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Mathematical treatment of oral sustained release drug formulations

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A mathematical model is described for an ideal sustained release dosage form in which there is a constant rate of release of drug from the maintenance dose. Kinetic equations related to this model are derived. The implications of these equations in the calculation of the dosage regimen for a sustained release product are considered.

THE objectives of oral sustained release drug formulations: (*i*) to give rapidly, blood concentrations of the drug, sufficient to elicit the desired therapeutic effect; (*ii*) to maintain these concentrations at an essentially constant level for a suitable period of time; (*iii*) to reduce the frequency of administration of the drugs compared with those in conventional forms; (iv) to give a more uniform biological response and a reduced incidence and intensity of side-effects. These last result from high drug concentration peaks which obtain after administration of conventional dosage forms (Mulligan 1954; Freed, Keatings & Hays, 1956; O'Connor 1958). In general, the total dose used in a sustained release formulation is the sum of the amount of the drug in the "free form," determined by conventional dosage, and that estimated to be required in the "maintenance form."

Despite the widespread use of sustained release drug formulations, little has been published on the method of calculation of the total dose required for the products or on the mathematical treatment of the drug

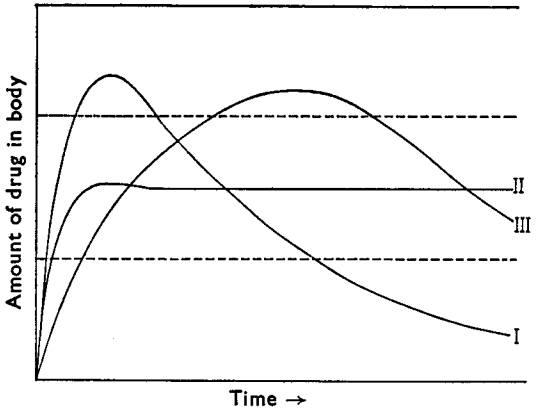

FIG. 1. Hypothetical drug level—time curves of a drug in various dosage forms. I. Drug in conventional dosage form. II. Sustained release formulation, the release of drug from the "maintenance form" occurring at a constant rate. III. Formulation in which the release of the drug from the "maintenance form" is by a first-order rate (c.f. applying the equation used by Weigand & Taylor, 1960.) Solid line marks limits of side-effects. Broken lines define limits of therapeutic range.

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biokinetic data. Nelson (1957) gave a method of deriving the "maintenance form" of the drug from data based on its biological half-life. Weigand & Taylor (1960) presented a mathematical model and derived equations based on a first order release rate of the drug from the maintenance dose. Nelson (1963) derived an equation for the variation in the body level of a drug after administration assuming a constant rate of release from the "maintenance form" of the drug. Although the derived equations are based on a hypothetical system, some guide to the formulation of oral sustained release dosage forms may be obtained.

In Fig. 1 are presented body drug level versus time curves for a drug presented in different forms. Curve (I) indicates that the conventional dosage form may result in concentrations above the therapeutic range, curve (II) is that resulting from an ideal sustained release formulation which is not achieved if the drug release from this product follows a first order rate (curve III).

A model system is represented in Fig. 2.

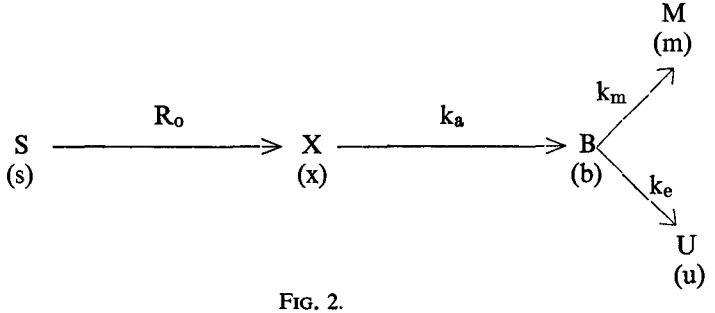

FIG. 2.

S, is the sustained release preparation, X, the gastrointestinal tract, B, the body (excluding the gut and urine), U, the urine, and M, the total metabolites in all compartments, whilst (s), (x), (b), (u) and (m) represent the amount of drug in each compartment. The assumptions made are that

(1) The transfer from one compartment to another is irreversible.

(2) The rate of transfer of drug from a compartment is directly proportional to the concentration or amount of drug in that compartment. Thus absorption, excretion and metabolism are first order processes, with rate constants k_a, k_e and k_m respectively.

(3) There is a fixed rate of release of drug from the "maintenance form" of the product (R_o).

(4) The release of drug from the "maintenance form" is rate determining in the absorption process.

(5) There is no decomposition of the drug at the absorption site.
There is no enterohepatic recycling or any diffusion of the drug from the blood into the stomach.

(7) The drug is completely absorbed.

(8) The rate constant for the absorption is unchanged along the gastrointestinal tract.

