crossover administrations. The results of this study ran contrary to a possible implication (*i.e.*, impairment of digoxin bioavailability by the antacid) of Khalil's *in vitro* findings in which the dissolution of digoxin tablets was virtually completely suppressed by the antacid (1).

Further experiments in humans are necessary to substantiate these findings in dogs.

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Blood Levels from a Sustained-Release Dosage Form

Keyphrases □ Dosage forms—sustained release, blood levels, fast and slow release drug components, equations □ Timed-release dosage forms—blood levels, fast and slow release components, equations □ Blood levels—sustained-release dosage form, fast and slow release components, equations

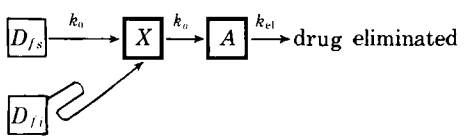
To the Editor:

The ideal oral dosage form for obtaining a desired plateau level of drug rapidly in the body is one that releases part of the dose instantaneously and the balance by a slow zero-order process. Pharmacokinetic approaches to calculate the desired proportion of fast and zero-order release components have been described (1, 2).

One method (1) gives the desired steady-state drug level at the peak time, t_p, for the fast release component and also later during the sustained-release period. Between these times, however, drug levels tend to be higher, producing a hump in the overall blood drug level *versus* time profile.

Another method (2) provides a constant plateau level of drug C_{ss}, which is reached slightly later than time t_p. The constancy of the drug levels and the somewhat simpler calculations probably make it the method of choice in most situations.

The objective of this communication is to describe a method of calculating fast and slow release drug components. While similar to the method of Robinson and Eriksen (2), it facilitates more rapid calculation of the drug fractions and permits considerable simplification of the rather lengthy equations used



Scheme I

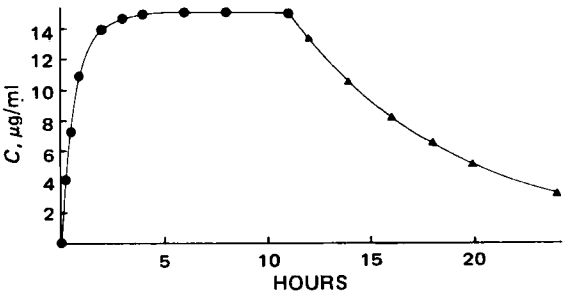


Figure 1—*Simulated blood level curve using data from Table I and Eqs. 6 (●) and 7 (▲).*

hitherto to describe this model. The overall process is described in Scheme I.

In the model, D_{fs} and D_{fi} are the sustained-release and fast release components of the total dose D, respectively; X is the amount of drug in solution and available for absorption in the gut; A is the amount of drug distributed in a single homogeneous volume, V, in the body to give a concentration, C; k_0 is the zero-order rate constant for release of D_{fs}; and k_a and k_{el} are first-order rate constants for drug absorption into the body and elimination by all routes, respectively. The crooked arrow represents instantaneous release of D_{fi} into X.

The assumptions in this model are as stated previously (1): all drug in the body is homogeneously distributed in one apparent volume, V, and the rate of drug absorption is invariant throughout the GI tract. The sustained-release component, D_{fs}, releases drug from time zero to time T, so $D_{fs} = k_0 T$ and both D_{fi} and D_{fs} contribute to the blood level beginning at time zero.

Integrated expressions to describe the amounts of drug D_{fs}, X, and A at any time during drug release are given by Eqs. 1–3:

$$D_{fs}(t) = D_{fs} - k_0 t \qquad \text{(Eq. 1)}$$

$$X = \frac{k_0}{k_a}[1 - e^{-k_a t}] + D_{fi}e^{-k_a t} \qquad \text{(Eq. 2)}$$

$$A = \frac{k_0}{k_{el}}(1 - e^{-k_{el}t}) + \left(\frac{k_a D_{fi} - k_0}{k_{el} - k_a}\right)(e^{-k_a t} - e^{-k_{el}t}) \qquad \text{(Eq. 3)}$$

To calculate D_{fi}, Rowland and Beckett (1) set A equal to A_{ss} at the single time t_p. This method, as previously stated, results in a hump in the drug blood level profile for an intermediate time following t_p. An alternative approach is based on k_0 being equal to $(k_{el})(A)$ at the steady state. Then substituting for k_0 in Eq. 3 and rearranging give Eq. 4, where $A = A_{ss}$:

$$D_{fi} = \left(\frac{1}{k_a} + \frac{(k_{el} - k_a)e^{-k_{el}t}}{k_{el}k_a(e^{-k_a t} - e^{-k_{el}t})}\right)(k_{el})(A_{ss}) \qquad \text{(Eq. 4)}$$

