Theoretical Formulation of Sustained-Release Dosage Forms

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The present investigation deals with the result of a mathematical and an analog computor analysis of the kinetic relationships governing the rate of release of drugs from sustained-release dosage forms. Two types of release have been considered, those described by zero-order and those that can be described by first-order kinetics. In addition, mathematical equations are derived that permit the calculation of doses and of release constants that will give a blood concentration *versus* time curve most closely approximating an "idealized" curve.

THE APPROACH most often used in the kinetic treatment of biologic data is that involving formulation of a mathematical model, the comparison of this model with *in vivo* findings, and finally the adjustment of the model and its constants to accommodate the *in vivo* results. Once a suitable model has been established, the complete interdependency of the model's parameters can be examined,[1] subject to the suitability of the model chosen. These parameters may be divided into two types, those under the control of the formulator, *i.e.*, the dosage form, release pattern, and rate, etc., and those that are imposed upon the model by the system studied, *i.e.*, the absorption, distribution, and excretion (ADE) pattern for the drug in the body. In the past, the major emphasis has been placed on the ADE parameters with relatively little attention being given to the dosage form release rate and pattern, not only because these studies are more difficult to carry out, but also because initially it was of particular concern to study the suitability of various models as simulations of the body's ADE capabilities. It seemed reasonable at that time to assume that in cases where the drug has been administered by injection or orally in some readily available form, *e.g.*, drug in solution, the effect of the dosage form release pattern might safely be neglected; for nonreadily available forms, particularly sustained-release dosage forms, this assumption cannot be made as the dosage form release pattern and its rate undoubtedly do play *major* roles in the blood concentration *versus* time curve obtained; indeed, it is the exploitation of this effect that makes sustained release possible. In addition to the rate and pattern of release from the dosage form, consideration must also be given to the effect of the relative amounts of the administered initial and maintenance dose on the resultant concentration in the blood. In the face of the recent barrage of studies supporting the suitability of the simpler kinetic models as descriptions of ADE phenomena, attention should now be paid to those aspects of the kinetic path less amenable to analysis, the dosage form release pattern and administered dose fractions. Indeed, a knowledge of the effects of these controllable parameters is essential in order to formulate sustained-release dosage forms having particular blood level characteristics.

Both Wiegand and Taylor (4, 5) and Wagner (6) have shown that the per cent released *versus* time data reported in the literature for many sustained-release preparations follow apparent first-order rate equations. Similarly, others (7, 8) have shown that some sustained-release preparations release drugs by apparent zero-order processes. From an experimental standpoint it would appear that these two mechanisms might adequately describe the rate of release for the majority of existing sustained-release dosage forms, and ADE equations involving both of these release patterns have already been described (5, 6, 9).

In order to obtain a constant blood level for some desired period of time from a sustained-release dosage form, Nelson (10) has stated that a constant (zero-order) rate of release from a dosage form is desired and has developed an approximate equation for calculating the amounts of sustained and initial drug forms required, based upon this assertion.

Utilizing essentially the same model as that of Nelson (10) but assuming first-order release, Wiegand and Taylor (1) have reported computer

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[1] Testing of the effect of various parameters in a model can be carried out very effectively on an analog computer, since variables can be changed and the effect read out immediately with a subjective appraisal being made even if complete mathematical solutions are unavailable. Utilization of the analog computer for this purpose is well documented (1–3), therefore, the required computer technology will not be stressed here. The circuits used in this study are given in the *Appendix*.

drawn curves showing the effect of altering the first-order release constant at a constant rate of absorption and elimination. In addition, they have also shown the effect of variation in the elimination constant on the blood concentration curve at a constant first-order rate of release from the dosage form and a constant rate of absorption. Computer drawn curves showing the effect of the fraction of the initial and maintenance dose at a constant rate of absorption, elimination, and first-order rate of release from the dosage form excretion have also been described (2), again using the same model.

In a recent paper supporting Nelson's assertion, Rowland and Beckett (9) have further claimed that first-order release from a dosage form *cannot* give the "idealized" blood concentration-time curve.

Unfortunately, experience suggests that the majority of sustained-release formulation techniques produce formulations that release drug at roughly a first-order rather than zero-order rate. In order to adequately compare these two availability patterns as to their potential to produce suitable sustained-action forms, a complete investigation of the effects of the various parameters in the models is essential. *Part* of such a study has been done for the first-order release case (1), but to the authors' knowledge a study of the effect of design parameters for a formulation having zero-order release characteristics has not been reported.

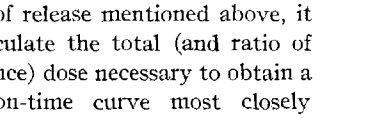
For both types of release mentioned above, it is desirable to calculate the total (and ratio of initial to maintenance) dose necessary to obtain a blood concentration-time curve most closely approximating the "idealized" case. Nelson (10) has given a method for calculating the maintenance dose of a constant rate of release dosage form, based on the biological half-life of the drug and the dose required to give the desired blood level, assuming, however, that the blood level *begins* at the concentration desired. The assumptions of these equations have been criticized recently (9), but completely corrected equations were not given. For first-order release from the dosage form, Wiegand and Taylor (4) have presented equations for calculation of the total dose remaining in a dosage form *in vitro*. These equations, while useful, cannot predict which combination of rate constant, fraction in initial form, and fraction in the maintenance form, will give a particular blood level.

In order to calculate the dosages required, methods must be available to obtain the optimum release rate constant. For zero-order release, one author (10) feels it is the product of the elimination constant and the dose required to give the desired blood level, while another (9) feels it is the product of the elimination constant and the desired blood level itself. For first-order release, there appears to be no suitable method available for obtaining the desired rate of release constant, or the fractions of initial and maintenance dose required.