The following equations then apply:

$$-\frac{ds}{dt} = R_o \quad .. \quad .. \quad .. \quad .. \quad .. \quad (1)$$

$$\frac{dx}{dt} = R_o - k_a.x \quad .. \quad .. \quad .. \quad .. \quad (2)$$

$$\frac{db}{dt} = k_a.x - k_e.b - k_m.b \quad .. \quad .. \quad .. \quad (3)$$

$$= k_a.x - k_d.b$$

$$\frac{du}{dt} = k_e.b \quad .. \quad .. \quad .. \quad .. \quad .. \quad (4)$$

Each compartment is now considered separately.

THE SUSTAINED RELEASE PREPARATION (S)

Let D_o be the amount of "free" drug and S_o the "maintenance form" in the sustained release dose. Integrating equation (1) gives:

$$s = S_o - R_o.t \quad .. \quad .. \quad .. \quad .. \quad (5)$$

The total drug in the "maintenance form" is then given by:

$$S_o = R_o.T$$

where T is the period of time over which the drug is released from the formulation, in order to maintain the desired body level of drug, for some number of hours, h.

$$\text{Total dose} = D_o + S_o \quad .. \quad .. \quad .. \quad (6)$$

THE GASTROINTESTINAL TRACT (X)

Integrating equation (2); since the amount of drug in the tract at zero time is that in the readily available form, D_o then

$$x = \frac{R_o}{k_a}\left[1 - e^{-k_a t}\right] + D_o e^{-k_a t} \quad .. \quad .. \quad (7)$$

THE BODY COMPARTMENT (B)

Putting k_d equal to k_e plus k_m where k_d is the overall rate constant for loss of drug from the body and substituting x from equation (7) into equation (3). Then:

$$\frac{db}{dt} = R_o\left[1 - e^{-k_a t}\right] + k_a D_o e^{-k_a t} - k_d b \quad .. \quad .. \quad (8)$$

Integrating and putting $b = 0$ when $t = 0$ then:

$$b = \frac{R_o}{k_d}\left[1 - e^{-k_d t}\right] - \frac{R_o}{k_d - k_a}\left[e^{-k_a t} - e^{-k_d t}\right]$$

$$+ \frac{k_a D_o}{k_d - k_a}\left[e^{-k_a t} - e^{-k_d t}\right] \quad .. \quad .. \quad .. \quad .. \quad (9)$$

The concentration of drug (c) in the plasma is then given by:

$$c = \frac{b}{V_d} \quad .. \quad .. \quad .. \quad .. \quad .. \quad (10)$$

where V_d is the apparent volume of distribution of the drug.

THE URINE (U)

Substituting b, from equation (9) into equation (4) and integrating, putting $u = 0$ when $t = 0$, gives:

$$u = \frac{k_e R_o}{k_d^2}\left[k_d t + e^{-k_d t} - 1\right] + \frac{k_e}{k_d - k_a}\left\{\left[\frac{1}{k_a}(e^{-k_a t} - 1) - \frac{1}{k_d}(e^{-k_d t} - 1)\right]\left[R_o - k_a D_o\right]\right\} \quad (11)$$

If the drug is in solution or conventional dosage form $R_o = 0$. Then substituting b from equation (9) in equation (10) the latter equation reduces to

$$c = \frac{k_a D_o}{V_d(k_d - k_a)}\left[e^{-k_a t} - e^{-k_d t}\right] \quad .. \quad .. \quad (12)$$

which is of the same form derived perviously (Gehlen, 1933; Teorell, 1937; Dost, 1953; Bray & White, 1957) for "free" drug forms.

Similarly equation (11), for conventional dosage forms reduces to

$$u = \frac{k_e\, k_a\, D_o}{k_d - k_a}\left[\frac{1}{k_d}(e^{-k_d t} - 1) - \frac{1}{k_a}(e^{-k_a t} - 1)\right] \quad .. \quad (13)$$

and when

$t = \infty$, then:

$$u_\infty = \frac{k_e}{k_d}.D_o \quad .. \quad .. \quad .. \quad .. \quad .. \quad (14)$$

Equations (13) and (14) are of the same form as those derived by Weigand & Taylor (1960) for non-sustained drug forms.

