imum cholesterol solubility coincided with the anhydrous–hydrate crystalline phase change.

The water content at which a given compound has the potential to convert to its hydrate is not predictable. A metastable form may remain supersaturated for long periods, particularly if the degree of supersaturation is not large. In addition, little is known about the effects of such crystal changes on solubility profiles in mixed solvents. Based on these and other considerations discussed below, compounds subject to such phase changes are not appropriate for modeling by the extended Hildebrand approach. Caffeine, theophylline, and theobromine all form hydrates, although they have been used as model compounds for evaluation of the extended Hildebrand approach (1–3). The purpose of this communication is to point out that knowledge of the crystal phase present at equilibrium is essential for the study of solubility. Furthermore it is especially important to identify the solid phase at equilibrium in mixed solvents.

To illustrate these points we examined the solid phases present when caffeine or theophylline were equilibrated at 25° in 0–50% water–dioxane solutions for 3–5 days[1]. These conditions were similar to those employed previously (1, 2). To avoid compositional bias, separate samples were equilibrated which contained either the anhydrous or monohydrate forms. At equilibrium the solid phases were filtered, dried under ambient conditions, and analyzed by differential scanning calorimetry (DSC)[2]. The hydrates were prepared by aqueous recrystallization and found to be monohydrates using Karl Fischer titrimetry[3]. At ambient conditions the hydrates were stable for at least 24 hr with respect to dehydration (7), and the anhydrous forms did not react with atmospheric moisture to form the hydrates. For some samples, solubilities were measured spectrophotometrically after 0.2-μm membrane filtration[4]. When heated in the DSC at 10°/min, the presence of water crystallization was verified by the broad dehydration endotherm centered at about 80° (caffeine) and 90° (theophylline). In these experiments the heat of dehydration was not measured and, thus, samples with the hydrate peak could also contain some anhydrous material. The solubilities were consistent with the previously reported data (1–3) except as described below.

For theophylline systems above ~5% water, the hydrate was always present at equilibrium. Below this concentration the anhydrous form was isolated. These findings were independent of the solid form initially added to the solvent, indicating that equilibrium was achieved with the more stable form. With a few exceptions, samples of caffeine equilibrated with 10–50% water, however, remained in the crystal form initially added. This apparent resistance to nucleation and crystallization of caffeine monohydrate led to significant differences in solubility. For example, at 50% water the solubilities were 71 mg/ml (hydrate) and 86 mg/ml (anhydrous). As the solvent water content decreased the solubilities became more similar [49 mg/ml (hydrate) *versus* 51 mg/ml (anhydrous)]. This behavior may explain the irregularity of the reported solubility profile in water–dioxane (3). With 0–5% water, samples initially prepared with hydrate were found to be anhydrous at equilibrium. There was no correlation between maximum solubility [at ~30–50% water (3)] and the crystal form change (at 5–10% water) in these systems. This is probably related to the extensive self-association of caffeine in water (8).

The regular solution theory (4) was developed to describe the solubility of molecular crystals, *i.e.*, single component substances. For solubility calculations the heat (or entropy) of fusion and the melting point of the solute are required. In the previous work these constants were obtained for the anhydrous forms by DSC (1–3). Since the equilibrium crystal form was most often the hydrate, these values should not have been used for calculation of solubility. The different calorimetric heats of solution (25°) in water for anhydrous caffeine (3.4 kcal/mole) and the hydrate (5.0 kcal/mole) show that the forms have quite different crystal energies (8). Further work will be required to develop the appropriate equations and physical constants for solubility modeling of hydrated (or solvated) crystalline compounds.

[1] Vibromixer E1, Chemapec Inc.
[2] DSC-1B, Perkin-Elmer.
[3] Auto-aquatrator, Precision Scientific Co.
[4] Alpha Metricel, Gelman.