In an effort to summarize the work in this area, the present investigation was designed to completely characterize the standard model for sustained-release dosage forms. In addition, it is the authors' purpose to report the analog computer, and where possible, mathematical solutions of the equations describing absorption, distribution, elimination, and availability relationships with the over-all goal of devising complete equations suitable for calculation of the doses and rate constants to give a desired blood level based on the type of release pattern employed or available. It will be apparent to the pragmatists among the readers that the ease with which a given type of release can be formulated must always be a consideration and the value of considering only those parameters within the reach of the experimenter will be appreciated.

GENERAL CONSIDERATION OF THE MODEL

In this study, the following model [after Teorell (11)] has been adopted, portions of which have been found to adequately describe actual biological processes.



(Eq. 1)

where

D = concentration of drug remaining in the dosage form,
G = concentration of drug at the sites of absorption,
B = concentration of drug in the fluids of distribution (for purposes of simplicity referred to as blood concentration),
U = concentration of drug in the urine or other permanent drug sink,
E = concentration of drug metabolized,
k_r = rate constant for release of drug from the dosage form, where the superscript 0 and 1 indicate the apparent order of release. The wavy arrow is used with k_r to indicate that the precise *form* of the release is a variable also,
k_a = rate constant for absorption,
k_e = rate constant for elimination of unchanged drug,
k_u = rate constant for elimination *via* all other routes.

For purposes of simplicity k_e and k_u have been combined into one rate constant k_d (where $k_d = k_e + k_u$).

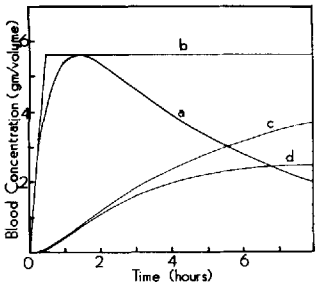


Fig. 1.—Comparable blood level *versus* time curves obtained for (a) an immediately available dose, (b) an "idealized" sustained-action formulation, (c) zero-order release maintenance from, (d) a first-order release maintenance form.

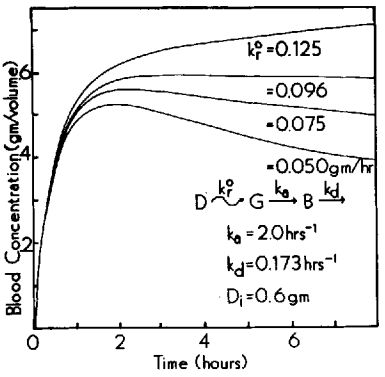


Fig. 2.—Blood level *versus* time curves showing the effect of variation in the zero-order release constant (using the ADE constants from *Reference 9*).

In using a model such as this, a problem arises in the treatment of the various components present from the standpoint of concentrations and compartments. Recent articles (9) have used amounts and concentrations interchangeably, but since the driving force in kinetic equilibria is concentration, amount can be used in its place to describe the kinetic relationships between compartments only when the volumes in each compartment are the same or when the assumption is made that the whole process takes place in the same compartment and volume. Since the one compartment–one volume idea is a useful and common, but tacit assumption, perhaps a brief explanation is necessary. The concept is more easily understood if the relationship of Eq. 1 is viewed as a chemical reaction involving four steps and taking place in a single given volume of solution, *i.e.*, a beaker. The model then becomes volume independent; the concentrations obtained have units of moles per unit volume or grams per unit volume; amounts and concentrations are interchangeable. Since the volume in each compartment of the body is different, conversion from concentrations as described by the equations, to amounts in the body compartments, then requires a knowledge of the relative compartment volumes and assumes complete uniformity within each compartment. Such a

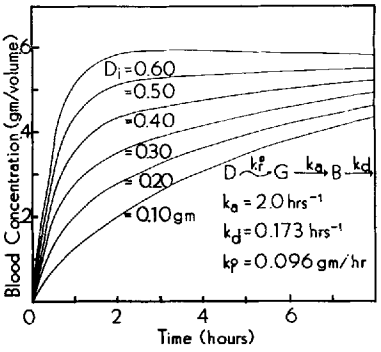


Fig. 3.—Blood level *versus* time curves showing the effect of variation in the initial dose (using ADE constants from *Reference 9*).

change is not of concern if fractions of total dose *only* are to be considered.

In this study the one volume–one compartment idea has been adopted for simplicity and thus the results are subject to the above assumptions. In addition, it is assumed that the equilibria (which must exist) for each component lie far to the right, so that reverse reactions are negligible, the drug is completely absorbed, and that after release it is immediately available.

The concentration of drug at the absorption site at time zero is the initial dose (D_i) and is equal to the fraction in the initial or in the immediately available dose (F_i) times the total dose given (W), *i.e.*, drug being in solution or in some rapidly dissolving drug form. The concentration of drug in the dosage form at time zero is the maintenance dose (D_m) and is that fraction of dose (F_m) required to maintain an optimum and as nearly as possible a constant concentration in the blood for a given length of time times the total dose given (W). It is proposed that release from the maintenance portion of the dosage form can be described by either zero- or first-order kinetics.

RESULTS AND DISCUSSION

Figure 1, curve a, illustrates the blood concentration *versus* time computer curve obtained for an immediately available dose using the model (Eq. 1), based on representative values of k_a = 2.0 hr.$^{-1}$ and k_e = 0.2 hr.$^{-1}$. Curves c and d (Fig. 1) are representative blood concentration curves for maintenance forms releasing drug by zero- and first-order kinetics, respectively.[2] Curve b (Fig. 1) illustrates the desired or "ideal" curve for a sustained-release dosage form, which includes both initial and maintenance dose. The design of a suitable sustained-action dosage form thus depends on finding the combination of a and c or a and d that produces the curve b, if such a combination exists, or as close an approximation as is possible.

