Calculation of Plasma Level *versus* Time Profiles for Variable Dosing Regimens

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Abstract □ Equations are presented and flow charts are given for obtaining plasma level *versus* time profiles utilizing a high-speed digital computer for drug dosing regimens in which both dose and dosing interval can vary. Examples are given for drugs that can be described by both the one- and two-compartment open models.

Keyphrases □ Dosage regimens—equations for obtaining plasma level-time profiles in which dose and interval vary □ Drug regimens—equations for obtaining plasma level-time profiles in which dose and interval vary □ Pharmacokinetic parameters—one- and two-compartment open model, plasma level-time profiles in which dose and interval vary, equations

The utilization of pharmacokinetic parameters to obtain the optimal dosage regimen for a drug is an important application of biopharmaceutics. Since most drugs are generally given in multiple doses over a period of time, efforts have been devoted toward the development of equations useful for the prediction of: (*a*) plasma levels of drug *versus* time (1–4), (*b*) maximum and minimum plasma levels once equilibrium has been established (5, 6), and (*c*) the average equilibrium plasma level for a drug given in multiple doses at constant dosing intervals. The equations developed by Swintosky *et al.* (6) and by Wiegand *et al.* (3) allow the initial dose to be different from the maintenance doses. However, no equation developed to date allows the drug to be administered at varying time intervals.

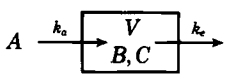
Giving a drug at uniform time intervals equal to its biological half-life ($T_{1/2}$) and using an initial dose twice the maintenance dose (assuming the absorption rate to be much greater than the elimination rate) would give the most nearly optimal dosing regimen with little or no accumulation (8). However, most drugs are not given in this manner. In hospitals, for one reason or another, drugs are frequently given twice (bid), three times (tid), or four times (qid) daily. The most common definitions given for these terms in hospital formularies are: bid = 10–6 (10 am and 6 pm) or 10–10, tid = 10–2–6 or 9–1–5, and qid = 10–2–6–10 or 9–1–5–9. Thus, in the typical hospital, drugs given either tid or qid are given every 4 hr during the day, with 12–16 hr between the last dose of one day and the first dose of the next day. In many instances this is true regardless of the $T_{1/2}$ of the drug. For example, the authors found that in a number of hospital formularies both tetracycline ($T_{1/2}$ of 6–10 hr) (9) and potassium penicillin G ($T_{1/2}$ of approximately 0.5 hr) (10) are directed to be given qid at 10–2–6–10. Family physicians frequently direct drugs to be taken near meal times and possibly also at bed time; drug package inserts frequently contain directions for the drug to be taken three or four times daily, with no definition being given for these terms. Because of the frequency with which drugs are taken at varying dosing intervals, it is of interest to obtain plasma level *versus* time profiles for drugs given under such conditions.

Multiple-dosing regimens can be simulated on analog computers (11–14), and the authors programmed an analog computer[1] to simulate both varying dose and time interval dosing regimens. However, the method is extremely cumbersome. Kirschner *et al.* (15) recently published a program for simulating variable dosing regimens on an analog/hybrid computer which, although it has the advantage of permitting the almost instantaneous viewing of the plasma level *versus* time profile, is expensive and not readily available. Due to the general availability of high-speed digital computers, the authors wrote FORTRAN IV programs for both the one- and two-compartment open models which simulate plasma level *versus* time profiles for dosing regimens in which both dose and dosing interval may be varied at will. Readily available plotting subroutines can be used to give automatic plotting of plasma levels *versus* time. In addition, the programs can be modified readily for drugs whose pharmacokinetic parameters vary with time.

THEORETICAL

The plasma level *versus* time profile for most drugs can be described adequately by viewing the body as consisting of either one or two compartments, with the drug being absorbed, distributed, and eliminated from the body through a series of first-order processes.

One-Compartment Open Model—In Model I, A is the amount of drug at the absorption site, k_a is the absorption rate constant, V is the volume of distribution, B is the amount of drug in the plasma, C is the concentration of drug in the plasma, and k_e is the elimination rate constant. The differential equations for this model are well known and have been solved repeatedly in the literature under the conditions that at time $t = 0$, $A = A_0$ and $B = 0$, which would correspond to the situation when a single dose of



Model I

[1] TR-20, Electronic Associates, Inc. West Long Branch, N.J.