(1) A. Martin, J. Newburger, and A. Adjei, *J. Pharm. Sci.*, **69**, 487 (1980).
(2) A. Adjei, J. Newburger, and A. Martin, *ibid.*, **69**, 659 (1980).
(3) A. Martin, A. N. Paruta and A. Adjei, *ibid.*, **70**, 1115 (1981).
(4) J. H. Hildebrand and R. L. Scott, "Regular Solutions," Prentice Hall, New York, N.Y., 1962.
(5) R. R. Pfeiffer, K. S. Yang, and M. A. Tucker, *J. Pharm. Sci.*, **59**, 1809 (1970).
(6) J. B. Bogardus, *J. Pharm. Sci.*, **71**, 370 (1982).
(7) E. Shefter and G. Kmack, *ibid.*, **56**, 1028 (1967).
(8) A. Cesaro, E. Russo, and V. Crescenzi, *J. Phys. Chem.*, **80**, 335 (1976).

Joseph B. Bogardus
College of Pharmacy
University of Kentucky
Lexington, KY 40506

Received January 10, 1983.
Accepted for publication February 18,1983.

Pharmacokinetic Absorption Plots from Oral Data Alone or Oral/Intravenous Data and An Exact Loo–Riegelman Equation

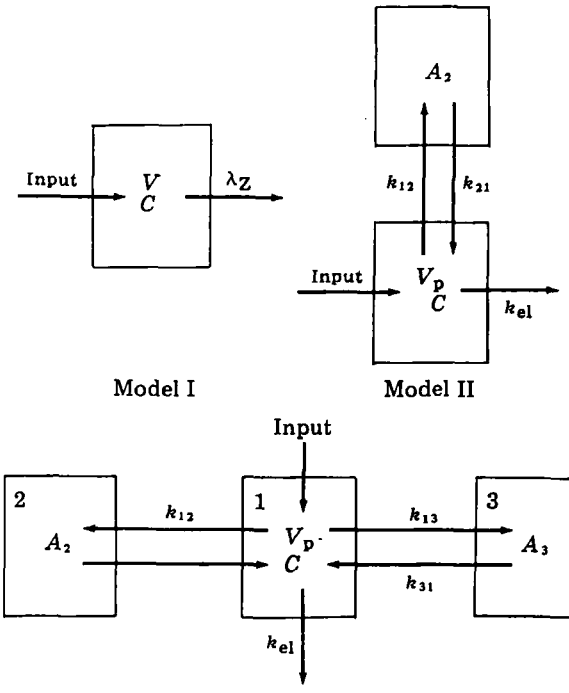
Keyphrases □ Deconvolution—amount absorbed as a function of time for all common disposition models; amount of drug in peripheral compartments of mammillary model from measurement in central compartment □ Wagner-Nelson equation—drug absorption □ Loo–Riegelman equation—drug absorption

To the Editor:

The purposes of this Communication are: (*a*) to give exact absorption equations when drug disposition is described by one, two, or three exponential terms; (*b*) when disposition is described by two exponential terms to show that one of the new absorption equations is an exact Loo–Riegelman equation and simpler and easier to use than the latter; and (*c*) to describe and illustrate use of the equations in a preliminary manner only.

The models to be considered are shown as models I, II, and III below.

0022-3549/83/0700-0838$01.00/0



The bolus intravenous (disposition) equations corresponding to models I–III are given as Eqs. 1–3, respectively.

Model I: $$C = C_1 e^{-\lambda_z t} \quad \text{(Eq. 1)}$$

Model II: $$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \quad (\lambda_1 < \lambda_2) \quad \text{(Eq. 2)}$$

Model III: $$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + C_3 e^{-\lambda_3 t} \quad (\lambda_1 < \lambda_2 < \lambda_3) \quad \text{(Eq. 3)}$$