The effect on the blood concentration *versus* time curve due to variation of the release rate con-

[2] The computer curves shown in this report were obtained using an Applied Dynamics AD-24-PB computer, a Moseley model 2D-2AM x-y recorder with a type F-1 photo electric curve follower, and an Electro-Instruments model 101-1518 x-y recorder.

stant as well as the effect of varying F_i and F_m are discussed under the appropriate headings for zero- and first-order release from the dosage form, and in addition, the mathematical relationships necessary to calculate both the total dosage and the required rate constant such that as close an approximation to the ideal as possible is obtained are discussed under their appropriate headings.

RELEASE BY ZERO-ORDER KINETICS

General Concepts.—From an immediately available dose, the blood concentration at any time, t, is a function of k_a, k_e, and concentration of drug in the gut (Eqs. 1 and 2),

$$B_t = \frac{D_i k_a}{k_d - k_a} (e^{-k_a t} - e^{-k_d t}) \qquad \text{(Eq. 2)}$$

where B_t is the concentration of drug in the blood at any time, and all other symbols represent quantities previously defined. The peak concentration and time to arrive at the peak are also functions of these parameters. The equation for the peak time (T_p) being:

$$T_p = \frac{2.3}{k_a - k_d} \left(\log \frac{k_a}{k_d}\right) \qquad \text{(Eq. 3)}$$

To obtain a constant blood level, one suspects, and can show mathematically, that a constant rate of availability from the dosage form is desired and once this desired rate is estimated (k_r^0), the required maintenance dose (D_m) may be found as the product of k_r^0, and the time over which sustained action is desired (h),

$$D_m = k_r^0 \times h \qquad \text{(Eq. 4)}$$

The desired rate of availability (k_r^0) can be roughly estimated, from the equations for the model, to be

$$k_r^0 = k_d \times B_d \qquad \text{(Eq. 5)}$$

where B_d is the desired blood level. The rational for this estimate can be shown by considering the differential equation for the blood level obtained from a sustained-action dosage form having both an initial and a zero-order maintenance form. From the general equations of the model in Eq. 1 one can obtain the relationship:

$$dB/d_t = k_r^0 - k_d(B_d) - e^{-k_a t}[k_r^0 - k_a(D_i)] \qquad \text{(Eq. 6)}$$

a constant blood level would require that $dB/d_t = 0$ therefore,

$$k_r^0 = k_d(B_d) - e^{-k_a t}[k_r^0 - k_a(D_i)] \qquad \text{(Eq. 7)}$$

if k_a is very large, *i.e.*, the absorption phase is not at all rate limiting

$$k_r^0 = k_d(B_d) \qquad \text{(Eq. 5)}$$

where B_d is the blood level to which the sustained action is aimed. Note that the assumption made to obtain Eq. 5 is in essence that the blood level *equals* B_d at time zero ($k_a = \infty$). This is of course not the true situation and while the use of Eq. 5 produces a reasonably flat blood level curve, it is *not the desired blood level* used in the calculation, but a somewhat higher one even if k_a is made very large. Variations in k_r^0 indicating this result are shown in Fig. 2 using the absorption and excretion constants of *Reference 9*. The k_r^0 calculated for a $B_d = 0.56$ is $k_r^0 = 0.096$

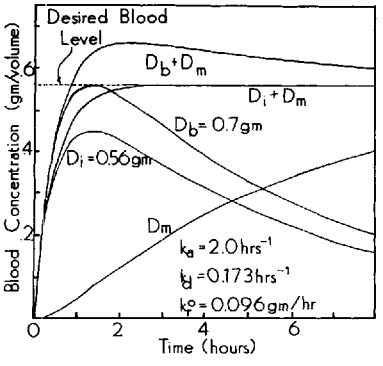


Fig. 4.—Blood level *versus* time curves showing the achievement of the desired blood level by adjustment of the initial dose provided. The blood levels that would be obtained for the initial dose required to obtain the desired level when alone (D_b), when in the presence of the maintenance dose (D_i), and those obtained with a maintenance (D_m) dose alone are also shown.

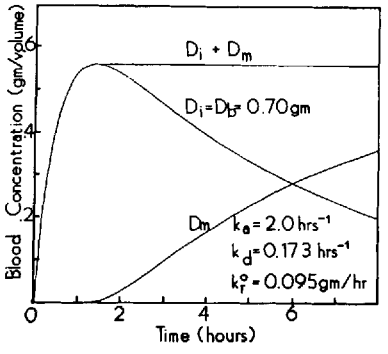


Fig. 5.—Blood level *versus* time curves showing nearly ideal sustained-action obtained by a delayed start of the maintenance dose. The blood levels that would be obtained for the initial dose (D_i) and maintenance dose (D_m) are also shown.

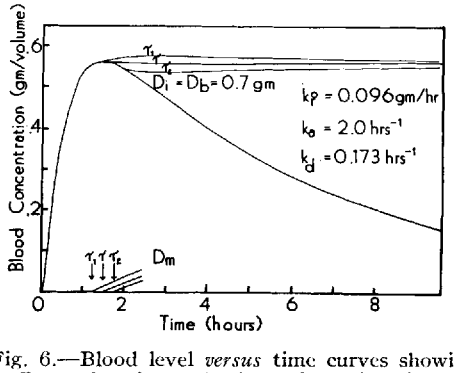


Fig. 6.—Blood level *versus* time curves showing the effects of various selections of starting time for the maintenance dose.

(the actual B_d obtained using these values can be seen to be about 0.59).

