Mathematical Model of Sustained-Release Preparations and Its Analysis

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A pharmacokinetic model, involving first-order processes for drug release, absorption, and elimination, may be used for the description of the behavior of sustained-release preparations consisting of slowly and immediately available fractions. The shift of the rate-determining step, as the relative rates of absorption and release are changed, can be shown both mathematically and by analog computer simulation. These theoretical results are used for interpretation of experimental data with a new sulfa drug of low solubility, 2-sulfanilamido-5-methyl-pyrimidine, compressed tablets of which behave as a sustained-release preparation.

THE WIDESPREAD use of sustained-release and depot preparations in drug therapy has made the full understanding of their actions and properties of considerable importance. A number of publications concerned with the actions, the properties, and the importance of such a full understanding have appeared in the last decade [*viz.*, Dost (2), Lazarus and Cooper (3), Levy *et al.* (4–6), Nelson *et al.* (7–9), Parrott (10), Robinson and Swintosky (11), Sjogren and Ostholm (12), Wagner *et al.* (13), Wiegand and Taylor (14), and others].

The most useful method for the examination of the interrelationships between drug preparations and the human body has been found to be through the use of a mathematical model, first fitting it to the actual data, and then examining the model found most useful for its functional behavior. In this way the important implications of the model may be discovered and those found important checked by further laboratory experiments. Because of the complexity of the differential equations involved, direct mathematical study is not always the most useful manner of determining the implications of a mathematical model for absorption, distribution, and excretion, and it has often been found more convenient to make use of an electronic analog computor [see Fish (16), Pace (17), and Garrett *et al.* (18)].

A recent paper by Taylor and Wiegand (15) was concerned with the analog investigation of the following model, which has been found to describe suitably the behavior of sustained-release preparations from which a certain fraction, f_r, of the administered dose becomes available through a first-order process while the remaining fraction, $1-f_r$, is available immediately:

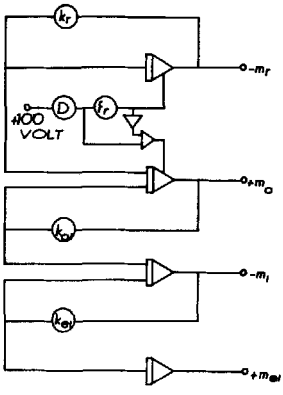

Fig. 1.—Unscaled analog computer program for the system of differential Eqs. for the model used and for initial conditions set forth in Eqs. 1, 2, and 3.

m_r the amount of undissolved drug in the gastrointestinal tract

k_r *the rate constant for the dissolution step*

m_0 the amount of dissolved drug in the gastrointestinal tract

k_{01} *the rate constant for absorption*

m_1 the amount of drug in the body (not including that in the gastrointestinal tract and the urine)

k_{e1} = *the rate constant for elimination* (the sum of the constants for renal excretion and metabolism)

$m_{e1} = m_2 + m_1{}^m$ the amount of the eliminated drug (including metabolized drug)[1]

This model involves three consecutive, irreversible first-order processes with the following initial conditions in the four compartments:

$$m_r{}^0 = Df_r,\ m_0{}^0 = D(1 - f_r),\ m_1{}^0 = 0,\ m_{e1}{}^0 = 0 \qquad \text{(Eqs. 1, 2, 3)}$$

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[1] In this paper the symbols as proposed by Nelson and Kruger-Thiemer (9) are used as far as possible. The use of amounts, m, rather than concentrations, c, throughout this paper should not be construed as reflecting an "amount" driven kinetic situation, but only as a system simplification for these theoretical discussions that does not change the relative results.