Table I—Definition of Terms Used in Scheme I

Term	Definition
NODOSE[a]	Number of doses administered
OUT[a]	Time increment during the dosing interval for which plasma levels are to be calculated
KA[a]	First-order absorption rate constant
KE[a]	First-order elimination rate constant
AO(I)[a]	FD/V for dose number I
TAU(I)[a]	Dosing interval for dose number I
AEND	Drug at absorption site at the end of a dosing interval
CO	Plasma level at the start of a dosing interval
TIME	Counter for incrementing time
TEND	Time at the end of a dosing interval
I	Counter for number of doses given
NO(I)	Number of times that plasma levels will be calculated for dose number I
TPRIME	Time after the start of a dosing interval
TMAX(I)	Time at which the plasma level will reach a maximum for dose number I
AMAX(I)	Actual total time from the start of the dosing regimen until the plasma level reaches a maximum during dose number I
CMAX(I)	Maximum plasma level during dose number I
J	Counter for number of times the plasma levels will be calculated during a dosing interval
T(I,J)	Time for plasma level number J in dosing interval I
C(I,J)	Plasma level number J in dosing interval I
A(I,J)	Drug at absorption site for reporting time number J in dosing interval I

[a] Input variables.

drug is given to a subject. In a multiple-dosing study, this would be true for only the first dose; at the start of any dose n after the first, at time $t = 0$, $A = A_0$ and $B = B_0$. By using these conditions, a general set of equations was developed which describe both A and B as a function of time during any dosing interval n, for which $n \geq 1$ (Eqs. 1 and 2):

$$A_n = (A_0)_n e^{-k_a t} \qquad \text{(Eq. 1)}$$

$$B_n = \frac{k_a(A_0)_n}{(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}) + (B_0)_n e^{-k_e t} \qquad \text{(Eq. 2)}$$

in which A_0 represents the amount of drug at the absorption site at the start of the dosing interval, t represents time after the start of the dosing interval, and B_0 is the amount of drug in the plasma at the start of the dosing interval. During the first dosing interval, A_0 is equal to the dose given times the fraction of the dose absorbed, and $B_0 = 0$. Under these conditions, Eqs. 1 and 2 reduce to the familiar equations for a single-dose study.

Equation 2 is the equivalent of Eq. 8 of Wiegand *et al.* (3), which was developed for the situation when two doses of drug were given. To solve their Eq. 8 for the situation in which $n > 2$, Wiegand *et al.* had to assume that the dosing intervals remained constant. In the present study, Eq. 2 was developed further through the use of a high-speed digital computer to have the advantage of permitting the dosing intervals τ to vary. This method utilizes the facts that: (*a*) after the first dose has been given, the B_0 term for dosing interval n is equal to the amount of drug in the plasma at the end of dosing interval $n - 1$; (*b*) after the first dose, the term A_0, which represents the amount of drug at the absorption site at the start of dosing interval n, is equal to D, the dose given, times F, the fraction of the dose absorbed, plus the amount of drug remaining at the absorption site from the previous dose or, as given in Eq. 3:

$$(A_0)_n = (FD)_n + (A_0 e^{-k_a \tau})_{n-1} \qquad \text{(Eq. 3)}$$

Thus, Eqs. 1 and 2 are used to calculate both A and B as a function of time during dosing interval $n - 1$. The values of A and B at the end of this dosing interval, $t = \tau$, are saved in the computer memory banks. During dosing interval n, the saved value of B calculated at $t = \tau$ of interval $n - 1$ is recalled from storage and serves as the B_0 term of Eq. 2, in which B as a function of time is calculated for interval n. The value of A calculated at $t = \tau$ of dosing interval $n - 1$ is recalled from storage and added to the FD term for dosing interval n. The sum represents the A_0 term of Eq. 1 for calculating A as a function of time during dose interval n. This process is repeated as many times as necessary and does not depend upon the dosing intervals being constant.