In Eqs. 1–3, C is the plasma (serum or whole blood) concentration of unchanged drug at time t, λ_z is the slope of the least-squares line when $y = \ln C$ and $x = t$, and C_i and λ_i are coefficients and exponents obtained by nonlinear least-squares fitting of C,t data. If the drug is administered by infusion and appropriate polyexponential functions fitted to the pre- and/or postinfusion C,t data, then the coefficients can be converted to those corresponding to a bolus intravenous injection as described by Wagner (1). There are 3 two-compartment disposition models (2) and model II is one of these. There are 21 three-compartment disposition models (3a, 4) and model III is one of these. The parameters k_{12}, k_{21}, and k_{el} of model I are estimated from the C_1, C_2, λ_1, and λ_2 of eq. 2 and the dose administered (3b). The parameters k_{12}, k_{21}, k_{13}, k_{31}, and k_{el} of model III are estimated from C_1, C_2, C_3, λ_1, λ_2, and λ_3 of Eq. 3 and the dose (5). In using the absorption equations given below it is extremely important to derive the microscopic rate constants for models I to III, which have central compartment input and elimination, and not for one of the other possible models whose disposition is also described by eqs. 2 and 3. Erroneous absorption data would be obtained if one used microscopic rate constants, derived for one of the other two- or three-compartment disposition models, with the absorption equations given below. However, Vaughan and Dennis (6) and Wagner (3c) have shown that the Loo–Riegelman equations (7) is model independent, and for similar reasons, the new absorption equations are also model independent, providing input is into the central compartment. (But elimination need not be from the central compartment.) It is also assumed that the central compartment is the one sampled. Thus, if oral data were generated from one of the two- or three-compartment disposition models other than model II or III, and one derived the parameters of model I or III and used these in the absorption equations below, one would obtain the correct input data as has been shown formerly by Wagner (3c) for the Loo–Riegelman equation.

The equations giving the amount absorbed per unit volume are:

Model I: $$\frac{A_T}{V} = C_T + \lambda_z \int_0^T C dt \quad \text{(Eq. 4)}$$

Model II: $$\frac{A_T}{V_p} = C_T + k_{el} \int_0^T C dt + k_{12} e^{-k_{21} T} \int_0^T C e^{k_{21} t} dt \quad \text{(Eq. 5)}$$

Model III: $$\frac{A_T}{V_p} = C_T + k_{el} \int_0^T C dt + k_{12} e^{-k_{21} T} \int_0^T C e^{+k_{21} t} dt + k_{13} e^{-k_{31} T} \int_0^T C e^{k_{31} t} dt \quad \text{(Eq. 6)}$$

In Eqs. 4–6, A_T is the amount of drug absorbed between time zero (time of administration) and the blood sampling time, T ($0 \le T \le t$), after a single dose of drug, t is clock time, V is the volume of the compartment of model I, V_p is the volume of the central compartment of models II and III, C_T (or C) is the plasma (serum or whole blood) concentrations of unchanged drug at time T, and the λ_Z and subscripted k parameters are first-order rate constants. Equation 4 is the Wagner–Nelson equation (8), and Eqs. 5 and 6 are new as written. Equation 5 is derived in the Appendix and Eq. 6 may be derived in a similar manner. The Loo–Riegelman equation provides approximate A_T/V_p data for model II, since it assumes a linear segment between any two C,t points where the differences are ΔC and Δt. Equations 7 and 8 are the long form of the Loo–Riegelman equation in the symbolism of this article.

$$\frac{A_T}{V_p} = C_T + k_{el} \int_0^T C dt + \left(\frac{A_2}{V_p}\right)_{T_n} \quad \text{(Eq. 7)}$$

$$\left(\frac{A_2}{V_p}\right)_{T_n} = \left(\frac{A_T}{V_p}\right)_{T_{n-1}} e^{-k_{21}\Delta t} + \frac{k_{12}}{k_{21}} C_{T_{n-1}} [1 - e^{-k_{21}\Delta t}] + \frac{k_{12}}{k_{21}} \Delta C - \frac{k_{12}}{k_{21}} \cdot \frac{\Delta C}{\Delta t} [1 - e^{-k_{21}\Delta t}] \quad \text{(Eq. 8)}$$

Equation 5 is an exact Loo–Riegelman equation. The third term on the right-hand side of Eq. 5 is an exact equation for $(A_2/V_p)_T$ and replaces the entire right-hand side of Eq. 8. In Eqs. 7 and 8 $(A_2)_{T_n}$ is the amount of drug in the peripheral compartment of model II at time T_n, and $(A_2)_{T_{n-1}}$ is the amount at the previous sampling time T_{n-1}. Similarly Eq. 6 is an exact equation for model III, and the last two terms of the right-hand side give the amounts of drug in the peripheral compartments 2 and 3 of model III divided by the volume V_p, *i.e.*, $(A_2/V_p)_T$ and $(A_3/V_p)_T$.