If the initial dose (D_i) is varied while a constant k_r^0 is used, a family of curves such as those in Fig. 3 are produced. It would appear that by a proper selection of D_i and k_r^0, a curve corresponding to the "idealized" one should be possible, but it is not. The "idealized" curve with a plateau slope equal to zero over the time period required cannot be obtained with a maintenance dose releasing drug in this fashion, although the slope is sufficiently close to zero to be considered "ideal." This can be seen in Figs. 2 and 3 but can more easily be demonstrated by noting that the derivative of the equation describing the blood level-time relationship (Eq. 6) *has* a real solution at $dB/dt = 0$ (Eq. 7), denoting a true maximum value for this equation (it is of course different from that of the immediately available dose), unless one is able to assume that the time to reach a *maximum* blood level was zero (and $k_a = \infty$).

The initial dose (D_i) of a sustained-release preparation cannot be assumed to be identical to that immediately available dose needed (D_b) to produce a peak equal to the desired blood level. Because the sustained portion of the dose also provides some drug for absorption over this early interval, too much drug becomes available for absorption and consequently a higher blood level is obtained than is desired. A correction on the immediately available dose is needed then such that less drug is initially available for absorption. While this does produce the desired blood level, a slightly longer time is required to reach the desired blood level; both of the above considerations are shown in Fig. 4. The correction needed should concern the time interval from time zero until absorption of the initial dose is complete, but as mathematically, absorption is never complete, for calculation purposes this may be assumed to correspond to the time to achieve the peak height, and simple subtraction of the quantity yielded by the maintenance dose in this interval produces a suitable correction. This correction is equal to $k_r^0 \times T_p$ where T_p is defined in Eq. 3,[3] so that,

$$D_i = D_b - (k_r^0 \times T_p) \qquad \text{(Eq. 8)}$$

This difficulty can be overcome more easily by using a sustained-release dosage form that begins its release of the maintenance drug *not* at time zero, but at the point where absorption of the initial dose is virtually over. This proposal is shown graphically in Fig. 5. For this type of dosage form, the initial dose and the time to reach the desired blood level remain the same, since the maintenance dose is not contributing drug over this time period [note that in the previous sample where both started together, adjustment of D_b to obtain D_i resulted in a slight delay in reaching the desired blood level (Fig. 4)]. If the maintenance form begins release of drug at times before or after the peak height time, the curve will tend to approach the desired blood level concentration at a rate which is dictated by the release constant of the maintenance form as shown in Fig. 6.

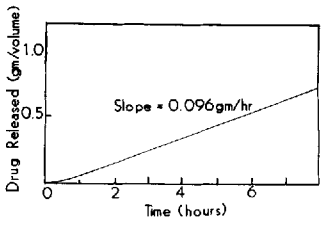


Fig. 7.—Dose release curve necessary to produce an "idealized" blood level *versus* time curve such as that shown in Fig. 5 (labeled $D_i + D_m$).

While a delayed start appears to be a difficult complication, sustained-action medication forms capable of providing it are currently available, *e.g.*, cored tablets, in which the core is commonly the maintenance dose that does not become available until some time after the initial dose has been absorbed. While not actually designed with this in mind, cored sustained-action tablets of superior action may well be assumed to owe their action to this type of behavior.

The general equations for the blood level *versus* time relationship in such a case can be solved to yield:

$$B_t = K_r^0 u(t-\tau)\left\{\frac{1}{k_d}(1 \times e^{-k_d(t-\tau)}) + \frac{1}{k_a - k_d}[e^{-k_a(t-\tau)} - e^{-k_d(t-\tau)}]\right\} + \frac{D_i k_a}{k_a - k_d}(e^{-k_d t} - e^{-k_a t}) \qquad \text{(Eq. 9)}$$

where $u(t-\tau)$ is the so-called "unit step" function whose value is 0 for all values of its argument ≤ 0 and $+1$ for all others. By making this substitution, one can see that before $t = \tau$, B_t describes the expected immediately available dose curve, while after $t = \tau$, the maintenance dose adds its effect onto whatever is left at that time. The value of such a dosage form is more apparent from the computer curves than from the equation.[4]

Calculation of the Desired Zero-Order Rate Constant.—Previous publications (10) have directed that the rate constant necessary for sustained release be set equal to k_d times the dose required to produce B_d. This has been criticized recently (9) and as found in this study the criticism is valid. The correct k_r^0 is the product of the elimination constant and the desired blood level (B_d).[5] The zero-order rate constant necessary can be obtained in another fashion also, utilizing the method of Stelmach, Robinson, and Eriksen (3), where using the desired blood concentration *versus* time curve as a computer

[3] This simple method for making the correction is of course only an approximation. The exact calculation would involve the solution of the complete equation for the blood level obtained from a zero-order sustained-action dosage formulation for the initial dose D_i, at some time after the expected peak. As no *mathematically* flat blood level *versus* time line is ever obtained using this formulation method, the equation is not soluble explicitly and the approximation given becomes the most desirable method for calculation of the correction.

[4] In the interests of complete precision, it must be pointed out that the blood level curves obtained from this type of dosage form are not mathematically straight either as absorption of D_i is mathematically "eternal." They represent major improvements on Eqs. 7 and 8 and also give complete mathematical linearity of B_d only when $k_a = \infty$, as discussed later.

[5] The use of the dose required to produce the desired blood level yields the same result as the blood level itself only if the one compartment–one volume model is used and k_a is assumed very large. In this case $B_d = W$.

input voltage, the dosage release *versus* time curve required is produced as an output. The slope of the dosage release curve can be seen to equal the zero-order rate constant required. This was tested using the plot of Fig. 5 as an input, with results shown graphically in Fig. 7.

The rate constant k_r^0 used for Fig. 5 had been set equal to 0.096 Gm./hr.; the slope of the line in Fig. 7 calculated by the computer as being required to produce the blood level curve (labeled $D_i + D_m$) in Fig. 5, was found to be equal to 0.096 Gm./hr.