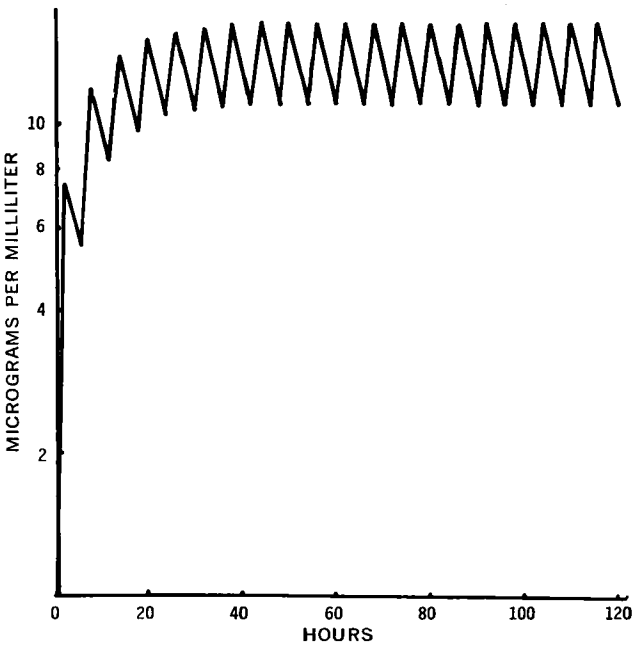


Figure 1—*Plasma level* versus *time profile for a drug with* $k_a = 1.0\ hr^{-1}$, $k_e = 0.116\ hr^{-1}$, *and* $A_0' = 10\ \mu g/ml$. *Drug was administered every 6 hr around the clock.*

The mass of drug in the plasma at any time t after the start of a dosing interval can be calculated using Eqs. 1-3 and converted into plasma levels by dividing by V, the volume of distribution. This necessitates knowing the values of F and V, which are not always available. The collection of terms, FD/V, is readily available from a plot of plasma level *versus* time for a single-dose study and, if the model is correct, is directly proportional to the dose given. Due to the relative ease with which the term FD/V can be obtained, the authors chose to solve directly for plasma concentration. Dividing both sides of Eq. 2 by V gives:

$$C_n = \frac{k_a(A_0')_n}{(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}) + (C_0)_n e^{-k_e t} \qquad \text{(Eq. 4)}$$

in which C_0 is the plasma concentration at the start of the nth dosing interval, and A_0' is equal to A_0/V. The term A_0 in Eqs. 1 and 2 must represent the same quantity in this model. Thus, Eqs. 1 and 3 become:

$$(A')_n = (A_0')_n e^{-k_a t} \qquad \text{(Eq. 5)}$$

and:

$$(A_0')_n = (FD/V)_n + (A_0' e^{-k_a \tau})_{n-1} \qquad \text{(Eq. 6)}$$

The time needed to attain a maximum plasma level for any single dosing interval n can be obtained by differentiating Eq. 4 with respect to time and setting the derivative equal to zero to give:

$$(T_{max})_n = \frac{2.303}{(k_a - k_e)} \log\left(\frac{k_a^2(A_0')_n}{k_e[k_a(A_0')_n + (k_a - k_e)(C_0)_n]}\right) \qquad \text{(Eq. 7)}$$

Substituting Eq. 7 into Eq. 4 gives the maximum plasma concentration attained for dosing interval n:

$$(C_{max})_n = \frac{(A_0')_n k_a}{k_e}\left(\frac{k_a^2(A_0')_n}{k_e[k_a(A_0')_n + (k_a - k_e)(C_0)_n]}\right)^{-\frac{k_a}{(k_a - k_e)}} \qquad \text{(Eq. 8)}$$

Table II—Portion of the Output from the Authors' FORTRAN IV Program Based upon Scheme I

DRUG GIVEN EVERY 6 HOURS AROUND THE CLOCK

DOSE NO. 1 TMAX = 2.44 HRS. ACTUAL = 2.44 HRS.

TIME (HRS.)	PLASMA CONC.	DOSING INTERVAL	CMAX	CMIN
1.00	5.912E 00	6 HRS.	7.538E 00	5.612E 00
2.00	7.439E 00			
3.00	7.424E 00			
4.00	6.906E 00			
5.00	6.257E 00			
6.00	5.612E 00			

DOSE NO. 2 TMAX = 1.98 HRS. ACTUAL = 7.98 HRS.

TIME (HRS.)	PLASMA CONC.	DOSING INTERVAL	CMAX	CMIN
7.00	1.092E 01	6 HRS.	1.191E 01	8.424E 00
8.00	1.191E 01			
9.00	1.141E 01			
10.00	1.045E 01			
11.00	9.415E 00			
12.00	8.424E 00			

DOSE NO. 3 TMAX = 1.81 HRS. ACTUAL = 13.81 HRS.

TIME (HRS.)	PLASMA CONC.	DOSING INTERVAL	CMAX	CMIN
13.00	1.343E 01	6 HRS.	1.417E 01	9.826E 00
14.00	1.414E 01			
15.00	1.339E 01			
16.00	1.222E 01			
17.00	1.099E 01			
18.00	9.826E 00			

During the first dosing interval, $C_0 = 0$, and Eqs. 6 and 7 reduce to the usual equations for T_{max} and C_{max} for a single-dose study.