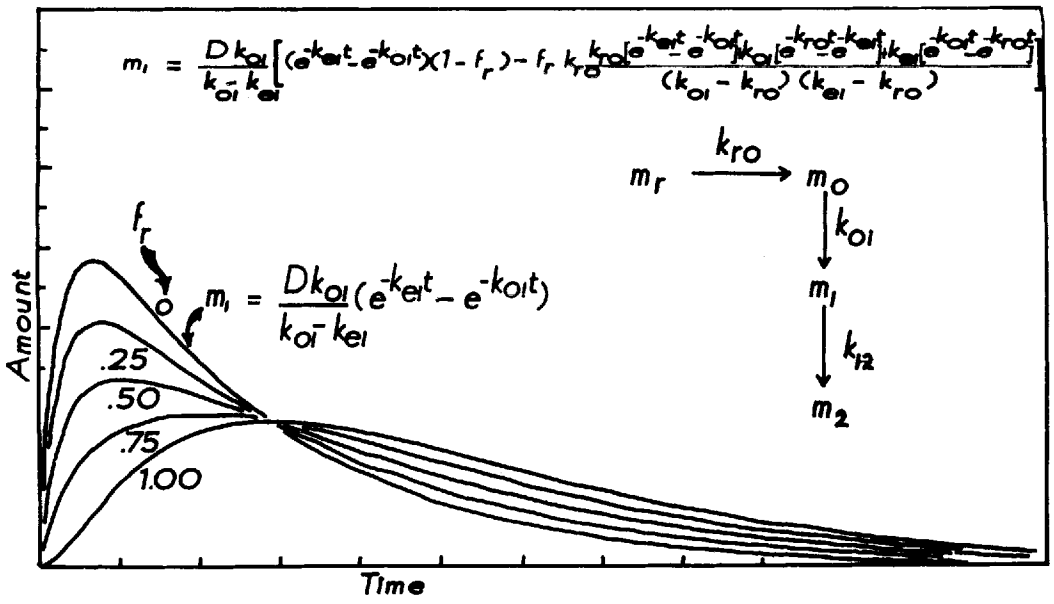

Fig. 2.—Family of computer drawn curves of m (blood amount) showing the effect of regular changes in the fraction of the total dose in sustained form (f_r).

The present paper is concerned with a more complete re-examination of this model.[2]

ADDITIVE BEHAVIOR OF TWO COMPONENTS OF SUSTAINED-RELEASE PREPARATION

Changing the sustained-release fraction, f_r, of the administered dose, D, from 0 to 1, in a stepwise fashion, a family of curves of the type shown in Fig. 2 is obtained. The most interesting feature of this figure is that this family of curves has a point of intersection that might be called the common point, which lies in the maximum point of the lowest curve corresponding to $f_r = 1$. The relationships suggested by this figure may be shown mathematically also.

Substituting $f_r = 0$ into Eq. 2 yields the well-known equation for a model consisting of two consecutive, irreversible first-order reactions, presented previously by Widmark and Tandberg (20), Teorell (19), Dost (2), and Taylor (14):

$$m_1 = \frac{D \cdot k_{01}}{k_{01} - k_{e1}} \cdot (e^{-k_{e1}t} - e^{-k_{01}t}) \quad \text{(Eq. 4)}$$

The substitution of $f_r = 1$ into Eq. 2 results in Eq. 5 for the model in which the total drug administered is going slowly into solution *via* a first-order process.

$$m_1 = D \cdot k_{01} \cdot k_r \times \frac{(k_{01} - k_{e1})\, e^{-k_r t} + (k_{e1} - k_r)\, e^{-k_{01}t} + (k_r - k_{01})\, e^{-k_{e1}t}}{(k_r - k_{01}) \cdot (k_r - k_{e1}) \cdot (k_{01} - k_{e1})} \quad \text{(Eq. 5)}$$

[2] The computer curves shown in this work were obtained with the more standard analog programming methods (using the differential forms) rather than the less accurate and more tedious "calculation" method of Taylor and Wiegand (1). The more standard program used by the present authors is shown in Fig. 1 (derived for the Applied Dynamics PB-24 computer, Ann Arbor, Mich.).