The linearity of the blood concentration-time curve with a delayed start can be shown by changing the time variable in Eq. 9 to describe only times *after* the peak time of the immediately available portion, so that

$$= t - \tau$$

and

$$\text{when } \pi = 0,\ B_\pi = B \text{ peak} = B_p$$

under these conditions, Eq. 9 becomes,

$$B_\pi = k_r^0 \left\{ \frac{1}{k_d}(1 - e^{-k_d\pi}) + \frac{1}{k_a - k_d}(e^{-k_a\pi} - e^{-k_d\pi}) \right\} + \frac{D_i k_a}{k_a - k_d}[e^{-k_d(\pi + \tau)} - e^{-k_a(\pi + \tau)}] \quad \text{(Eq. 9}a\text{)}$$

setting the first derivative of B_π with respect to π equal to zero produces an expression for B_π independent of time (and thus flat), only if $e^{-k_a\pi}$ is assumed to be zero ($k_a \to \infty$) and $k_a \gg k_d$. Under those restrictions,

$$\frac{D_i k_a}{k_a - k_d} e^{-k_d\tau} = K_r^0 \left\{ \frac{1}{k_a - k_d} + \frac{1}{k_d} \right\} \quad \text{(Eq. 9}b\text{)}$$

and as the left side of Eq. 9*b* is an approximation for the desired blood level which is produced by the immediately available dose D_i (where $D_i = D_b$), one again finds,

$$k_r^0 \cong B_p k_d \cong B_d k_d \quad \text{(Eq. 5)}$$

Note that the blood concentration after the peak time (B_π) is a constant and identical to the peak blood level if and only if $k_a = \infty$, as one might expect.

Calculation of the Total Dose for Release by Zero-Order Kinetics.—As pointed out previously (10) a dosage form releasing drug at a rate equal to the rate at which drug is eliminated *will* give a very nearly constant blood level, but differentiation must be made between a dosage form releasing drug from time zero and one releasing drug at the peak height time, in the calculation of total dose.

Release from Time Zero.—For a maintenance form releasing drug from time zero, the following equations hold.

$$W = D_i + D_m \quad \text{(Eq. 10)}$$

where $D_i = D_b - (T_p \times k_r^0)$. In this equation $(T_p \times k_r^0)$ is the concentration of drug contributed by the maintenance form that represents the correction on the initial or immediately available dose, and

$$D_m = k_r^0 \times h$$

Therefore

$$W = D_b - (T_p \times k_r^0) + k_r^0 \times h \quad \text{(Eq. 11)}$$

where

- W = total dose,
- D_i = initial dose,
- D_m = maintenance dose,
- D_b = dose required to give the desired blood level, when given in an immediately available form,
- T_p = peak height time,
- k_r^0 = zero-order rate of release constant,
- h = total desired time for sustained action in hours.

Delayed Start Maintenance Dose.—When the maintenance dose begins release of drug at the peak height time, the equation for total required dose (W) becomes

$$W = D_b + k_r^0 \times (h - T_p) \quad \text{(Eq. 12)}$$

and

$$D_i = D_b$$
$$D_m = k_r^0(h - T_p)$$

where the symbols have the same significance as above.

RELEASE BY FIRST-ORDER KINETICS

General Concepts.—The relationship between the initial and maintenance dose of an absorption, distribution, and excretion model with first-order availability is shown in Fig. 8 for various values of k_a (and fractions of dose as maintenance from, F_m) at constant k_r' and k_d. As expected, k_a influences the curve very little but primarily *before* the peak height time; the intersection points remaining essentially in the same place as F_m and k_a change. The common intersection point for various fractions of dose has been recognized and reported previously by Kruger-Thiemer and Eriksen (2). Mathematically, the intersection point lies at the peak time (T_p) for the maintenance dose alone, representing a solution of the equation,

$$k_r'(k_d - k_a)e^{-k_r'T_p} = k_d(k_a - k_r')e^{-k_dT_p} + k_a(k_r' - k_d)e^{-k_aT_p} \quad \text{(Eq. 13)}$$

as has also been noted previously (2).

Figure 9 demonstrates the effect of altering k_r' at a constant k_d and k_a; this effect has also been suggested by previous workers (5). An interesting point may be noted in this family of curves, when k_a is much larger than k_r' and k_d, the intersection point is a function only of k_r' and k_d. The intersection point occurring at later times for smaller values of k_r'. The same observation can be made mathematically by letting k_a become enough larger than k_d and k_r' that its exponential term may be disregarded at an early time and then solving Eq. 13 for the intersection point of T_p

$$T_p = \frac{2.3}{k_r' - k_d} \log \frac{[k_r'(k_a - k_d)]}{[k_d(k_a - k_r')]} \quad \text{(Eq. 14)}$$

or if $k_a \gg k_d$ and k_r',

$$T_p \cong \frac{2.3}{k_r' - k_d} \log \left(\frac{k_r'}{k_d} \right) \quad \text{(Eq. 15)}$$

It becomes rapidly apparent with the computer that no combination of rate constants and/or doses will reduce a flat, constant blood level using a first-order availability model. Mathematically, this can be shown also by considering the solution for the maximum of the equation for the blood level produced by the authors' three-step model with first-order availability:

$$B_t = \frac{D_m k_a k_r'}{(k_d - k_r')(k_a - k_r')}(e^{-k_r' t} - e^{-kdt}) + \frac{D_i k_a - \frac{D_m k_a k_r'}{k_a - k_r'}}{(k_d - k_r')}(e^{-kat} - e^{-kdt}) \quad \text{(Eq. 16)}$$

[after Wiegand and Taylor (5)], and

$$\mathring{B}_t = \frac{D_m k_a k_r'}{(k_d - k_r')(k_a - k_r')}(+k_d e^{-kdt} - k_r' e^{-k_r' t}) + \frac{D_i k_a - \frac{D_m k_a k_r'}{k_a - k_r'}}{(k_d - k_r')}(k_d e^{-kdt} - k_a e^{-kat}) \quad \text{(Eq. 17)}$$

Although the actual solution for t at $\mathring{B}_t = 0$ can only be found by successive approximation, this equation obviously has three solutions, two trivial ($t = 0$ and ∞) and one real; a plot that has a maximum cannot be flat.