In calculating the total dose and the "maintenance form" of the drug required to give the desired therapeutic level Nelson (1957) relates all equations to the dose which gives the therapeutic response in the conventional dosage form. This is in the general form.

$$W_t = W_o + \frac{0{\cdot}693\ W_o.f.h.}{t^1/_2} \quad .. \quad .. \quad .. \quad (15)$$

in which W_t is the total dose in the sustained release product; W_o is the dose giving clinical response in the conventional dosage form; $t^1/_2$ is the biological half-life of the drug in the body; h is the number of hours required for a sustained body level of drug; and f relates the optimum therapeutic body level of the drug with the peak body level obtained with the conventional dosage form. This equation can lead to a higher drug quantity than is actually required, if no account is taken of the effect of the "maintenance form" of the drug, which is released from zero time;

this makes its contribution along with the "free form" of the drug. In consequence the initial dose will be too large. Since this value is used to calculate the "maintenance form" of the drug (equation 15), instead of being based on the optimum therapeutic level in the body, this form will also be excessive. The following example is used to demonstrate the above considerations. Consider a drug with the following properties, $W_o = 1g$, $k_d = 0{\cdot}173\ hr^{-1}$ ($t^1/_2 = 4$ hr) $k_a = 2{\cdot}0\ hr^{-1}$, $f = 0{\cdot}7$, and $h = 10$ hr.

Applying equation (15)

$$W_t = 1{\cdot}0 + \frac{0{\cdot}693 \times 1{\cdot}0 \times 0{\cdot}7 \times 10}{4}$$

$$= 1{\cdot}0 + 1{\cdot}21$$

$$= 2{\cdot}21g$$

Using the same parameters as above and adopting the equations outlined in the present article, the values for the initial dose in the "free form" (D_o) and maintenance dose (S_o) are given in Table 1.

TABLE 1. CALCULATION OF INITIAL DOSE AND MAINTENANCE DOSE FOR OPTIMUM THERAPEUTIC LEVEL

Parameter required	Value	Equation used
1g Conventional dosage form (*a*) Peak body level (b_{max}) .. .. (*b*) Time to attain peak level	 0·79 g 1·43 hr	 (12) (8)
Optimum therapeutic level (b_{opt})	0·56 g	$b_{opt} = f.b_{max}$ (f = 0·7)
Rate constant (R_o)	0·096 g/hr	Since require rate in = rate out of body for sustained level, $R_o = k_d.b_{opt}$
Initial dose in the "free form" in the sustained release preparation (D_o)	0·60 g	(9) by: substituting b = 0·56 g t = 1·43
Total maintenance dose (S_o)	1·09 g	$S_o = R_o.T = R_o(h+1{\cdot}43)$
Total dose	1·69 g	

Thus there is a difference in the value of the total dose (W_t) from that calculated using equation (15): the results are shown graphically in Fig. 3. Curves are derived from equation (12) for a drug in solution, and equation (9) for sustained release dosage forms. Fig. 3 shows that the values given in Table 1, produce a constant body level of the drug, and maintain it at this level (b_{opt}) for the time required. On the other hand, using the values derived from equation (15) and substituting them in equation (9), the body level of drug rises higher than the initial dose in solution and could increase the incidence of side effects, the level always being above the therapeutic optimum.

Other workers have used equations similar to equation (15) and based W_0 on clinical data i.e. the dose which gives an optimum therapeutic level in the body (Robinson & Swintosky, 1959; Swintosky, 1960). Calculation of the "maintenance form" is still based on W_0 and not on the amount of the drug in the body at therapeutic level. The difference between calculation of the "maintenance form" presented here, and that

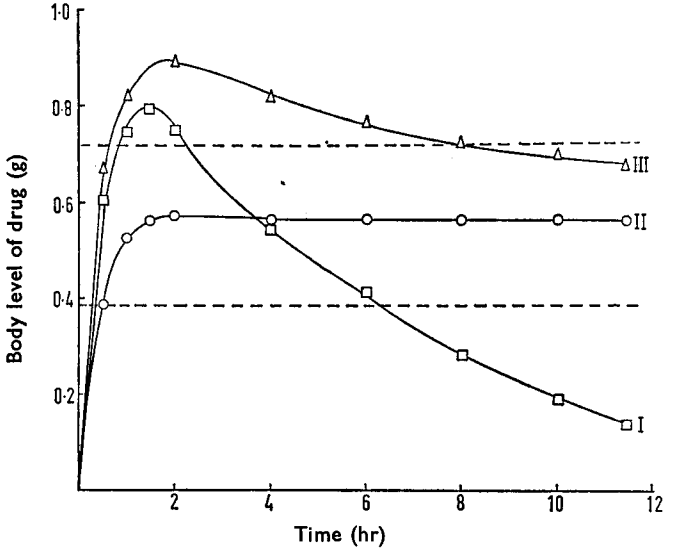

FIG. 3. Calculated plot for drug in solution, and for sustained release dosage forms, showing change in the body level of the drug with time. I. 1·0 g drug in solution (Eq. 12). II. Sustained release dosage form using values given in Table 1 (total dose 1·69 g; Eq. 9). III. Dosage form using values derived from equation 15. (Total dose 2·21 g; Eq. 9.) Broken lines define limits of therapeutic range.

using equation (15), will not be significantly different if there is little loss of drug from the body during attainment of the optimum therapeutic level. Hence the correction in calculating the maintenance form of the drug will only become large if the drug is rapidly eliminated from the body.

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The paper was presented by MR. ROWLAND.