When estimating A_T/V or A_T/V_p with Eqs. 4 to 6, the areas (*i.e.*, integrals) may be determined by segmenting each area into trapezoids using the regular trapezoidal rule when concentrations are increasing or remaining constant and the logarithmic trapezoidal rule when the concentrations are decreasing (9).

The apparent fraction of drug absorbed to time T, F_a, is given as:

$$F_a = \frac{A_T/V_p}{A_\infty/V_p} = \frac{A_T}{A_\infty} \qquad \text{(Eq. 9)}$$

where A_∞/V_p is the asymptotic value of A_T/V_p and is given as:

$$\frac{A_\infty}{V_p} = k_{el}\int_0^\infty C dt \qquad \text{(Eq. 10)}$$

When using Eq. 4 it is usually preferable to obtain A_∞/V_p by averaging the values of the right side of Eq. 4 for those points used to estimate the apparent elimination rate constant, λ_z (3d). When using Eqs. 5, 6, 9, and 10 the subscripted k parameters would be obtained from intravenous data, and the remainder of the variables in the equations would be obtained from extravascular data.

The differential forms of Eqs. 4–6 are shown as:

Model I:
$$\left(\frac{dA}{dt}\right)_T = V\left(\frac{dC}{dt}\right)_T + V\lambda_z C_T \qquad \text{(Eq. 11)}$$

Model II:
$$\left(\frac{dA}{dt}\right)_T = (k_{12}+k_{el})V_p C_T + V_p\left(\frac{dC}{dt}\right)_T - k_{12}k_{21}e^{-k_{21}T}V_p\int_0^T Ce^{k_{21}t}dt \qquad \text{(Eq. 12)}$$

Model III:
$$\left(\frac{dA}{dt}\right)_T = (k_{12}+k_{13}+k_{el})V_p C_T + V_p\left(\frac{dC}{dt}\right)_T - k_{12}k_{21}e^{-k_{21}T}V_p\int_0^T Ce^{k_{21}t}dt - k_{13}k_{31}e^{+k_{el}T}\int_0^T Ce^{k_{31}t}dt \qquad \text{(Eq. 13)}$$

In Eqs. 11–13, $(dA/dt)_T$ is the rate of absorption at the specific time T, $(dC/dt)_T$ is the rate of change of drug concentration with respect to time at T, and other symbols have been defined formerly. Equation 11 has been derived formerly (8, 3e). Equations 12 and 13 in different form were derived by a deconvolution technique (10, 11) (see *Appendix*). Use of Eqs. 11–13 requires an estimate of the derivative $(dC/dt)_T$ at each sampling time T; such estimates may be obtained by fitting C,t data with a cubic spline function as described by Pedersen (10, 11) or a spline and Akima method as described by Wagner (3f). Equations 5–8, 12, and 13 require prior intravenous data for application. Equations 4 and 11 may be applied to extravascular data without intravenous data, and such application is appropriate when bolus intravenous data are fitted well to Eq. 1 as is sometimes the case (12–15). A special application of Eqs. 4 and 9 when input obeys zero-order kinetics will be the subject of a subsequent article.

Oral and intravenous data were simulated using Model II with first-order input and parameter values of $k_{12} = 1.5\ hr^{-1}$, $k_{21} = 0.5\ hr^{-1}$, $k_{el} = 0.5\ hr^{-1}$, $k_a = 4\ hr^{-1}$, $V_p = 10$ liters, $FD_{po} = 1000$ mg. These parameters with Model II gave $\lambda_1 = 0.15669\ hr^{-1}$ and $\lambda_2 = 2.3933\ hr^{-1}$. Equation 14 corresponds to Eq. 2 for this simulation. The simulated

$$C_{iv} = 17.2675e^{-0.10436t} + 82.7325e^{-2.3956t} \qquad \text{(Eq. 14)}$$

oral data were given by:

$$C_T = 17.7301e^{-0.10436T} + 206.2640e^{-2.3956T} - 223.9941e^{-4T} \qquad \text{(Eq. 15)}$$

For this example the actual F_a values, shown in the last column of Table I, are given as:

$$F_a = 1 - e^{-k_a T} = [1 - e^{-4T}] \qquad \text{(Eq. 16)}$$

Table I lists the sampling times, T, the C_T values obtained with Eq. 15, and the stepwise calculation of the component parts of Eq. 5 in columns 3–8. Note that a number in column 8 is the product of the numbers in the same row of columns 6 and 7 and that a number in column 9 is the sum of the numbers in the same row of columns 2, 4, and 8. Numbers in columns 3 and 6 were obtained by applying a combination of the regular and logarithmic trapezoidal rules (see text) to the numbers in columns 2 and 5, respectively, and the time values in column 1.