The flow diagram from which this FORTRAN IV computer program[2] was written is shown in Scheme I, and the computer variables are defined in Table I. The output from the program is a matter of personal preference. A sample of the output used by the authors is shown in Table II.

To illustrate the desirability of being able to vary dosing intervals to correspond to those dosing intervals in actual use, the plasma level profile was generated for a drug with: $k_a = 1.0\ hr^{-1}$, $k_e = 0.116\ hr^{-1}$ ($T_{1/2} = 6$ hr), and $A_0' = 10\ \mu g/ml$ [obtained by dividing by k_a the intercept on the Y-axis of a semilogarithmic plot of concentration *versus* time for a single-dose study and multiplying by $(k_a - k_e)$]. This drug would theoretically be given at its half-life of 6 hr. The plasma level *versus* time profile for this drug, given at 6-hr intervals around the clock, was generated using the computer program based upon Scheme I. Data for the 20th dosing interval obtained using this program and Eq. 13 of Wiegand *et al.* (3) are given in Table III to demonstrate the validity of the method. The complete plasma level *versus* time profile is given in Fig. 1. Since no loading dose was used, the drug accumulates and finally equilibrates with a maximum plasma level of 16.5 $\mu g/ml$ and a minimum plasma level of 11.2 $\mu g/ml$.

This drug given every 6 hr around the clock would be given four times daily. If, however, four times daily is defined as qid as in all formularies examined by the authors, the drug would be given at 4-hr intervals during the day, with the last dose at 9 or 10 pm. Use of the common 10-2-6-10 regimen would result in the plasma level *versus* time profile shown in Fig. 2. The broken lines in Fig. 2 indicate the equilibrium maximum and minimum plasma level attained on the every 6-hr dosing schedule. For 6 hr of every day the plasma level on the 10-2-6-10 dosing schedule is above and for 8 hr it is below the respective daily maximum and minimum plasma levels attained on the every 6-hr dosing schedule. The marked fluctuations demonstrated in Fig. 2 would be undesirable for drugs with narrow ranges between minimal effective and toxic plasma levels (*i.e.*, theophylline and procainamide) but would probably not be important if the range between effective and toxic plasma levels were wide enough. Therefore, the clinical importance of a marked daily fluctuation in plasma levels would have to be assessed for a given drug.

Two-Compartment Open Model—Although Wagner and Metzler (4) showed that for many drugs the one-compartment open model can be used for predicting plasma levels for doses given at constant intervals, the two-compartment open model (Model II)

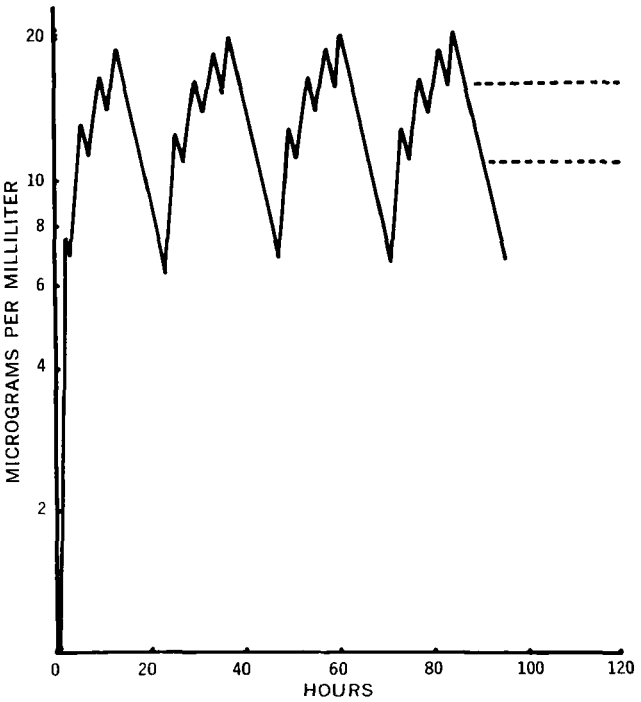
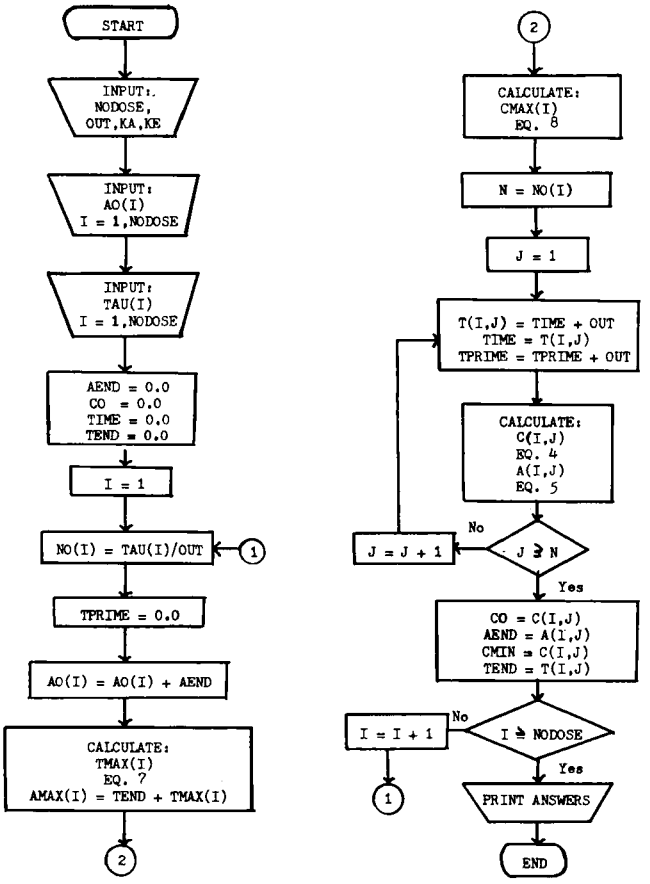