The existence of the common point for all curves with the same k_r, k_{01}, k_{e1} may be shown by calculating the point(s) of intersection of the two curves for $f_r = 0$ and $f_r = 1$. One equates m_1 from Eqs. 4 and 5 so that the following condition results for the time value, t_i, of the point of intersection:

$$k_r \cdot (k_{01} - k_{e1}) \cdot e^{-k_r t_i} + k_{01} \cdot (k_{e1} - k_r) \cdot e^{-k_{01} t_i} + k_{e1} \cdot (k_r - k_{01}) \cdot e^{-k_{e1} t_i} = 0 \quad \text{(Eq. 6)}$$

While Eq. 6 cannot be solved explicitly for t_i, one can see that it contains three solutions for t_i, two trivial ones, $t_i = 0$, $t_i = \infty$, and the intermediate solution in which we are interested. From this equation the time value, t_i, of the point of intersection for actual value of the parameters, k_r, k_{01} and k_{e1}, may be calculated using the customary methods for numerical solution of transcendental equations. One obtains the same equation, Eq. 6, for the point of intersection of the curve for $f_r = 0$ (Eq. 4) and *any* other of the curves shown (*e.g.*, any arbitrary value of f_r between 0 and 1). During this calculation f_r cancels out, the mathematical indication of the independency of the point of intersection on the value of f_r; the entire family of curves intersects at a common point.

Proof that the common point is situated in the maximum of the curve for $f_r = 1$ can be verified by setting the first derivative of Eq. 5 with respect to the time equal to zero. This results in exactly the same equation, Eq. 6, as previously obtained, indicating that the time corresponding to this maximum, $t_{max.}$, and the time of the point of intersection of the family of curves, t_i, are identical.

This apparent additivity suggests a rearrangement of the equation obtained by Taylor and Wiegand (1) (our Eq. 2) into an equation representing the sum of Eqs. 4 and 5 and yields Eq. 7:

$$m_1 = \frac{D \cdot (1 - f_r) \cdot k_{01}}{k_{01} - k_{el}} \cdot (e^{-k_{el}t} - e^{-k_{01}t}) + \frac{D \cdot f_r \cdot k_{01} \cdot k_r \cdot (k_{01} - k_{el}) \cdot e^{-k_r t} + (k_{el} - k_r) \cdot e^{-k_{01}t} + (k_r - k_{01}) \cdot e^{-k_{el}t}}{(k_r - k_{01}) \cdot (k_r - k_{el}) \cdot (k_{01} - k_{el})} \quad \text{(Eq. 7)}$$

from which Eqs. 4 and 5 may still be obtained by setting $f_r = 0$ and 1 alternately.

Using the symbols F_4 and F_5 for the right-hand sides of Eqs. 4 and 5, respectively, the structure of Eq. 7 becomes apparent

$$m_1 = F_4 \cdot (1 - f_r) + F_5 \cdot f_r \quad \text{(Eq. 8)}$$

Thus, the amount in the body, m_1, (not including that in gastrointestinal tract and in urine) for any time and for any value of f_r between 0 and 1 is equal to a linear combination of the drug amounts for $f_r = 0$ and $f_r = 1$, the coefficients of which are equal to the two fractions of the dose for instantaneous $(1-f_r)$ and sustained (f_r) release. In terms of the experimental conditions this implies that both parts of the dosage form, that for instantaneous and that for sustained release, behave independently within the body, so that *the final curve of the drug amount within the body is merely the sum of the two curves that would result from separate administration of the two components of the sustained-release dosage form* (*e.g.*, this conclusion might be checked experimentally using a sustained-release preparation one of the two parts of which, either instantaneous or sustained release, is radioactively labeled). The result of this study clearly demonstrates that the functional behavior of the curves described by Eqs. 2 or 7 may be examined best by separate examination of Eqs. 4 and 5.

ASYMPTOTICAL SIMILARITY BETWEEN SLOW SUSTAINED-RELEASE AND SLOW ABSORPTION MODELS

Figure 3 shows two families of curves in which the first (Fig. 3, A) corresponds to the simplified model for $f_r = 0$, *i.e.*, Eq. 4, using values of k_{01} from 1.0 to 0.0078 hr.$^{-1}$, and the second (Fig. 3, B) corresponds to the simplified model for $f_r = 1$, *i.e.*, Eq. 5, using a constant value of $k_{01} = 1.0$ hr.$^{-1}$ and varying values of k_r from infinity to 0.0078 hr.$^{-1}$. In both cases the values of k_{el} have been set equal to 0.1 hr.$^{-1}$.