Table I—Simulation Example

		Components of Eq. 5							Calculated[b]	Actual
T, hr	C_T Eq. 15, μg/ml	$\int_0^T C dt$,[a] μg hr/ml	$k_{el}\int_0^T C dt$ μg/ml	$C_T e^{+k_{21}T}$, μg/ml	$\int_0^T C_T e^{+k_{21}T}dt$,[a] μg hr/ml	$k_{12}e^{-k_{21}T}$, hr^{-1}	$k_{12}e^{-k_{21}T}\int_0^T C_T e^{+k_{21}T}dt$, μg/ml	A_T/V_p, μg/ml	F_a (Eq. 5, 9)	F_a (Eq. 16)
0	0	0	0	0	0	0	0	0	0	0
0.05	17.23	0.43	0.22	17.67	0.44	1.46	0.64	18.09	0.181	0.181
0.1	29.72	1.60	0.80	31.24	1.66	1.39	2.31	32.83	0.328	0.330
0.2	44.46	5.31	2.66	49.14	5.68	1.36	7.72	54.84	0.547	0.551
0.3	50.25	10.05	5.03	58.38	11.06	1.29	14.27	69.55	0.694	0.699
0.4	50.90	15.11	7.56	62.17	17.09	1.23	21.02	79.48	0.793	0.798
0.5	47.78	20.09	10.05	62.63	23.33	1.17	27.30	86.13	0.860	0.865
0.6	45.33	24.79	12.40	61.19	29.52	1.11	32.77	90.50	0.903	0.909
0.75	39.45	31.14	15.57	57.40	38.41	1.03	39.56	94.58	0.944	0.950
1	30.67	39.86	19.93	50.57	51.89	0.910	47.22	97.82	0.976	0.982
1.5	20.28	52.42	26.21	42.93	75.21	0.758	57.01	103.50	1.03	0.9975
2	16.03	61.46	30.73	43.57	96.84	0.552	53.46	100.22	1.00	0.9997
3	13.12	75.98	37.99	58.80	148.02	0.335	49.59	100.70	1.00	1.00
4	11.69	88.37	44.19	86.38	220.61	0.203	44.78	100.66	1.00	1.00
6	9.48	109.47	54.74	190.41	497.40	0.0747	37.16	101.38	1.01	1.00
12	5.07	151.74	75.87	2045.38	7204.77	0.00372	26.80	107.74	1.08	1.00
18	2.71	174.35	87.18	21959.36	9774.89	0.000185	1.81	91.70	0.92	1.00

[a] A combination of the regular and logarithmic trapezoidal rules (see text) was used to estimate these integrals using data in the adjacent columns and the time values. [b] Estimation of AUC $0-\infty$ by the usual method (ref. 3g) directly from the T,C_T data gave AUC $0-\infty = 200.33$ μg hr/ml, hence $A_\infty/V_p = k_{el}(\text{AUC } 0-\infty) = (0.5)(200.33) = 100.2$ μg/ml, and this value was used to calculate the F_a values using Eq. 9.

Table II compares the F_a values estimated by the new Eq. 5 and Eq. 9 with those calculated by the long form of the Loo–Riegelman equation (Eqs. 7 and 8) and Eq. 9. For this example with error-free data the accuracy of the two methods are essentially identical as the percent errors in Table II indicate. In using Eqs. 5 and 6 one must be careful to carry enough decimal places since at the higher time values one is multiplying a very large number ($\int_0^T Ce^{k_{21}t}dt$) by a very small number ($k_{12}e^{-k_{21}T}$). Care must be taken also to estimate the asymptote A_∞/V_p correctly with Eq. 10 and not average terminal A_T/V_p values as done in application of the Wagner–Nelson method.