Figure 2—*Plasma level* versus *time profile for a drug with* $k_a = 1.0\ hr^{-1}$, $k_e = 0.116\ hr^{-1}$, *and* $A_0' = 10\ \mu g/ml$. *Drug was administered at 10–2–6–10. Broken lines indicate equilibrium maximum and minimum plasma levels obtained for the same drug given every 6 hr around the clock.*

[2] Available from the authors upon request.



Scheme I—Flow diagram for the one-compartment open model

might have to be used in some instances. In Model II, A represents drug at the absorption site, k_a is the first-order absorption rate constant, k_{bt} and k_{tb} are the first-order disposition rate constants, k_e is the elimination rate constant, M_1 and M_2 represent the amount of drug in each compartment, V_1 and V_2 are the volumes of distribution for each compartment, and C_1 represents the plasma level of the drug. Integrating the differential equations

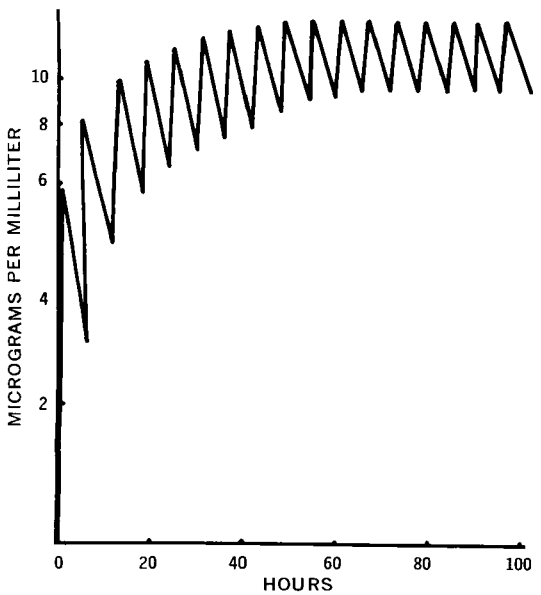
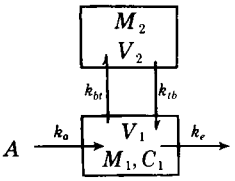


Figure 3—*Plasma level* versus *time profile for a drug with* $k_a = 2.0\ hr^{-1}$, $k_{bt} = 0.226\ hr^{-1}$, $k_{tb} = 0.255\ hr^{-1}$, $k_e = 0.123\ hr^{-1}$, $A_0 = 500$ *mg, and* $V_1 = 60$ *liters. Drug was administered every 6 hr around the clock.*