A sustained-release product having a *satisfactorily* flat blood level curve using a first-order release pattern can be designed, however, and that design depends upon the proper selection of both the dose fraction in each form and the maintenance dose release constant. The closest approach to the "idealized" blood level can be found by computer experimentation to require a combination of initial and maintenance does such that the intersection (T_p, Eqs. 14 and 15) occurs at a time equal to or greater than the desired sustained-action interval (h) (Fig. 10). In addition, the further past the desired time for sustained release this point lies, the more combinations of F_i and F_m are available that will give the desired type of blood concentration curve. From the intersection (T_p) equation (Eq. 14) it is observed that the smaller the value of k_d the larger the value of k_r' may be and still produce a satisfactory dosage form. For cases where k_d is large, however, the value of k_r' necessary to give an intersection point at or beyond the desired time can be very small, and, thus, the necessary dose present in the maintenance form may become quite high.

The rather remarkable improvement afforded in the zero-order release case, by delaying the start of the maintenance dose, suggests its use here also with the results shown in Fig. 11. As in the zero-order case, the blood level is obtained at a rate determined by the initial dose, and the subsequent levels by the maintenance dose. Quite opposite to the observation with first-order release started at time zero, however, the most "uniform"[6] blood levels are obtained, when the elimination rate (k_d) is high, by making k_r' high, too. The generally "sustained" shape of this curve suggests that the delayed start principle height be extremely useful for sustained release here too, especially for drugs with large elimination (k_d) constants.

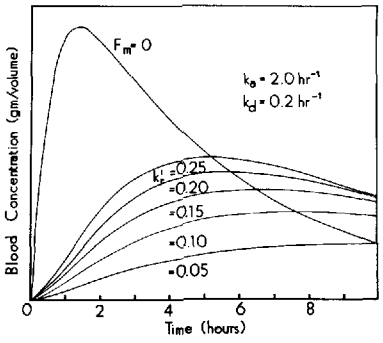


Fig. 9.—Blood level *versus* time curves showing the change in intersection point for various first-order release rate constants.

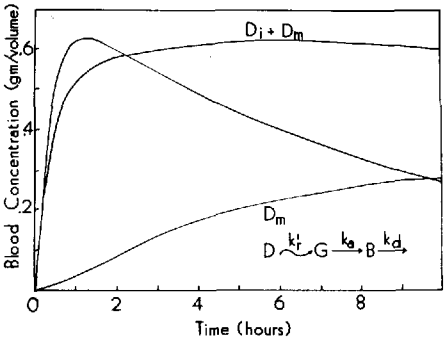


Fig. 10.—Blood level *versus* time curve showing the degree of sustained action obtainable with first-order release. The blood levels *versus* time curves obtained from the initial (D_i) and maintenance (D_m) doses are also shown. Key: $K_a = 3.0$ hr.$^{-1}$; $k_d = 0.10$ hr.$^{-1}$; $K_r' = 0.065$ hr.$^{-1}$.

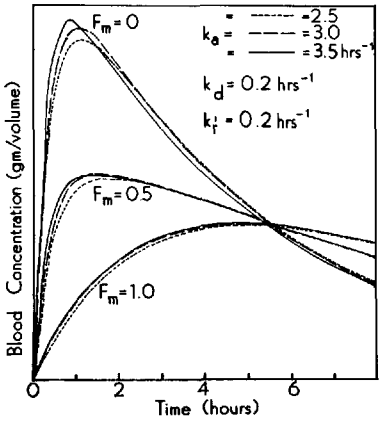


Fig. 8.—Blood level *versus* time curves showing the same intersection point despite variation in absorption rate constant (k_a) for several maintenance dose/initial dose ratios.

[6] A "uniform" or "sustained" blood level in this case represents a nonhorizontal blood level oscillating about some average value.

The general equation for the blood level *versus* time relationship when a delayed start of release and first-order kinetics is used is:

$$B_t = \frac{D_m k_r'}{(k_a - k_r)} u(t - \tau) \left\{ \frac{k_a}{(k_d - k_r')} [e^{-k_r'(t-\tau)} - e^{-k_d(t-\tau)}] + \frac{k_a}{(k_a - k_d)} [e^{-k_a(t-\tau)} - e^{-k_d(t-\tau)}] \right\} + \frac{D_i k_a}{(k_d - k_a)} \left\{ e^{-kat} - e^{-kdt} \right\} \quad \text{(Eq. 18)}$$

using the same "unit step" concept discussed before and τ the time of the delayed start. The similarity in form to Eqs. 9 and 16 are apparent.

Calculation of the First-Order Rate of Release Constant.—It was stated earlier that the intersection points of the blood level curves obtained for immediate and sustained-release forms should be equal to or longer than the desired time for sustained release (h), in order to achieve the closest approximation to the "idealized" blood concentration-time curve when a maintenance dosage beginning immediately is used. As this intersection point depends essentially on k_d and k_r', (if k_a is assumed large) and k_d is a parameter over which the formulator has no control, k_r' must be altered to move this intersection point to the desired time. With k_a and k_d given, Eq. 14 (or Eq. 15) may be used to solve for the rate constant required, to make the intersection point equal to, or greater than, the desired sustained-action time (h). Alternatively, as has been suggested for zero-order release, calculation of the necessary first-order availability constant can be carried out using the desired blood level curve and the computer method of Stelmach, Robinson, and Eriksen (3).