If absorption is first order then one can obtain an estimate of the absorption rate constant, k_a, by applying the method described by Wagner and Ayres (16). With reference to Table II one performs linear least-squares regression using the $x = \Delta F_a$ (second column of Table II) and $y = F_a$ (column 3); *i.e.*, the x,y pairs for this example are: 0.219, 0.328; 0.147, 0.547; 0.099, 0.694; 0.067, 0.793; and 0.043, 0.860. For this example the equally spaced $\Delta t = 0.1$ hr. The equation of such a line is:

$$(F_a)_i = (F_a)_\infty - \left[\frac{1}{1 - e^{-k_a \Delta t}}\right] \cdot \Delta F_a \qquad \text{(Eq. 17)}$$

ordinate: $(F_a)_i$; intercept: $(F_a)_\infty$; slope: $\left[\frac{1}{1 - e^{-k_a \Delta t}}\right]$; abscissa: ΔF_a

For the above data set the intercept was 0.994 (instead of the theoretical 1.00) and the slope was −3.0368.

$$k_a = \frac{-\ln\left[1 - \frac{1}{\text{slope}}\right]}{\Delta t} = \frac{-\ln\left[1 - \frac{1}{3.0368}\right]}{0.1} = 3.99 \text{ hr}^{-1} \qquad \text{(Eq. 18)}$$

where the known value was 4.0 hr^{-1}.

More extensive applications of the equations in this article will be published subsequently.

APPENDIX

Derivation of Eq. 5—Let D = the dose, and, at some time T let A_r = the amount of drug remaining at the absorption site, A_T = the amount absorbed, A_1 = amount in the central compartment of model II, A_2 = the amount in the peripheral compartment, and A_e = the amount of drug which has been eliminated by metabolism and excretion. Then mass balances give:

$$D = A_r + A_1 + A_2 + A_e \qquad \text{(Eq. 19)}$$

$$A_T = D - A_r \qquad \text{(Eq. 20)}$$

$$A_T = A_1 + A_2 + A_e \qquad \text{(Eq. 21)}$$

Now:

$$A_1 = V_p C_1 \qquad \text{(Eq. 22)}$$

The clearance equation for model II is:

$$\frac{dAe}{dt} = V_p k_{el} C_1 \qquad \text{(Eq. 23)}$$

which, upon integration between the limits $t = 0$ and $t = T$ yields:

Table II—Comparison of Results with Eqs. 5 and 9 *versus* Eqs. 7–9

Time, hr	ΔF_a	F_a Eqs. 5, 9	F_a Eqs. 7–9	% Error in F_a Eqs. 5, 9	% Error in F_a Eqs. 7–9
0.05		0.181	0.181	0	0
0.1		0.328	0.328	−0.61	−0.61
	0.219				
0.2		0.547	0.547	−0.54	−0.54
	0.147				
0.3		0.694	0.694	−0.72	−0.72
	0.099				
0.4		0.793	0.792	−0.63	−0.75
	0.067				
0.5		0.860	0.859	−0.58	−0.69
	0.043				
0.6		0.903	0.903	−0.66	−0.66
0.75		0.944	0.944	−0.63	−0.63
1		0.976	0.977	−0.61	−0.51
1.5		1.03	0.999	Mean −0.62	−0.64
2		1.00	1.00		
3		1.00	1.01		
4		1.00	1.00		
6		1.01	1.00		
12		1.08	1.00		
18		0.92	1.00		

$$A_e = V_p k_{el} \int_0^T C_1 dt \qquad \text{(Eq. 24)}$$

The differential equation for the peripheral compartment of model II is:

$$\frac{dA_2}{dt} = k_{12} V_p C_1 - k_{21} A_2 \qquad \text{(Eq. 25)}$$

Rearrangement of Eq. 25 and multiplication of both sides by $e^{k_{21}t}$ gives:

$$e^{k_{21}t}\left[\frac{dA_2}{dt} + k_{21}A_2\right] = k_{12}V_p C_1 e^{k_{21}t} \qquad \text{(Eq. 26)}$$