Model II

describing this model under the conditions that at the start of any given dosing interval n, time $t = 0$, $M_1 = M_1^0$, and $M_2 = M_2^0$ gives:

$$A_n = (A_0)_n e^{-k_a t} \quad \text{(Eq. 9)}$$

$$(M_1)_n = \left(\frac{P_2\alpha - P_1\alpha^2 - P_3}{(\alpha - \beta)(k_a - \alpha)}\right)e^{-\alpha t} + \left(\frac{P_2\beta - P_1\beta^2 - P_3}{(\alpha - \beta)(\beta - k_a)}\right)e^{-\beta t} - \left(\frac{P_1 k_a^2 - P_2 k_a + P_3}{(\beta - k_a)(k_a - \alpha)}\right)e^{-k_a t} \quad \text{(Eq. 10)}$$

$$(M_2)_n = \left(\frac{Q_2\alpha - Q_1\alpha^2 - Q_3}{(\alpha - \beta)(k_a - \alpha)}\right)e^{-\alpha t} + \left(\frac{Q_2\beta - Q_1\beta^2 - Q_3}{(\alpha - \beta)(\beta - k_a)}\right)e^{-\beta t} - \left(\frac{Q_1 k_a^2 - Q_2 k_a + Q_3}{(\beta - k_a)(k_a - \alpha)}\right)e^{-k_a t} \quad \text{(Eq. 11)}$$

in which:

$$P_1 = (M_1^0)_n \quad \text{(Eq. 12)}$$

$$P_2 = (M_1^0)_n(k_a + k_{tb}) + k_{tb}(M_2^0)_n + k_a(A_0)_n \quad \text{(Eq. 13)}$$

$$P_3 = k_a k_{tb}[(A_0)_n + (M_1^0)_n + (M_2^0)_n] \quad \text{(Eq. 14)}$$

$$Q_1 = (M_2^0)_n \quad \text{(Eq. 15)}$$

$$Q_2 = (M_2^0)_n(k_{bt} + k_e + k_a) + k_{bt}(M_1^0)_n \quad \text{(Eq. 16)}$$

$$Q_3 = k_a k_{bt}[(A_0)_n + (M_1^0)_n + (M_2^0)_n] + k_a k_e (M_2^0)_n \quad \text{(Eq. 17)}$$

$$\alpha = \tfrac{1}{2}\left[(k_{bt} + k_e + k_{tb}) + \sqrt{(k_{bt} + k_e + k_{tb})^2 - 4k_{tb}k_e}\right] \quad \text{(Eq. 18)}$$

$$\beta = \tfrac{1}{2}\left[(k_{bt} + k_e + k_{tb}) - \sqrt{(k_{bt} + k_e + k_{tb})^2 - 4k_{tb}k_e}\right] \quad \text{(Eq. 19)}$$

At the start of the first dosing interval, $M_1^0 = M_2^0 = 0$ and $A_0 = FD$, where F is the fraction of the dose D that is absorbed. After the first dose has been given, the terms M_1^0 and M_2^0 at the start of dosing interval n are equal to the amounts of drug left in their respective compartments at the end of dosing interval $n - 1$, and $(A_0)_n$ is given by Eq. 3. Plasma concentrations can be obtained by dividing the amount of drug in Compartment 1 by its volume of distribution or:

$$(C_1)_n = (M_1)_n / V_1 \quad \text{(Eq. 20)}$$

The flow diagram from which the FORTRAN IV computer pro-

Table III—Validity of Scheme I; Data for the 20th Dosing Interval for a Drug with $k_a = 1.0\ hr^{-1}$, $k_e = 0.116\ hr^{-1}$, and $A_o' = 10\ \mu g/ml$

Time after Start of Dose, hr	Plasma Levels, μg/ml	
	Present Work	Literature[a]
0	11.22	11.22
1	15.92	15.92
2	16.35	16.35
3	15.37	15.37
4	13.98	13.98
5	12.55	12.55
6	11.22	11.22

[a] Equation 13 of Wiegand *et al.* (3).

Table IV—Definition of Terms Used in Scheme II

Term	Definition
KA[a]	First-order absorption rate constant
KE[a]	First-order elimination rate constant
KBT[a]	First-order rate constant for transfer from Compartment 1 into Compartment 2
KTB[a]	First-order rate constant for transfer from Compartment 2 into Compartment 1
V1[a]	Volume of distribution for Compartment 1
NODOSE[a]	Number of doses to be administered
OUT[a]	Time increment during the dosing interval for which plasma levels are to be calculated
AO(I)[a]	Dose for interval number I
TAU(I)[a]	Dosing interval for dose number I
M10	Amount of drug in Compartment 1 at the start of a dosing interval
M20	Amount of drug in Compartment 2 at the start of a dosing interval
AEND	Drug at the absorption site at the end of a dosing interval
TIME	Counter for incrementing time
I	Counter for number of doses given
NO(I)	Number of times that plasma levels will be calculated for dose number I
TPRIME	Time after the start of a dosing interval
J	Counter for the number of times the plasma levels will be calculated during a dosing interval
T(I,J)	Time for plasma level number J in dosing interval I
A(I,J)	Drug at absorption site for reporting time number J in dosing interval I
M1(I,J)	Amount of drug in Compartment 1 for reporting time number J in dosing interval number I
M2(I,J)	Amount of drug in Compartment 2 for reporting time number J in dosing interval I
C1(I,J)	Plasma level number J in dosing interval I

[a] Input variables. AO(I) and V1 should be in the appropriate units in order to yield the plasma concentration in the units desired, *i.e.*, AO(I) in milligrams and V1 in liters would give plasma levels in micrograms per milliliter.