When a delayed start is used, two approaches to the desired k_r' are possible; the maintenance dosage form can provide drug in an approximately zero-order fashion (but *actually* first order) with an over-all rate of $k_d B_d$, or the peak of the blood level produced by a maintenance dose alone may be positioned at a point between the initial dose peak and the desired sustained-action time.

In the first case, the sustained portion should begin releasing at the T_p of the initial portion. The drug released from the dosage form in t hours may be set equal to the drug lost over the same interval assuming constant blood level,

$$D_m(1 - e^{-k_r' t}) = k_d B_d t \quad \text{(Eq. 19)}$$

and the approximation relating the release rate and the administered dose,[7]

$$k_r' D_m \cong k_d B_d = k_r^0 \quad \text{(Eq. 20)}$$

results. Using the maximum dose that the patient will swallow or that can be accommodated in the dosage form, k_r' can be estimated; for any satisfactory degree of sustained action a first-order release form will require roughly 10× the dose required for a zero-order form.

In the second case, a more rapid release rate may be used and a later time of onset tolerated producing, in general, a more practical dosage form. Experimentation on the computer suggests that for the ADE constants normally found, the point where 99% of the initial dose has been absorbed is the most suitable onset point for the maintenance dose,

$$\tau = \frac{4.6}{k_a} \quad \text{(Eq. 21)}$$

The k_r' required to obtain a maintenance dose generated peak at roughly the midpoint between the

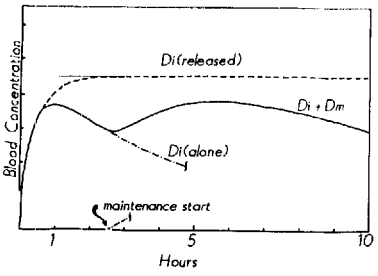


Fig. 11.—Blood level *versus* time curves showing the degree of sustained action obtained by a delayed start of a first-order release maintenance dose. Portions of the blood level *versus* time curves obtained from the initial (D_i) and maintenance (D_m) doses are also shown.

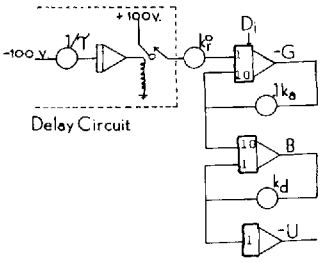


Fig. 12.—Scaled analog computer program for the system shown in Eq. 1, using a zero-order delayed start maintenance dose.

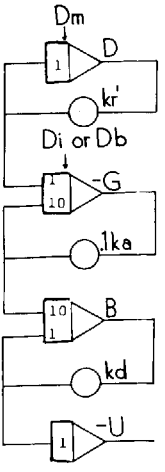


Fig. 13.—Scaled analog computer program for the system shown in Eq. 1, using a first-order immediate start maintenance dose.

[7] This is the "rate in equals rate out" equation of Nelson (10) and again implies $k_a = \infty$ and its applicability one can also verify by solving the maintenance only portion of Eq. 16 for B in the case where k_a and $k_d >> k_r'$.

initial dose blood level peak and the desired sustained-action time (h) may be estimated solving Eqs. 14 or 15 for k_r' at

$$T_p = \frac{h - \tau}{2} \qquad \text{(Eq. 21}a\text{)}$$

Calculation of the Total Dose for Release by First-Order Kinetics.—The total dose required for adequate sustained release (W) will again be described by Eq. 10 and may be approximately solved for both methods of first-order release.

Release from Time Zero.—

$$D_i = D_h - D_{correction} \qquad \text{(Eq. 22)}$$

as before, a correction ($D_{correction}$) for D_h is required which may be thought of as equal to the amount of drug contributed to the blood by the maintenance dose, during the phase controlled by the initial dose, and which can be estimated using reasoning similar to that used in deriving Eqs. 19 and 20.

$$D_{correction} = D_m(k_r'T_p) \qquad \text{(Eq. 23)}$$

Thus, Eq. 22 is found to be approximately[8]

$$D_i = D_h - D_m \times k_r' \times T_p \qquad \text{(Eq. 24)}$$

The maintenance dose required to keep the blood level at approximately the desired value can be calculated by equating the desired "rate in" (k_dB_d) with the actual "rate in"[8]

$$k'_rD_me^{-k_r't} = k_dB_d$$

$$D_m = \frac{k_dB_d}{k_r' - (k_r')^2t} \cong \frac{k_dB_d}{k_r'} \qquad \text{(Eq. 25)}$$

The approximation is sufficiently accurate for most purposes, although the first is better, the time when the desired blood level is reached being used for t.

The total dose (W) then is

$$W = D_h - D_mk_r'T_p + \frac{k_dB_d}{k_r'} \qquad \text{(Eq. 26)}$$

Delayed Start Maintenance.—The immediately available dose (D_i) completely dictates the attained blood level as described for the care of release by zero-order process; but the maintenance dose required for a satisfactorily "uniform" blood level depends on the delay time, τ, and the placing of the maintenance peak.

A precise delay time value is not critical; it may be calculated easily from Eq. 21, and k_r' calculated from Eqs. 14 or 15 as mentioned before (to place the "maintenance peak" at roughly the midpoint of the desired sustained-action time, h, Eq. 21a).

