 mg/kg at 30 min and 4 hr after intraperitoneal administration. Four animals were injected with each dose. After 30 min, each animal was examined for toxicity in the rotorod test. Immediately thereafter, anticonvulsant activity was evaluated by subjecting one mouse to the MES test and another to the sc Met test. The same tests were repeated 4 hr later on the two remaining mice.

All compounds were solubilized in either 0.9% NaCl or 30% polyethylene glycol 400 and administered intraperitoneally in a volume of 0.01 ml/g. The ED_{50} and TD_{50} values and their confidence limits were determined by the method of Litchfield and Wilcoxon (11). The MES activity is defined as abolition of the hindlimb tonic extensor component of the maximal electroshock seizure elicited in mice with a 60-Hz alternating current of 50 mamp delivered for 0.1 sec *via* corneal electrodes. The sc Met activity is defined as failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5 sec).

[3] All compounds were tested for anticonvulsant activity by the Antiepileptic Drug Development Program administered by the Section on Epilepsy, National Institutes of Health, Bethesda, MD 20014. The compounds were evaluated using the Anticonvulsant Screening Project test systems (9, 10).

[4] Neurological toxicity is defined as failure of an animal to remain for 1 min on a rod rotating at 6 rpm.

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First-Pass Effect: Nonlinear Concept Comprising an Explicit Solution of Integrated Michaelis–Menten Equation

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Received January 24, 1980, from the *Freie Universität, Klinikum Steglitz, Medizinische Klinik, Nephrologie, Hindenburgdamm 30, 1000 Berlin 45, Germany.* Accepted for publication August 6, 1980.

Abstract □ The first-pass effect results from metabolism during the first liver passage of a drug given by mouth. The metabolism is described by the Michaelis–Menten equation, but the integrated form of the Michaelis–Menten equation has no explicit solution for concentration and its handling requires a computer. However, the presented nonlinear equation of the first-pass effect is an explicit integration of the Michaelis–Menten equation and involves only general mathematics. However, the problem of evaluating the Michaelis–Menten constants V_m and K_m is not resolved. Therefore, linear equations are also derived, which correspond to previous clearance models.

Keyphrases □ Pharmacokinetics—first-pass effect, nonlinear approach to solution of Michaelis–Menten equation □ First-pass effect—nonlinear approach to solution of integrated Michaelis–Menten equation □ Michaelis–Menten kinetics—first-pass effect, nonlinear approach □ Clearance—first-pass effect, nonlinear approach to solution of integrated Michaelis–Menten equation

First-pass effect is defined as the reduced systemic bioavailability resulting from metabolism during the first liver passage of an orally administered drug (Fig. 1) (1). The mathematical description of this effect usually is based on first-order compartment or clearance models (1–3). However, metabolism follows nonlinear kinetics

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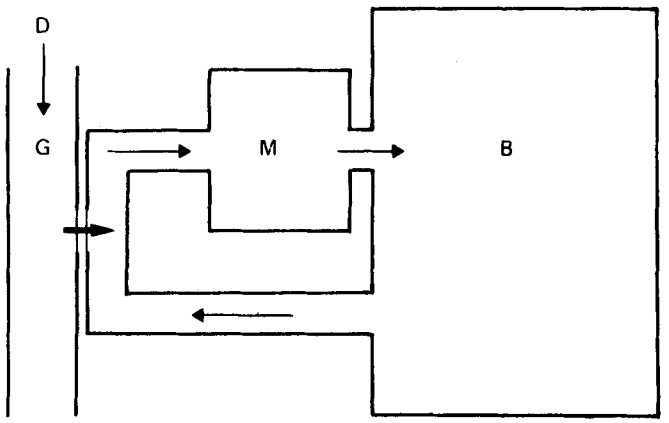

Figure 1—*Scheme of the first-pass effect. The amount given as the oral dose (D) equals the amount in the gut (G) plus the amount that is metabolized by the liver plus the amount that reaches the systemic circulation (B).*

described by the Michaelis–Menten equation (4):

$$\frac{dC}{dt} = \frac{V_m C}{K_m + C} \qquad \text{(Eq. 1)}$$

These first-order models are only valid under the condition $C \ll K_m$. A model that is independent of this premise will be deduced here from the Michaelis–Menten equation.