The curves with the highest maximum in Fig. 3, A and B, are identical, for $k_r = \infty$ means instantaneous release, *i.e.*, in this case Eq. 5 reduces to Eq. 4 by rearrangement of Eq. 5 before the substitution of $k_r = \infty$, or by use of L'Hospital's rule for indeterminate forms of the type ∞ / ∞.

Obviously, the lowest members of the two families of curves (Fig. 3), having identical values for k_{01} and k_r, respectively, are more similar to each other than the intermediate and the higher ones. These curves have suggested an asymptotical similarity of these two different models. The mathematical demonstration of this similarity may be found by substituting very high values of k_{01} (rising to infinity) into Eq. 5. As Eq. 5 has a symmetrical structure with respect to k_{01} and k_r, the mode of calculation is quite the same as above for $k_r = \infty$, so one finally obtains Eq. 9:

$$m_1 = \frac{D \cdot k_r}{k_r - k_{el}} \cdot (e^{-k_{el}t} - e^{-k_r t}) \quad \text{(Eq. 9)}$$

which has obviously the same structure as Eq. 4. The result is not surprising, indicating only the shift in the rate-determining step; it has already been predicted (7). The similarity of Eqs. 4 and 9 is the reason for the asympotic similarity of the lower curves in Fig. 3, A and B, because before going to $k_{01} = \infty$ all the terms in Eq. 5 that are lacking in Eq. 9 have coefficients of the type k_r/k_{01} or k_{el}/k_{01}. The smaller these two ratios, the more similar the curves in Fig. 3, B, will be to the curves in Fig. 3, A.

There is no *real* equality in Fig. 3, but only a similarity between the lower curves. The two before mentioned ratios k_r/k_{01} or k_{el}/k_{01} may become negligible either by decreasing k_r and k_{el} or by increasing k_{01}. As long as k_{01} has a finite value, the initial slopes for the curves in Fig. 3, B, will be zero, while the curves in Fig. 3, A, have initial slopes higher than zero, a fact that may be verified by differentiation of Eqs. 5 and 4 with respect to the time followed by substitution of $t = 0$.

The difference in the initial slopes of the lower curves in the Fig. 3, A and B, are easily visible from these fully drawn theoretical curves. However, it would be nearly impossible to recognize these differences in initial slope from actual experimental data, considering the usual experimental errors.

ESTIMATION OF RATE CONSTANTS OF SUSTAINED-RELEASE OR SLOW ABSORPTION PREPARATIONS

Figure 3 shows another feature of practical importance. In cases of slow absorption and/or slow sustained release a significant absorption may last much longer than anticipated so that the slope of the descending part of the concentration curve in the blood plasma (after the curve maximum) may not reflect the elimination process alone. As pointed out recently by Wagner (21), a graphical estimation or calculation of the rate constant for elimination, k_{el}, from the apparent slope of the descending part of the curve in a semilogarithmical plot may result in too low a value. Since the customary methods for the calculation of the rate constant for absorption [Dost (2), Kruger-Thiemer (22, 23), Nelson (24), Wagner (25), Schlender and Kruger-Thiemer (27)], are based on the knowledge of the rate constant for elimination, the calculated value of k_{01} will be incorrect in such cases, too. This difficulty cannot be overcome by the method of Dost and Medgyesi (26) or even by methods using digital computation (27) unless the error of the points of measurement is much lower than usual. In such cases it seems to be necessary to estimate the rate constant for elimination (and the corresponding biological half-life, $t_{50\%} = \ln 2/k_{el}$) from independent experiments with *intravenous* administration of the same drug, to the same test subject.