To avoid a hump in the blood level profile, A must be maintained at A_{ss}, which requires that Eq. 4 be time independent. Since $k_a > k_{el}$ in the usual case, time independency occurs only when $e^{-k_a t}$ becomes insignificant relative to $e^{-k_{el}t}$. Then Eq. 4 simplifies to:

$$D_{fi} = A_{ss} = \frac{k_0}{k_{el}} \qquad \text{(Eq. 5)}$$

Table I—Calculation of Sustained-Release Parameters for Theophylline

Parameter	Value	Method of Calculation
A_{ss}	480 mg	$A_{ss} = C_{ss}V$
D_{fi}	480 mg	Eq. 5
k_0	57.6 mg/hr	$k_0 = (k_{el})(A_{ss})$
D_{fs}	633.6 mg	$D_{fs} = k_0 T^b$
D^a	1113.6 mg	$D_{fs} + D_{fi}$
D_{fi}/D_{fs}	0.76	

[a] D may be contained in two or more dosage units, provided k_0 is 57.6 mg/hr and D_{fi}/D_{fs} is constant. [b] T = 11 hr.

Substitution from Eq. 5 into Eq. 3 gives Eq. 6*a* or 6*b*:

$$A = D_{fi}[1 - e^{-k_a t}] \qquad \text{(Eq. 6a)}$$

or:

$$C = \frac{A_{ss}}{V}[1 - e^{-k_a t}] \qquad \text{(Eq. 6b)}$$

which provides a simple expression to describe blood levels from this type of formulation for all values of $t \leq T$. After this time, the first-order decline in blood levels is given by:

$$C = C_{ss}e^{-k_{el}(t-T)} \qquad \text{(Eq. 7)}$$

where $t \geq T$.

The value of D_{fi} is independent of k_a and t_p. However, the lag time between t_p and the time taken for A to approach A_{ss} increases as k_a decreases. Since the blood levels of a drug administered as a zero-order release dosage form with no fast release component are given by:

$$C = \frac{k_0}{k_{el}}[1 - e^{-k_{el}t}] + \frac{k_0}{k_a - k_{el}}[e^{-k_a t} - e^{-k_{el}t}] \qquad \text{(Eq. 8)}$$

the reduction in the time taken to reach plateau blood levels with the introduction of a fast release component is clearly a function only of the relative values of k_a and k_{el}.

The method may be demonstrated using theophylline as an example. A recent study in normal human subjects yielded average values for k_a, k_{el}, and V of 1.3 hr^{-1}, 0.12 hr^{-1}, and 32 liters, respectively (3). With the assumption that a desirable therapeutic blood level C_{ss} is 15 μg/ml (4), values for a suitable sustained-release formulation are given in Table I.

The blood level resulting from these calculations is given in Fig. 1. The t_p value resulting from the fast release component is 2.0 hr (5), and the time taken for blood levels to reach 95% of their asymptotic value is only slightly greater at 2.3 hr (Eq. 6*b*).

This approach is not meant to imply that the ideal sustained-release blood profile can be obtained in all patients. Each individual patient will have different rates of absorption and elimination, as exemplified in Ref. 3. However, this method provides a simple approach which is of general application for dosage calculation with this type of sustained-release formulation.

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Effect of Propantheline on Nitrofurantoin Absorption

Keyphrases □ Propantheline—effect on nitrofurantoin absorption □ Nitrofurantoin—absorption, effect of propantheline □ Absorption—nitrofurantoin, effect of propantheline

To the Editor:

Since an adverse reaction to nitrofurantoin therapy is gastric upset, the manufacturers recommend that the drug be given with food or milk to minimize this effect (1). However, concurrent administration of food with nitrofurantoin apparently not only reduces the possibility of GI reaction but also significantly increases the bioavailability of the drug, especially in relation to the macrocrystalline form (2). The increase in absorption has been attributed to food causing an increase in the gastric emptying time, which would also increase the residence time of the drug in the gastric fluids, thereby allowing for a greater amount of nitrofurantoin to be dissolved prior to its passage into the duodenum where absorption is optimal.

Since other studies showed that increases in the serum level of digoxin (3) and the urinary excretion of riboflavin (4) occur when these drugs are administered with propantheline due to its effect of reducing gastric motility, it was felt that concurrent administration of nitrofurantoin with propantheline would be a good means of confirming whether increased gastric emptying time modifies nitrofurantoin absorption, as postulated by Bates *et al.* (2).

Six healthy subjects (three males and three females) were administered a single 100-mg oral dose of nitrofurantoin macrocrystals[1] with 100 ml of water. A crossover design was employed; three subjects received 30 mg of propantheline[2] 45 min prior to nitrofurantoin administration while the other three subjects received only nitrofurantoin. One week later the experimental conditions were re-

[1] Macrodantin Capsules, 100 mg, Eaton Laboratories, Norwich, N.Y.
[2] ProBanthine Tablets, 15 mg, Searle Laboratories, Chicago, Ill.