Table I—Simulated Data for a 500-mg Dose every 2 hr [a]

Time, hr	Single Dose Concentration, μg/ml	Steady-State Concentration, μg/ml	Concentration Converted to Single Dose, μg/ml[b]
0	—	11.6	—
0.083	85.2	96.4	85.3
0.167	61.8	72.5	61.8
0.25	46.3	56.6	46.4
0.5	23.8	32.8	23.8
0.75	16.1	24.1	16.1
1.0	12.8	19.9	12.9
1.5	9.5	15.0	9.5
2	7.4	11.6	7.3
AUC[c]	56.159	—	55.996
AUMC[c]	84.198	—	83.391
V_{ss}[d]	13.3 liter	—	13.3 liter
CL[d]	8.9 liter/hr	—	8.9 liter/hr
$\bar{t}$[d]	1.5 hr	—	1.5 hr

[a] Single dose described by $C = 100e^{-5t} + 20e^{-0.5t}$. [b] Computed as $C = C_{sst} - 11.6e^{-0.5t}$. [c] Computed using trapezoidal rule. [d] V_{ss} = [Dose(AUMC)]/AUC^2, CL = Dose/AUC, $\bar{t}$ = AUMC/AUC.

where $C(t)$ is the calculated concentration after a single dose at time t, $C_i(t)$ is the observed concentration during the ith dosing interval at time t, $C_i(0)$ is the postabsorptive, postdistributive drug concentration at the start of the ith dosing interval, and k_n is the terminal rate constant.

To illustrate this method, data were simulated (4) for two different sets of conditions. The first data set represented concentration–time values after an intravenous bolus dose (Table I). The second set of data are values representative of extravascular administration (Table II). The last data set consists of concentration–time values for intermittant intravenous infusion (Table III). In all cases, a single-dose curve was constructed by means of Eq. 8 from the steady-state values. The AUC and AUMC values between the single dose situation and the curve derived using reverse superposition varied slightly because of rounding-off errors, but no appreciable differences were apparent between respective pharmacokinetic parameters.

Since reverse superposition applies also during multiple dosing before steady state occurs, this method could be applied at any time during therapy. This approach could be useful when patients receiving the study drug are investigated, since it is often difficult to ensure steady-state conditions (*i.e.*, compliance, errors in administration time, *etc.*) Caution must be used when the dosing interval is short relative to the terminal half-life of the drug. Under these conditions half-life may be difficult to calculate, and errors may occur in the estimation of $C(t)$ as well as in the estimation of AUC and AUMC from the derived single dose curve.

Table II—Simulated Data for a 500-mg Dose every 6 hr [a]

Time, hr	Single Dose Concentration, μg/ml	Steady-State Concentration, μg/ml	Concentration Converted to Single Dose, μg/ml[b]
0	0	15.4	0
0.25	4.4	19.4	4.4
0.5	7.3	21.8	7.3
1.0	10.3	24.1	10.1
2.0	11.5	23.7	11.5
3.0	10.8	21.7	10.8
4.0	9.7	19.4	9.7
5.0	8.7	17.3	8.7
6.0	7.7	15.4	7.7
AUC[c]	122.49	—	122.57
AUMC[c]	1140.68	—	1140.76
$\bar{t}$[d]	8.6 hr	—	8.6 hr

[a] Single dose described by $C = 15.5e^{-0.116t} - 15.5e^{-1.5t}$ assuming complete bioavailability. [b] Computed as $C = C_{sst} - 15.4e^{-0.116t}$. [c] Computed using trapezoidal rule. [d] $\bar{t}$ = AUMC/AUC, the mean residence time after oral administration.

Table III—Simulated Data for a 500-mg Dose Infused Over 0.5 hr Administered every 2 hr [a]

Time, hr	Single Dose Concentration, μg/ml	Steady-State Concentration, μg/ml	Concentration Converted to Single Dose, μg/ml[b]
0	0	12.5	—
0.25	41.9	52.7	41.7
0.5	58.3	68.0	58.2
0.583	42.4	51.9	42.6
0.667	32.5	41.5	32.5
0.75	26.1	34.8	26.2
1.0	17.1	24.6	17.0
1.25	13.5	20.2	13.5
1.5	11.4	17.3	11.4
2.0	8.8	13.4	8.8
AUC[c]	62.49	—	62.45
AUMC[c]	104.30	—	104.30
V_{ss}[d]	11.4 liter	—	11.4 liter
CL[d]	8.0 liter/hr	—	8.0 liter/hr
$\bar{t}$[d]	1.7 hr	—	1.7 hr

[a] Single intraveneous bolus dose described by $C = 100e^{-5t} + 20e^{-0.5t}$. [b] Computed as $C = C_{sst} - 12.5e^{-0.5t}$. [c] Computed using trapezoidal rule. [d] V_{ss} = [Dose(AUMC)/(AUC)^2] − [T(Dose)]/2AUC, where T = Infusion duration. See Table I for other equations.