THEORY

Absorption of a dose (D) from the intestinal tract is supposed to be a first-order process (2):

$$\frac{dG}{dt} = -K_a G \qquad \text{(Eq. 2)}$$

Therefore, the amount in the gut (G) diminishes in an exponential fashion with a constant absorption rate (K_a):

$$G = D \exp(-K_a t) \qquad \text{(Eq. 3)}$$

At every time interval in the circulation of portal blood (T = 1 min), a fractional amount (M) is absorbed and transported into the liver:

$$M = \frac{dG}{dt} T \qquad \text{(Eq. 4)}$$

This actually absorbed amount becomes metabolized by liver enzymes, and this metabolism follows Michaelis–Menten kinetics. The Michaelis–Menten constants ($V_{\bar{m}}$, $K_{\bar{m}}$) are described here in mass rate terms:

$$\frac{dM}{dt} = \frac{V_{\bar{m}} M}{K_{\bar{m}} + M} \qquad \text{(Eq. 5)}$$

The difference between the absorbed and the metabolized amount is the rate at which the drug enters the systemic circulation (dB/dt):

$$\frac{dB}{dt} = \frac{dG}{dt} - \frac{dM}{dt} \qquad \text{(Eq. 6)}$$

The integrated rate reveals the systemically available amount (B):

$$B = \int_0^t \frac{dB}{dt}\, dt \qquad \text{(Eq. 7)}$$

The relation between the systemically available (B) and the applied amount (D) expresses the bioavailability factor (F):

$$F = \frac{B}{D} \qquad \text{(Eq. 8)}$$

$$F = \int_{t_1}^{t_2} \left[K_a \exp(-K_a t) - \frac{V_{\bar{m}} K_a T \exp(-K_a t)}{K_{\bar{m}} + D K_a T \exp(-K_a t)} \right] dt \qquad \text{(Eq. 9)}$$

The solution of this integral (5) comprises an explicit solution of the Michaelis–Menten equation:

$$F = \exp(-K_a t_1) - \exp(-K_a t_2) - \frac{V_{\bar{m}}}{D} \left[t_2 - t_1 + \frac{1}{K_a} \ln \frac{D K_a T + K_{\bar{m}} \exp(K_a t_1)}{D K_a T + K_{\bar{m}} \exp(K_a t_2)} \right] \qquad \text{(Eq. 10)}$$

Unfortunately, this integral shows no convergency. Therefore, the initial (t_1) and final (t_2) conditions must be defined:

$$t_1 = 0 \qquad \text{(Eq. 11)}$$

$$t_2 = 10 \ln(2)/K_a \qquad \text{(Eq. 12)}$$

The final condition (t_2) is given by the time [10 half-lives of absorption = $10 \ln(2)/K_a$], where >99% of the applied amount (D) has already been absorbed from the gut. So the first-pass effect (F) or the bioavailability of a metabolized drug can be described as a nonlinear process:

$$F = 1 - \frac{V_{\bar{m}}}{D K_a} \left[10 \ln(2) + \ln \frac{D K_a T + K_{\bar{m}}}{D K_a T + K_{\bar{m}} \exp[10 \ln(2)]} \right] \qquad \text{(Eq. 13)}$$

For the calculation of the nonlinear first-pass effect, the constant parameters ($V_{\bar{m}}$, $K_{\bar{m}}$, and K_a) have to be determined *in vivo*. This evaluation is possible using computers. The integrated Michaelis–Menten equation has been computer fitted to the plasma concentration decline of phenytoin and ethanol (6–10). The parameters (V_m and K_m) derived from the plasma concentration decline can be related to the mass rate terms ($V_{\bar{m}}$ and $K_{\bar{m}}$). The concentration decline (dC/dt) is the mass rate (dM/dt) per volume of distribution (V_d):

$$\frac{dC}{dt} = \frac{dM}{dt} \Big/ V_d \qquad \text{(Eq. 14)}$$

The concentration (C) submitted to metabolism is the amount (M) in the liver blood volume (V_l):

$$C = \frac{M}{V_l} \qquad \text{(Eq. 15)}$$

The concentration rate terms and mass rate terms are related *via* the volume of distribution (V_d) and the liver blood volume (V_l):

$$\frac{V_{\bar{m}}}{V_m} = \left(\frac{K_{\bar{m}} + C V_l}{K_m + C} \right) \frac{V_d}{V_l} \qquad \text{(Eq. 16)}$$

The substrate mass ($K_{\bar{m}}$) equals the concentration at the half-maximal metabolism rate (K_m) in the liver blood volume (V_l):

$$K_{\bar{m}} = K_m V_l \qquad \text{(Eq. 17)}$$

So the mass rate of metabolism ($V_{\bar{m}}$) can be derived (based on Eq. 16) from the concentration rate term (V_m), which is determined from the plasma concentration decline (dC/dt):

$$V_{\bar{m}} = V_m V_d \qquad \text{(Eq. 18)}$$

The first-pass effect can be evaluated (Eq. 13) if the maximal metabolism velocity expressed as a concentration rate term (V_m), the concentration at the half-maximal metabolism rate (K_m), the volume of distribution (V_d), and the liver blood volume (V_l) have been determined from plasma concentration data. These parameters (V_m, K_m, and K_a) can be evaluated only by computer. For an overall determination of these parameters (V_m, K_m, and K_a), simplified equations can be derived and applied without advanced computer equipment.