Tables I and II and Fig. 4 demonstrate an actual example of that kind. These experiments, the details of which will be published elsewhere (28), were performed with 2-sulfanilamido-5-methylpyrimidine, a sulfa drug on the German market

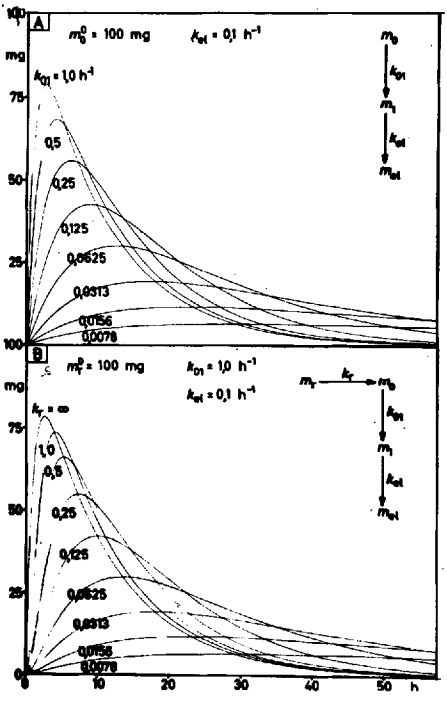

Fig. 3.—Families of computer drawn curves of m (blood amount) for the model used. Key: A, the simplified form of Eq. 4, varying k_{01}; B, the simplified form of Eq. 5, varying k_r.

TABLE I.—BLOOD PLASMA CONCENTRATION OF 2-SULFANILAMIDO-5-METHYL-PYRIMIDINE AFTER ORAL OR INTRAVENOUS ADMINISTRATION OF 2000 mg.

Time After Admin. t, (hr.)	Mode of Administration[a] (Test) Oral[b] (1) c_1' (mg./L.)	Oral[c] (2) c_1' (mg./L.)	Intravenous (3) c_1' (mg./L.)
1.0			579.8
1.33		97.9	
2.0	36.1		
4.0	74.5	149.4	473.4
6.0	88.5	144.8	445.0
8.0	100.0	120.7	412.0
24	68.4	89.6	245.4
32	80.1	68.3	153.2
48	49.9	68.8	82.0

[a] Test subject: male, 45 years, 75.0 Kg. [b] Commercial tablets. [c] Freshly precipitated suspension (neutralized solution of the sodium salt).

since 1961.[3] Table I contains the chemically measured [method of Bratton and Marshall (29)] drug concentrations in the blood plasma, c_1', after oral or intravenous administration of 2000 mg. of 2-sulfanilamido-5-methyl-pyrimidine.

The data in Table II show that the biological half-lives after oral administration are significantly higher than the biological half-life after intravenous administration. The 95% confidence limits of the latter value are much narrower than the confidence limits of the foregoing values. The same situation prevails for the apparent plasma distribution coefficient (apparent relative volume of distribution with respect to the plasma concentration). But it is unlikely that the mode of administration would influence the processes of distribution and elimination (metabolism and renal excretion) so greatly. It seems much more appropriate to assume that the apparent biological half-life and the apparent plasma distribution coefficient after oral administration should have approximately the same values as after intravenous administration. Using the assumption that the differences noted are due to a slow absorption or a slow sustained release, a provisional calculation has been made using the method of Dost and Medgyesi (26), in which the value of the rate constant for elimination after intravenous administration, $k_{el} = 0.0170$ hr.$^{-1}$, has been used (therefore, only two points of measurement, related by $t_2 = 2 \cdot t_1$, are necessary instead of three as in the original method). Using the data from $t = 4$ and 8 hr. of test *1* (Table I) produced a rate constant for absorption (or for sustained release) of k_{01} (or k_r) = 0.1775 hr.$^{-1}$ by substitution into the equation

$$e^{-k_{01}t_1} = \frac{c_1'^2}{c_1'^1} - e^{-k_{el}t_1} \qquad \text{(Eq. 10)}$$

which results from $t_2 = 2 \cdot t_1$ and Eq. 4 or Eq. 9 ($c_1'^2$ denotes the plasma concentration value at the time t_2). The corresponding value of the apparent plasma distribution coefficient, Δ', is 0.166 ml./Gm., which lies within the confidence limits of the corresponding value after intravenous administration (Table II) and supports the assumption underlying this calculation that Eqs. 4 or 9 may be used for the description of this part of the experimental curve. Using these three parameters one predicts 29.9 mg./L. as the expected value of c_1' at 48 hr. after the administration. This value is appreciably lower than the measured value of 49.9 mg./L. and might be explained by the following calculation. Repeating the foregoing calculation with the points of measurement at 24 and 48 hr. we get the rate constant for absorption, $k_{01} = 0.0437$ hr.$^{-1}$, and the apparent plasma distribution coefficient, $\Delta' = 0.149$ ml./Gm., the last of which is again rather close to the confidence limits of the corresponding value after intravenous administration. The apparent