But Eq. 26 may be written as:

$$\frac{d(A_2 e^{k_{21}t})}{dt} = k_{12} V_p C_1 e^{k_{21}t} \qquad \text{(Eq. 27)}$$

Integrating Eq. 27 between the limits $t = 0$ and $t = T$ yields:

$$A_2 e^{k_{21}T} = k_{12} V_p \int_0^T C_1 e^{k_{21}t} dt \qquad \text{(Eq. 28)}$$

hence

$$A_2 = k_{12} e^{-k_{21}T} V_p \int_0^T C_1 e^{k_{21}t} dt \qquad \text{(Eq. 29)}$$

Substituting for A_1, A_2, and A_e from Eqs. 22, 29, and 24, respectively, into Eq. 21, followed by dividing by V_p gives:

$$\frac{A_T}{V_p} = C_1 + k_{el} \int_0^T C_1 dt + k_{12} e^{-k_{21}T} \int_0^T C_1 e^{k_{21}t} dt \qquad \text{(Eq. 30)}$$

Equation 30 is the same as Equation 5, since C_1 of Eq. 30 is equivalent to C_T or C of Eq. 5 and $e^{-k_{21}T}$ and $e^{k_{21}t}$ of Eq. 30 are equivalent to $e^{-k_{21}T}$ and $e^{k_{21}t}$, respectively, of Eq. 5.

Derivation of Eq. 12—To convert Eq. 67 of Veng-Pedersen (10) to Eq. 12, one must use the equalities shown below:

$$-\frac{a_1\lambda_1 + a_2\lambda_2}{(a_1 + a_2)^2} = \frac{V_p}{D_{iv}}(k_{12} + k_{el}) \qquad \text{(Eq. 31)}$$

$$\frac{a_1a_2(\lambda_1 - \lambda_2)^2}{(a_1 + a_2)^3} = \frac{V_p}{D_{iv}}(k_{12}k_{21}) \qquad \text{(Eq. 32)}$$

$$\frac{a_1\lambda_2 + a_2\lambda_1}{a_1 + a_2} = \frac{V_p}{D_{iv}}k_{21} \qquad \text{(Eq. 33)}$$

$$-\frac{\lambda_1\lambda_2}{a_1\lambda_2 + a_2\lambda_1} = \frac{V_p}{D_{iv}}k_{el} \qquad \text{(Eq. 34)}$$

Derivation of Eq. 13—Using similar equalities based on model III (5, 10) Veng-Pedersen's Eq. 74 may be converted to Eq. 13.

(1) J. G. Wagner, *J. Pharmacokinet. Biopharm.*, **4**, 443 (1976).
(2) J. G. Wagner, *J. Pharmacokinet. Biopharm.*, **3**, 457 (1975).
(3) J. G. Wagner, "Fundamentals of Clinical Pharmacokinetics," 2nd ed., Drug Intelligence Publications, Hamilton, Ill., 1979; (a) pp. 114, 116; (b) p. 88; (c) p. 196; (d) p. 175, Eq. 4–10; (e) p. 174; (f) p. 419; (g); p. 344.
(4) Von G. Heinzel, M. Wolf, R. Hammer, F.-W. Koss, and G. Bozler, *Arzneim.-Forsch.*, **27**, 912 (1977).
(5) M. Gibaldi and D. Perrier, "Pharmacokinetics," 2nd ed., Dekker, New York, N.Y., 1982, p. 92.
(6) D. P. Vaughan and M. Dennis, *J. Pharmacokinet. Biopharm.*, **8**, 83 (1980).
(7) J. C. K. Loo and S. Riegelman, *J. Pharm. Sci.*, **57**, 918 (1968).
(8) J. G. Wagner and E. Nelson, *ibid.*, **52**, 610 (1963).
(9) W. L. Chiou, *J. Pharmacokinet. Biopharm.*, **6**, 539 (1978).
(10) P. Veng-Pedersen, *J. Pharm. Sci.*, **69**, 298 (1980).
(11) P. Veng-Pedersen, *J. Pharm. Sci.*, **69**, 305 (1980).
(12) D. L. Smith, J. G. Wagner, and G. C. Geritsen, *J. Pharm. Sci.*, **56**, 1150 (1967).
(13) L. Endrenyi, T. Inabi, and W. Kalow, *Clin. Pharmacol. Ther.*, **20**, 701 (1976).
(14) J. J. MacKichan, M. S. Dubrinska, P. G. Welling, and J. G. Wagner, *ibid.*, **22**, 609 (1977).
(15) B. H. Dvorchik and E. S. Vesell, *ibid.*, **23**, 617 (1978).
(16) J. G. Wagner and J. W. Ayres, *J. Pharmacokinet. Biopharm.*, **5**, 533 (1977).

