sorption may be influenced by the differences in pH described here.

Under any circumstances, the intraluminal pH will have an important effect on the disintegration and dissolution characteristics of dosage forms administered to intact animals. This is particularly true of special dosage forms such as suspensions, coated tablets, and timed-release products where pH is an inherent part of the product design. Just as differences in biliary recycling between species can influence the pharmacokinetics of drugs administered in intact animals, intraspecies differences in intestinal pH can also be expected to influence the site and extent of absorption as well as the intestinal contribution to the volume of distribution (7).

When selecting an animal model for pharmacokinetic or bioavailability studies, intestinal pH should be considered as a potential determinant of the outcome. Of course, some drugs are potentially too toxic (*e.g.*, methotrexate) to be tested for bioavailability in normal human subjects, so for these drugs the development of suitable animal models is especially important.

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COMMUNICATIONS

Effect of an Antacid on Absorption of Digoxin in Dogs

Keyphrases □ Digoxin—effect of antacids on absorption, dogs □ Absorption—digoxin, effect of antacid, dogs □ Antacids—effect on absorption of digoxin, dogs

To the Editor:

Recently, Khalil demonstrated that the *in vitro* dissolution of digoxin tablets[1] was suppressed by a commercial antacid containing aluminum hydroxide (0.31 g/5 ml) and magnesium trisilicate (0.60 g/5 ml). The present study examined the effect of this commercial antacid[2] on the absorption of digoxin in dogs after oral administration.

Following overnight fasting, each of four mongrel dogs was given either two digoxin tablets[3] (1.0 mg) or 20 ml of the commercial antacid plus two tablets at weekly intervals in accordance with a crossover design. The antacid was given by stomach intubation, and 50 ml of water was given to each dog following administration of the dosage formulation.

Blood (4 ml) was withdrawn from the radial vein at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 7, and 24 hr following drug administration (Table I). The plasma samples were analyzed using a commercial digoxin assay kit[4]. A standard curve was obtained for each animal using its blank plasma.

Analysis of variance on each data point indicated that there was no significant difference ($p \leq 0.01$) between concentrations at any time point following the

Table I—Mean Plasma Digoxin Concentrations (Nanograms per Milliliter) following Digoxin or Commercial Antacid plus Digoxin Administrations

	0.5 hr	1.0 hr	1.5 hr	2.0 hr	2.5 hr	3.0 hr	4.0 hr	7.0 hr	24.0 hr
				Antacid plus Digoxin Tablets					
Mean	2.13	6.43	6.52	5.81	5.25	5.45	5.00	2.93	0.99
SD	3.14	2.43	1.75	1.83	1.59	2.57	1.38	0.82	0.10
				Digoxin Tablets					
Mean	1.51	4.23	5.33	6.64	5.50	5.24	4.98	3.52	1.26
SD	2.03	2.59	3.45	1.82	2.07	2.54	1.69	0.76	0.39

[1] Lanoxin tablets BP.

[2] Gelusil, Warner Chilcott Co., Canada.

[3] Lanoxin tablets, 0.5 mg, Burroughs Wellcome Co., Canada.

[4] Bio-R.I.A., Montreal, Quebec, Canada.

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

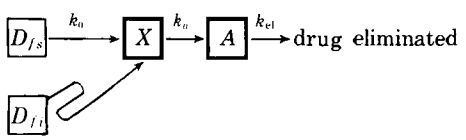
To the Editor:

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

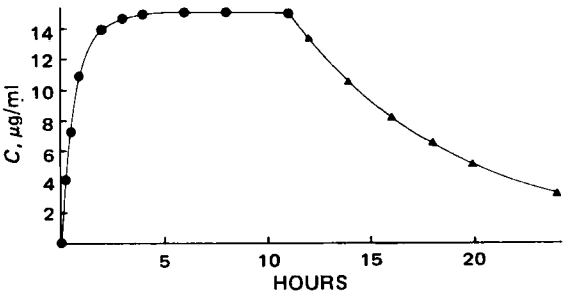


Figure 1—*Simulated blood level curve using data from Table I and Eqs. 6 (●) and 7 (▲).*

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:

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