Nonlinear Michaelis–Menten kinetics can be schematically divided into three sections (Fig. 2):

1. The initial part follows zero-order kinetics, showing linearity in the nontransformed plot, and is defined by $C \gg K_m$ or $M \gg K_{\bar{m}}$.
2. The final part follows first-order kinetics, showing linearity in the semilogarithmic plot, and is defined by $C \ll K_m$ or $M \ll K_{\bar{m}}$.
3. The intermediate part shows no linearity.

For the zero-order part, the Michaelis–Menten equation may be simplified (Eq. 19) (2) and the maximal metabolism rate (V_m) can be determined from the concentration decline (Eq. 20):

$$-\frac{dC}{dt} = V_m \qquad \text{(Eq. 19)}$$

$$V_m = \frac{C_1 - C_2}{t_1 - t_2} \qquad \text{(Eq. 20)}$$

For the first-order part, the Michaelis–Menten equation also may be simplified (2):

$$-\frac{dC}{dt} = \frac{V_m}{K_m} C = \frac{\ln(2)}{T/2} C \qquad \text{(Eq. 21)}$$

Therefore, K_m can be derived from the elimination half-life ($T/2$) of the

first-order process:

$$K_m = V_m \frac{T/2}{\ln(2)} \qquad \text{(Eq. 22)}$$

The absorption rate constant (K_a) is often unknown also; its calculation takes some computer assistance (11), but a simplified evaluation of K_a is given by the time in which the maximal concentration is reached after oral dosing (Eq. 23 derived from the Bateman function):

$$\ln(K_a) - K_a t_{max} = \ln\left[\frac{\ln(2)}{T/2}\right] - \frac{\ln(2)}{T/2} t_{max} \qquad \text{(Eq. 23)}$$

The solution for K_a needs a stepwise iteration, but it can be done by any desk calculator.

After determination of V_m (according to Eq. 20), the K_m value can be derived from a linear kinetic model (Eq. 22). The term K_m also can be determined from the intrinsic hepatic clearance (Cl_{int}) (3, 12, 13). The following parameters are the terms of the authors [$V_{max} = V_{\bar{m}}$, $K_M = K_m$, $K_e = \ln(2)/(T/2)$, $C_{L,u} = C_{HV}$, and $Cl_H = Cl_1$]:

$$\frac{dM}{dt} = K_e M \qquad \text{(Eq. 24)}$$

$$\frac{dM}{dt} = K_e V_d C_S \qquad \text{(Eq. 25)}$$

$$\frac{dM}{dt} = Cl_H C_S \qquad \text{(Eq. 26)}$$

$$\frac{dM}{dt} = Cl_{int} C_{HV} \qquad \text{(Eq. 27)}$$

$$\frac{dM}{dt} = \frac{V_{\bar{m}} C_{HV}}{K_m + C_{HV}} \qquad \text{(Eq. 28)}$$

$$\frac{dM}{dt} = \frac{Q Cl_H C_{HV}}{Q - Cl_H} \qquad \text{(Eq. 29)}$$

$$K_{Mapp} = K_M + C_{L,u} = V_{max}\left(\frac{1}{Cl_1} - \frac{1}{Q}\right) \qquad \text{(Eq. 30)}$$

EXAMPLES AND DISCUSSION

Bioavailability generally is measured by comparison of the different areas under the concentration–time curves (AUC) after oral and intravenous dosing (2).

But the AUC method only gives rough data on bioavailability. It gives no insight into the underlying process.

If the bioavailability is reduced because of metabolism during the first liver passage, nonlinear enzyme kinetics have to be assumed. The evaluation of the first-pass effect requires the use of the troublesome Michaelis–Menten equation. The present equation of the first-pass effect comprises an explicit solution of the integrated Michaelis–Menten equation. This approach may be of some value, particularly since it requires only general mathematics (Eq. 13).

The validity of this equation of the first-pass effect can be illustrated by examples, to which the parameters (V_m, K_m, K_a, V_d, and F) are referred in the literature (6, 8–10, 14–18). The first-pass effect calculated by this equation shows good agreement with the values calculated by computer (Table I).

