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.

Table I—Cumulative Excretion (Milligrams) of Nitrofurantoin for Six Subjects under Propantheline and Control Conditions

Subject	Control (Nitrofurantoin Only)	Nitrofurantoin and Propantheline
1	17.2	30.2
2	29.0	34.7
3	12.3	19.5
4	15.2	31.8
5	13.0	33.6
6	16.0	22.3
Mean ± *SE*	17.1 ± 2.49	28.7 ± 2.57

versed. All subjects fasted overnight and for 4 hr after drug administration. Total urine specimens were collected for 24 hr. Nitrofurantoin in the urine was determined by a spectrophotometric method (5) specific for unchanged drug.

The results (Table I) indicate a statistically significant increase in nitrofurantoin excretion when propantheline was coadministered as compared with the control condition ($p < 0.01$ as determined by paired t-test). No statistical significance was observed for differences in urinary volume or urinary pH between the two conditions. Thus, the results are consistent with the hypothesis that a delay in gastric emptying possibly will increase the bioavailability of nitrofurantoin and indicate that this effect might explain why food produces similar effects.

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Simple Method for Monitoring Flow Rate during Gravity Perfusion

Keyphrases □ Flow rates—apparatus for continuous monitoring during perfusion studies □ Perfusion studies—apparatus for continuous monitoring of flow rate □ Equipment—apparatus for monitoring flow rate during gravity perfusion

To the Editor:

The apparatus described here fills the need for an inexpensive, easily constructed device for continuously monitoring flow rates during perfusion studies. Although extremely simple in design, it can be employed to advantage with modern electronic recording equipment.

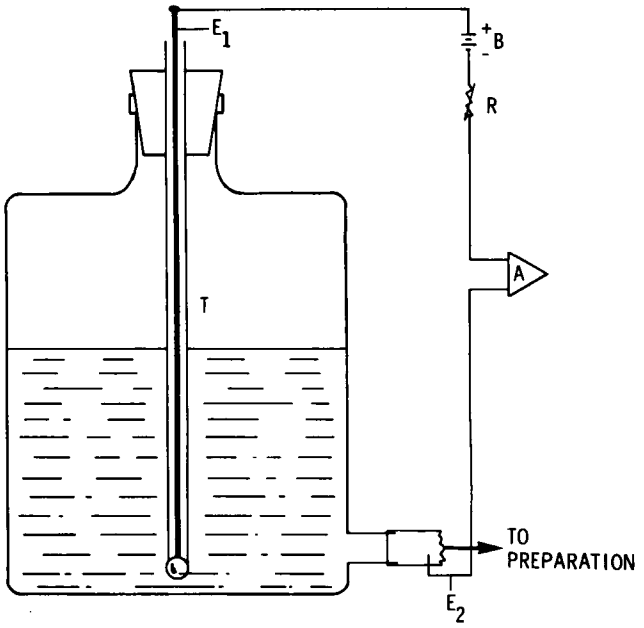

Figure 1—*Components of device for continuously monitoring flow rates during perfusion studies.*

The device makes use of the familiar air bubbles which emerge from the pressure regulating tube (T) of the well-known Marriotte bottle. The last 1 or 2 cm of this tube is coated on both the inner and outer surfaces, most simply by dipping the tubing in melted paraffin. One electrode (E_1)—essentially a length of stainless steel wire insulated except at the tip—is passed down the glass tubing (Fig. 1). A second electrode (E_2), which can be much shorter, is placed in the perfusion solution, usually through a piece of rubber tubing leading from the outlet of the reservoir.

Leads from these two electrodes are connected to the input of the recorder amplifier (A) with an ordinary 1.5-v flashlight battery (B) and variable resistor (R) placed in the circuit as indicated. As the perfusion proceeds, the column of air in the glass tubing (T) descends and "breaks off" in the form of air bubbles. These bubbles serve to break the circuit, and this breakage is registered on the recorder. Changes in flow caused by interventions that alter the perfusion rate are rapidly indicated on the chart. This system avoids the time-consuming process of collecting and measuring the effluent to determine whether a change in flow has actually occurred. The amount of change can thus be measured, either by collecting the effluent or counting the marks on the chart recorder over a specific length of time.

By its nature, a tracing provides a stronger visual impact than does a number, and this advantage is particularly noticeable when other parameters are being recorded simultaneously on the same strip chart. The system has been very valuable also for demonstrations to large classes, using closed circuit T.V. with the camera focused on the chart. The apparatus described here has been employed extensively