The maintenance dose required to produce a secondary blood level peak equal to the first may be calculated as the maintenance dose (alone) required to produce a peak sufficient to increase the blood level remaining from the initial dose to the desired value. At the desired time for the secondary peak T_p^*, the residual blood level is

$$B_r = \frac{D_ik_a}{k_a - k_d}\,(e^{-k_dT_p^*} - e^{-k_aT_p^*}) \qquad \text{(Eq. 27)}$$

and the peak blood level from the maintenance dose is that calculated from Eq. 16 at $t = (T_p^* - \tau)$ and $D_i = 0$. If it is assumed as before that at the time involved $e^{-k_aT_p}$ becomes negligible, both these equations can be simplified and D_m easily calculated. Under these circumstances,

$$B_r \cong \frac{D_ik_a}{k_a - k_d}\,(e^{-k_dT_p^*}) \qquad \text{(Eq. 28)}$$

Then

$$D_m = \frac{k_d}{k_r'}\,(B_d - B_r)e^{+k_r'(T_p - \tau)} \qquad \text{(Eq. 29)}$$

Figure 10 shows the computer generated blood level produced for the ADE constants used before, calculated for such a delayed first-order start. In addition, the drug delivered from the dosage form is also shown to indicate the separation of starting times.

SUMMARY AND CONCLUSIONS

The general phenomena involved in the ADE kinetics of many drugs are found to be described by rather simple "overall" expressions and these phenomena according to the descriptive equations that happen to fit, *i.e.*, absorption is described as "first order," etc.; while there is little real doubt that such a naive approach is incorrect, the fact that such simple equations *can* adequately describe the concentrations of biologic interest, should be of real use (if not importance) in the formulation of effective sustained-action dosages. As discussed in this report, however, even these "simple" equations cannot be mathematically solved to produce explicit solutions for the dosage fractions and rate constants required, but instead suitable approximations must (and can) be made that permit *useful* solutions for the single sustained-release dose case. These approximations and the assumptions upon which they have been made have not always been explicitly described when (and if) they have been published before and the present authors felt sufficient benefit would accrue from collecting them both in one place that this has been done for the two theoretical cases described before: (a) simultaneous start of initial and "zero-order" sustained dosages and (b) simultaneous start of initial and "first-order" sustained dosages. The methods for calculating the dose fractions of both the initial and the sustained portions as well as the rate constant most suitable for producing a sustained blood level are described fully.

Secondarily, but of interest in order to complete the picture, the effect of delaying the start of the sustained portion of the dosage form has been shown to produce in one case (c) the best theoretical sustained-action blood level picture available and in the other (d) a novel and perhaps not unusable blood level situation: (c) initial release followed by "zero order" sustained dosage after some delay and (d) initial release followed by "first order" sustained dosage after some delay.

The aim and the result of the analysis in this report has been to show the theoretically available blood level situations resulting from a *single* complete (sustained *and* initial) dosage form designed to produce the most constant blood level over the desired sustained-action time and but for the irksome (though real) vagaries of the human gastrointestinal tract would describe the blood level–time pictures actually observed.

[8] The approximations made here are similar to those made for the zero-order case (see *Footnote 3*). The exact solution is similarly not possible and experimentation convinces us that for practical situations, this approximation is suitable.

APPENDIX

Figures 12 and 13 show the computer circuits used in simulating the solutions shown in this work. Of prime concern and utility here is the "nonlinear delay input" by programmed relay shown in Fig. 12. The remaining programs required (immediate start, zero-order, and delayed start, first-order) have been published and discussed previously (3).

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Kinetics of Deterioration of Trimethylene Bis-(4-formylpyridinium Bromide) Dioxime in Dilute Aqueous Solutions

By R. I. ELLIN, D. E. EASTERDAY, P. ZVIRBLIS, and A. A. KONDRITZER

The degradation of trimethylene bis-(4-formylpyridinium bromide) dioxime, TMB-4, occurs by two mechanisms. The first is a hydrolytic reaction of the acid form of the oxime catalyzed by hydrogen ion, and the second, a dehydration reaction. The latter may proceed by either of two pathways—a hydroxyl ion catalyzed dehydration of the acid form of the oxime, or a spontaneous dehydration of the oximate species. Velocity and various thermodynamic constants were determined for each of the mechanisms postulated. General equations were derived that relate the half-life of TMB-4 solutions to pH and temperature.

FOLLOWING THE introduction of pyridinium oximes for the management of intoxication by organophosphorus anticholinesterase compounds, an active search has taken place for more effective compounds. As a result, 1,1′-trimethylene bis-(4-formylpyridinium bromide) dioxime, referred to as TMB-4, was synthesized and shown to be a potent reactivator of phosphorylated cholinesterases (1, 2). Grob has reported (3) that TMB-4 in one-tenth to one-fifteenth the dose of 2-PAM iodide was more effective in humans against the weakening of the response of a muscle to electrical stimulation of its motor nerve. A better therapeutic index for TMB-4 has been demonstrated in laboratory animals (4), and the use of a mixture of 2-PAM and TMB-4 has been reported to be superior to any single oxime tested (5). In view of these reports the establishment of the conditions of maximal stability of TMB-4 in aqueous solution becomes important and worthwhile.

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Mechanisms for the degradation of pyridinium aldoximes in aqueous solution have been postulated in previous reports (6, 7). Recent studies by Kosower (8) support the conclusion that the rate-limiting step for the degradation of pyridinium oximes in basic solution is the formation of cyanopyridinium ion. The mechanisms postulated for the breakdown of TMB-4 are presented in Scheme I. The reaction of TMB-4 in basic solution may be explained by an ElcB unimolecular elimination mechanism (9). Hydroxyl ion attack at each methine hydrogen atom results in the removal of a proton and the formation of a carbanion as the rate-controlling step. Subsequent loss of hydroxide ion from the oximino nitrogen leads to the formation of a triple bond; for TMB-4 the corresponding dinitrile would be the final product of this process. Hydroxide ion attack on the cyano group or addition to the pyridine ring forms dicarbamido and dihydroxy dipyridinium ions, respectively. The latter, on further reaction with hydroxide ion, readily lose a proton to form the corresponding dipyridone. Reaction of TMB-4 with hydrogen ion leads to various states of equilibrium involving the splitting out of hydroxylamine and the formation of