The present equation of the first-pass effect has two questionable premises (Eq. 13). First, it reflects only the amount actually absorbed from the intestine (Eq. 4). It disregards the amount that has already reached the systemic circulation.

The substrate to be metabolized consists of the actually absorbed, as well as the already systemically available, amount. The already systemically available amount competes with the actually absorbed amount for the receptor, so the first-pass effect will be overestimated if enzyme saturation is reached. Enzyme saturation will be reached particularly after multiple dosing where cumulation of the drug in the body occurs.

Therefore, after multiple dosing, a higher bioavailability generally has to be expected than after a single dose of a drug subjected to first-pass metabolism (19). The present equation does not yet give the solution for this problem, but it may be a step toward the correct description. The case of enzyme induction, also relevant in steady-state kinetics, is not covered by the present equation.

The second limitation of the present concept may be the assumption that absorption from the intestine follows first-order kinetics, but this simplification may be legitimate (7, 11, 20).

These questionable premises are also involved in other concepts of the

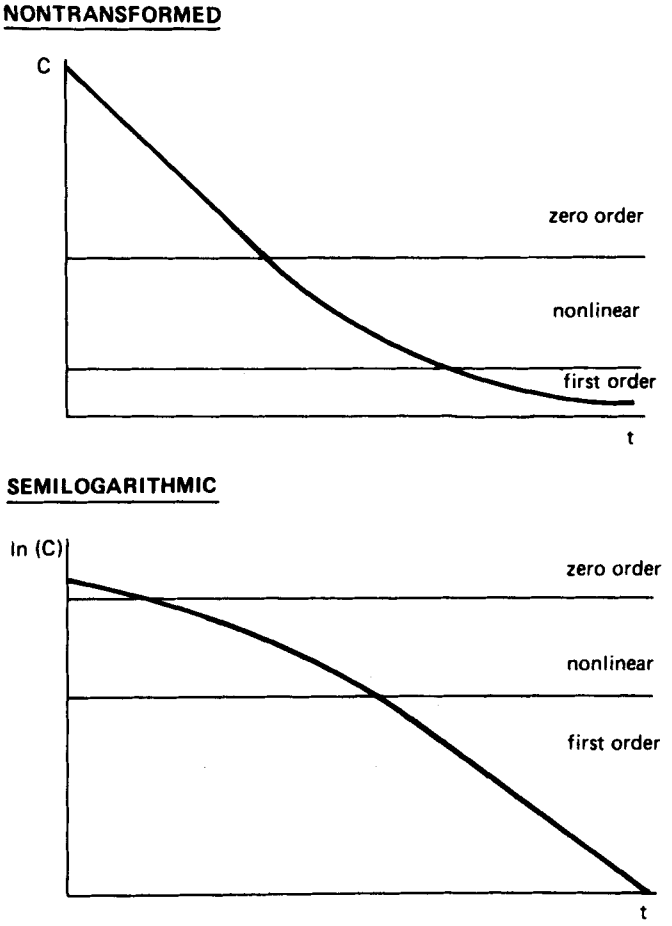

Figure 2—*Nontransformed and semilogarithmic graphs of the concentration decline in saturable pharmacokinetics with zero-order, nonlinear, and first-order parts.*

first-pass effect. This fact becomes evident if $C \ll K_m$ or if first-order kinetics are valid. Then the present concept (Eq. 9) can be transformed to the conventional clearance concepts (1, 3).

For first-order kinetics, there may be the simplified integration (of Eq. 9):

$$F = K_a\left(1 - \frac{V_{\bar{m}}}{K_{\bar{m}}} T\right)\left[\frac{\exp(-K_a t_2)}{K_a} - \frac{\exp(-K_a t_1)}{K_a}\right] \qquad \text{(Eq. 31)}$$

and for $t_1 = 0$, $t_2 = \infty$:

$$F = 1 - \frac{V_{\bar{m}}}{K_{\bar{m}}} T \qquad \text{(Eq. 32)}$$

Table I—Bioavailability (F) of Phenytoin and Ethanol Calculated by the Present Concept (Eq. 13) Compared with the Values Referred to in the Literature

Drug	Parameter		
	Literature	Calculated[a]	Equation
Phenytoin (6, 8, 14–18)	V_m = 0.4 mg/(liters × hr)	$V_{\bar{m}}$ = 18 mg/hr	17
	K_m = 11 mg/liter	$K_{\bar{m}}$ = 16.5 mg	18
	K_a = 0.4 hr^{-1}		
	V_d = 45 liters		
	F = 0.98	F = 0.98	13
Ethanol (9, 10)	V_m = 0.202 g/(liters × hr)	$V_{\bar{m}}$ = 8.9 g/hr	17
	K_m = 0.818 g/liter	$K_{\bar{m}}$ = 0.123 g	18
	$K_a = k_e$ = 10 hr^{-1}		
	V_d = 44 liters		
45 g	F = 1.0	F = 0.92	13
11.3 g	F = 0.785	F = 0.78	13

[a] The liver blood volume is considered constant (V_l = 1.5 liters).