John G. Wagner
College of Pharmacy and Upjohn Center for Clinical Pharmacology
The University of Michigan
Ann Arbor, MI 48109

Received October 25, 1982.
Accepted for publication February 7, 1983.

BOOKS

REVIEWS

Good Manufacturing Practices for Pharmaceuticals—A Plan for Total Quality Control. 2nd Ed. By SIDNEY H. WILLIG, MURRAY M. TUCKERMAN, and WILLIAM S. HITCHINGS IV. Marcel Dekker, New York, NY 10016. 1982. 259 pp. 15 × 23 cm. Price $49.75 (20% higher outside the U.S. and Canada)

In the preface to the second edition of this book, the authors state the following:

> "This volume is a revised and expanded second edition. Substantial changes have been made in organization in order to have the text follow 21 CFR 210 and 211 (43 FR 54076, September 29, 1978). Many examples of violations which led to recall have been added to the text in order to illustrate problems encountered by the industry and to suggest ways in which they could have been avoided. In addition, several new chapters, which are not direct comments on the regulations but which are, nevertheless, pertinent to compliance, have been added. These chapters deal with repackaging and relabeling; FDA inspection; recalls; safeguarding controlled substances; and how the manufacturer is designated on the label, as well as an appendix giving the standards for potable water. These additions, made in response to users of the first edition, should make this second edition even more useful."

This statement fulfills the promises of this excellent book. The authors present each of the parts of the Current Good Manufacturing Practices (CGMP) with clear explanations and discussions. They present, in detail, not only their own interpretation of the regulations, but relevant interpretations by others. The authors also include both their own and FDA views of the underlying CGMP regulations, specifically and overall, in a philosophical vein, a most refreshing approach. In addition, practical examples and court cases are presented where relevant.

Particularly useful are the authors' clear discussion and clarification of the intent of the regulations. These discussions frequently include additional information which can be very useful for professionals in the pharmaceutical industry. Some examples should give an idea of the kinds of material included in this volume:

- Details of screening, hiring, and administrating quality control personnel.
- Details of building specifications and segregation of pharmaceutical manufacturing facilities.
- A comprehensive list of raw material specifications.
- Details of paperwork including records, procedures, flow of records, assignment of control numbers, and storage.
- Receipt of raw materials and certificates of analysis.
- Analytical production and quality control procedures and controls.
- Description of labels.
- In-process controls.
- Laboratory controls: containers (glass and otherwise) and stability (physical, chemical, and container).
- Requirements and recommendations for records and reports. Design of records and reports—what kinds and how long to keep them.
- Numbering system for quality control records and systems.
- Problems with returned or salvaged product.
- FDA inspections and legal aspects.
- Recalls.

The CGMP regulations often are broad in their definitions. This book clarifies the regulations with many practical examples. The authors expand on the regulations, demonstrating their relation and applicability to the function and implementation of the Quality Control department. The authors further expand the discussion by freely offering their own opinions. Although one may not agree with their views all of the time, they are always stimulating and provocative. For example, the philosophy behind the following statement (page 22) could be fuel for a very interesting discussion:

> "The quality control supervisor must have a questioning nature. Some say a supervisor must be naturally distrustful. This applies to all matters in his or her area, including calculations and conclusions reached by peers and superiors from an organization viewpoint. It certainly applies to findings submitted by vendors and vendees of the operation and by its subcontractors. If the supervisor is other than such, the reputation will be that of a buck passer."

This unique and information-packed book should be an indispensable part of the libraries of all industrial pharmaceutical quality control, manufacturing, pharmacy, and legal departments.

Reviewed by Sanford Bolton
College of Pharmacy
St. John's University
Jamaica, NY 11439