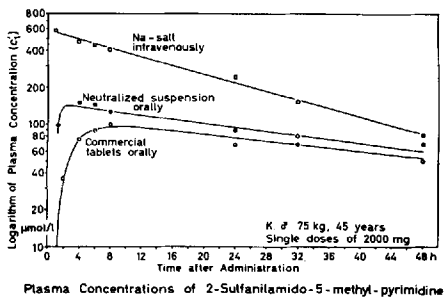

Fig. 4.—Sample experiment showing plasma concentration/time relationship for 2-sulfanilamido-5-methyl-pyrimidine.

[3] Marketed as Pallidin, by E. Merck AG., Darmstadt, Germany. The authors are grateful for the support of these studies by the manufacturer of this drug.

TABLE II.—APPARENT BIOLOGICAL HALF-LIVES, $t'_{50\%}$, APPARENT PLASMA DISTRIBUTION COEFFICIENTS, Δ', ABSORBED FRACTION OF THE DOSE, δ_1, AND RATE CONSTANT FOR ABSORPTION, k_{01}, CALCULATED FROM DATA OF TABLE I

Test	Mode of Admin.	Apparent Biological Half-Life, $t'_{50\%}$, hr.	Apparent Plasma Distribut. Coeff., Δ' (ml./Gm.)	Absorbed Fraction Dose, δ_1	Rate constant for Absorption k_{01} (hr.$^{-1}$)
1	Oral[a]	40.8 (20.8–80.2)[b]	0.910 (0.666–1.243)	0.19 (0.15–0.25)	0.397 (0.222–0.712)
2	Oral[c]	36.3 (22.3–59.0)	0.691 (0.550–0.868	0.25 (0.21–0.31)	3.384 (1.546–7.408)
3	Intra-venous	17.1 (15.7–18.7)	0.174 (0.159–0.189)	1.00[d]	...

[a] Commercial tablet. [b] Figures in parentheses are 95% confidence limits (Student *t* test of the average mean logarithmic values). The calculation of the data in this table was done using a digital computer program for fitting a curve to Eq. 4 (to be published) at the Calculation Center, University of Kiel (Dr. B. Schlender), Germany, with the electronic digital computer XI (Electrologica, Inc., Amsterdam, The Netherlands). [c] Freshly precipitated suspension (neutralized solution of the sodium salt). [d] By definition the entire dose is injected into the body.

rate constant for absorption (or release) for the time interval from 24 to 48 hr. is less than one-third of the value for the time interval from 4 to 8 hr. This relates well to the fact that the usual time of passage through the small intestine is approximately 8 to 12 hr., and that the rate of absorption in the large intestine is slower than in the small intestine [*cf.*, Eriksen *et al.* (30) and Diller and Bunger (31)]. Therefore, it might be necessary for a proper description of the experimental data to use the idea of a variable rate constant for absorption (or release) changing with time. Pharmacokinetic approaches of this type have been given by Wagner and Nelson (21, 32) and Stelmach *et al.* (33). In experiment *1* (Tables I and II) the rate constant for absorption (or release) in the time interval from 24 to 48 hr. is according to the calculation method of Dost and Medgyesi (26) in the same order of magnitude as the rate constant for elimination, $k_{e1} = 0.0404$ hr.$^{-1}$. From Fig. 3 and the foregoing discussion it is clear that this is one of the reasons for the apparently low slope of the curves after oral administration in Fig. 4, resulting in erroneous values for the biological half-life. The other reason is the higher value of the rate constant for absorption within the first 8 hr. Both reasons together allowed the digital computer to find a curve fitting solution according to Eq. 4, as shown in Fig. 4, which contains the erroneously high value of the biological half-life. A more detailed analysis of our experiments (Table I) is not feasible because of the low number of points of measurement.

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