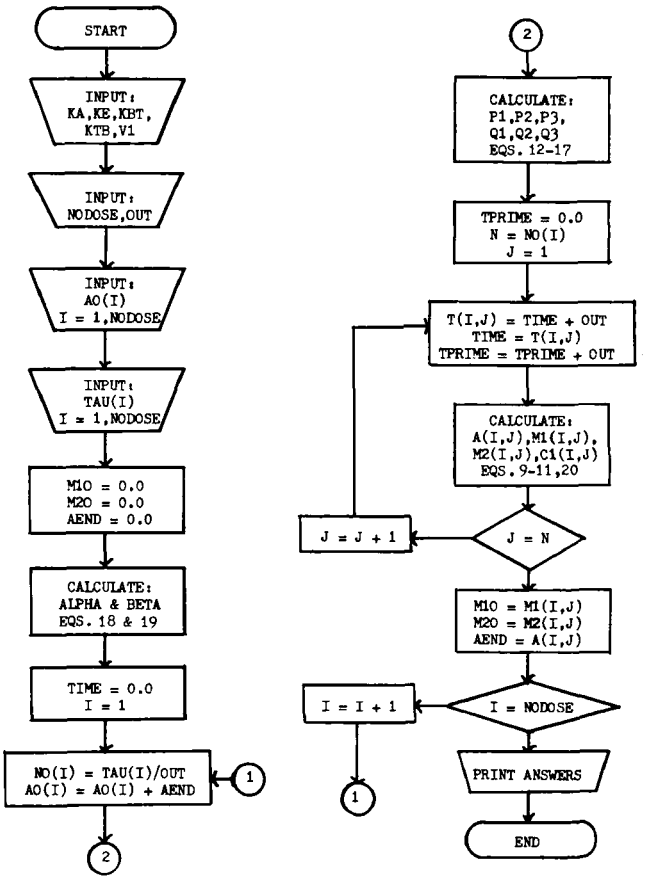
gram was written for this model is shown in Scheme II, and the computer variables are defined in Table IV.

As an example, data were generated for a drug given every 6 hr around the clock with: k_a = 2.0 hr^{-1}, k_{bt} = 0.226 hr^{-1}, k_{tb} = 0.255 hr^{-1}, k_e = 0.123 hr^{-1}, FD = 500 mg (assuming complete absorption), and V_1 = 60 liters. The computer program for the 20th dosing interval is given in Table V. The values obtained are exactly the same as those obtained with Eq. 5 of Wagner and Metzler (4). The complete plasma level *versus* time profile is shown in Fig. 3. Since no loading dose was used, the drug accumulates and finally equilibrates with a maximum plasma level of 13.9 μg/ml and a minimum plasma level of 9.7 μg/ml. The plasma level *versus* time profile was also generated for a 10-2-6-10 dosing regimen (Fig. 4). As with the one-compartment open model, the 10-2-6-10 dosing schedule gave a much more irregular pattern than the schedule in which the drug was given every 6 hr around the clock. Once again, the clinical significance of this would have to be assessed for individual drugs.

SUMMARY

The presented method for generating plasma level *versus* time profiles is general and can be used for studying time-release systems with either zero- or first-order release, constant intravenous infusions, urinary excretion patterns, or any other type of dosing regimen; it is not restricted to the one- or two-compartment open models. Although the authors used a digital computer to generate the plasma level *versus* time profiles, a programmable desk calculator with a sufficient number of program steps and storage registers can be used also. The authors, for example, have programmed a 258-step, 20-storage register calculator[3] for the one-compartment open model.

[3] Model 1775, Monroe Co., Orange, N.J.



Scheme II—Flow diagram for the two-compartment open model

The method can be summarized as follows:

1. Integrate the differential equations describing the model under the condition that at time t = 0, drug is present in each compartment and at the absorption site.