In the case of first-order kinetics, the elimination half-life ($T/2$) is related to the metabolism constants (V_m and K_m) (2):

$$\frac{V_m}{K_m} = \frac{\ln(2)}{T/2} \quad \text{(Eq. 33)}$$

and the following deduction can be assumed (considering Eqs. 17, 18, and 32):

$$F = 1 - \frac{\ln(2)}{T/2}\frac{V_d}{V_l}T \quad \text{(Eq. 34)}$$

$$F = 1 - \frac{\text{systemic clearance}}{\text{hepatic blood flow}} \quad \text{(Eq. 35)}$$

$$F = \frac{Cl_H F}{Q(1-F)} \quad \text{(Eq. 36)}$$

$$F = \frac{Cl_H}{Cl_{\text{int}}} \quad \text{(Eq. 37)}$$

$$F = \frac{Q(1-F)}{Cl_{i(\text{tot})}} \quad \text{(Eq. 38)}$$

$$F = \frac{Q}{Q - Cl_{i(\text{tot})}} \quad \text{(Eq. 39)}$$

The conventional clearance concepts of the first-pass effect in terms of the authors (1, 3, 12, 19) can be derived from the present concept under the special condition of first-order kinetics.

APPENDIX 1: NOMENCLATURE

C = concentration
t = time
t_{max} = t at maximal C
V_m = maximal metabolism rate (concentration rate term)
$V_{\bar{m}}$ = maximal metabolism rate (mass rate term)
K_m = Michaelis constant or concentration at $V_m/2$
$K_{\bar{m}}$ = Michaelis constant or mass at $V_{\bar{m}}/2$
V_l = liver blood volume
T = circulation time of V_l (T = 1 min for V_l = 1.5 liters)
V_d = volume of distribution
K_a = absorption rate constant
$T/2$ = elimination half-life
D = dose
G = amount in GI tract
M = absorbed amount
B = amount in systemic circulation
F = bioavailability factor
exp( ) = e-function of ( )
ln( ) = logarithmus numeralis from ( )
Cl = clearance

APPENDIX 2

The nonlinear equation of the first-pass effect (Eq. 13) is derived in the following way:

$$-\frac{dG}{dt} = K_a G \quad \text{(Eq. A1)}$$

$$G = D\exp(-K_a t) \quad \text{(Eq. A2)}$$

The (−) sign changes to a (+) sign since the decrease of the GI amount ($-dG/dt$) is the increase of the absorbed amount ($+dG/dt$), which is further considered:

$$\frac{dG}{dt} = K_a D\exp(-K_a t) \quad \text{(Eq. A3)}$$

$$M = \frac{dG}{dt}T \quad \text{(Eq. A4)}$$

$$\frac{dM}{dt} = \frac{V_{\bar{m}}M}{K_{\bar{m}} + M} \quad \text{(Eq. A5)}$$

$$\frac{dB}{dt} = \frac{dG}{dt} - \frac{dM}{dt} \quad \text{(Eq. A6)}$$

$$\frac{dB}{dt} = K_a D\exp(-K_a t) - \frac{V_{\bar{m}}M}{K_{\bar{m}} + M} \quad \text{(Eq. A7)}$$

$$\frac{dB}{dt} = K_a D\exp(-K_a t) - \frac{V_{\bar{m}}\frac{dG}{dt}T}{K_{\bar{m}} + \frac{dG}{dt}T} \quad \text{(Eq. A8)}$$

$$\frac{dB}{dt} = K_a D\exp(-K_a t) - \frac{V_{\bar{m}}K_a DT\exp(-K_a t)}{K_{\bar{m}} + K_a DT\exp(-K_a t)} \quad \text{(Eq. A9)}$$

$$B = \int_0^t \frac{dB}{dt}dt \quad \text{(Eq. A10)}$$

$$F = \frac{B}{D} = \int_0^t \left[K_a\exp(-K_a t) - \frac{V_{\bar{m}}K_a T}{K_{\bar{m}}\exp(K_a t) + K_a DT}\right]dt \quad \text{(Eq. A11)}$$

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