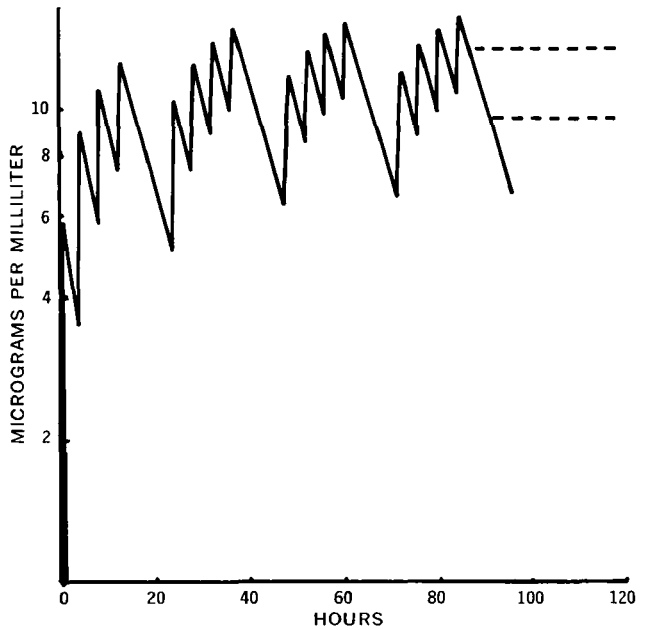


Figure 4—*Plasma level* versus *time profile for a drug with* k_a = *2.0* hr^{-1}, k_{bt} = *0.226* hr^{-1}, k_{tb} = *0.255* hr^{-1}, k_e = *0.123* hr^{-1}, A_0 = *500 mg, and* V_1 = *60 liters. Drug was administered at 10–2–6–10. Broken lines indicate the equilibrium maximum and minimum plasma levels obtained with the same drug given every 6 hr around the clock.*

2. During the first dosing interval, initialize the amount of drug in all compartments to zero. The amount of drug at the absorption site is proportional to the dose given and should be expressed in terms appropriate for the model. For example, in the one-compartment open model, the authors chose to use the collection of terms FD/V to represent the dose given. If this collection of terms is not directly proportional to the dose, it should be determined from a single-dose study at the dose given.

3. Using the integrated expressions, generate the amount of drug in each compartment and at the absorption site as a function of time.

4. At the start of the next dosing interval, initialize the amount of drug in each compartment equal to the amount of drug in that compartment at time $t = \tau$ of the previous dosing interval. The amount of drug at the absorption site is set equal to the sum of the amount of drug remaining at the absorption site at time $t = \tau$ of the previous dosing interval plus the amount given in terms appropriate for the model.

5. Repeat Steps 3 and 4 as often as desired.

In the authors' present digital computer programs, all rate constants are entered once and considered to remain constant throughout the dosing period. The amount of drug given and the length of the dosing interval must be entered for each dosing interval. If any rate constant is known to vary from dose to dose, that rate constant can be entered for each dosing interval in the same manner that the dose given and the dosing interval are entered. This is accomplished through the use of a FORTRAN DIMENSION statement and the use of subscripted variables for the terms in question[4].

NOMENCLATURE

A = amount of drug at the absorption site
A' = A/V, in which V is the volume of distribution
A_0 = amount of drug at the absorption site at the start of a dosing interval
A_0' = A_0/V, in which V is the volume of distribution
B = amount of drug in the plasma for the one-compartment open model
B_0 = amount of drug in the plasma at the start of a dosing interval for the one-compartment open model
C = plasma concentration of drug for the one-compartment open model
C_0 = plasma concentration of drug at the start of a dosing interval for the one-compartment open model
C_1 = plasma concentration for the two-compartment open model
C_{max} = maximum plasma level attained during a dosing interval for the one-compartment open model
D = dose given at the start of a dosing interval
F = fraction of a dose that is absorbed
k_a = first-order absorption rate constant
k_e = first-order elimination rate constant
k_{bt} = first-order rate constant for transfer of drug from Compartment 1 into Compartment 2
k_{tb} = first-order rate constant for transfer of drug from Compartment 2 into Compartment 1
M_1 = amount of drug in Compartment 1 (plasma)
M_1^0 = amount of drug in Compartment 1 at the start of a dosing interval
M_2 = amount of drug in Compartment 2 (tissue)
M_2^0 = amount of drug in Compartment 2 at the start of a dosing interval
n = number of the dosing interval
t = time after the start of a dosing interval
T_{max} = time needed to reach the maximum plasma level for a given dosing interval for the one-compartment open model
V = volume of distribution for the one-compartment open model
V_1 = volume of Compartment 1
V_2 = volume of Compartment 2
τ = length of a dosing interval

[4] Anyone having difficulties in doing this should feel free to contact the authors.

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