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Larry A. Bauer [x]
Milo Gibaldi
School of Pharmacy
University of Washington
Seattle, WA 98195

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Test for Selection of Erythromycin Stearate Bulk Drug for Tablet Preparation

Keyphrases □ Bioavailability—erythromycin stearate tablet formulation, dissolution rate, high-performance liquid chromatography □ Erythromycin stearate—bioavailability, tablet formulations, dissolution rate, high-performance liquid chromatography □ High-performance liquid chromatography—erythromycin stearate tablet formulation, bioavailability

To the Editor:

Bioavailability testing of experimental erythromycin stearate tablet formulations showed significant differences between tablets declaring 250 and 500 mg, where the concentrations of antibiotic and excipients were identical and the tablets differed only in fill weight and geometry. Different lots of erythromycin stearate were used in these formulations. It was learned, subsequently, that the dissolution rate (and presumably bioavailability) of erythromycin from the tablets could be correlated with the intrinsic dissolution rate of the batch of erythromycin stea-

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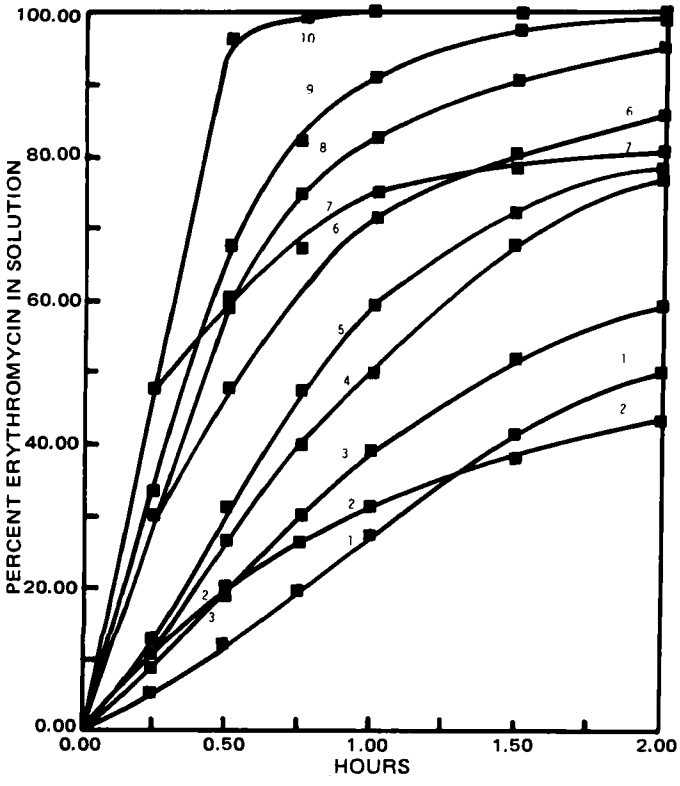

Figure 1—*Dissolution profile of various lots of erythromycin stearate as a function of time (0.05 M pH 6.6 phosphate buffer).*

rate used. A dissolution test method was developed for erythromycin stearate bulk drug and tablets using conditions under which decomposition of the antibiotic does not occur.

Erythromycin, its esters, salts, and their preparations have been reported to show significant differences in bioavailability (1). Stavchansky *et al.* (2) described attempts to correlate the known bioavailability of erythromycin stearate tablets from various sources with different *in vitro* test methods, including disintegration, dissolution, and dissolution–dialysis. Their findings were inconclusive, perhaps because their dissolution experiments were confounded by the decomposition of the antibiotic under the conditions used: their test method did not discriminate between intact and decomposed erythromycin.

Tsuji and Goetz (3) described a high-performance liquid chromatographic (HPLC) method for erythromycin which is selective for the intact drug and correlates with microbiological potency assay. In this laboratory, the method afforded a single peak for erythromycin at about 7.9 min. At 37°, the conventional temperature used in dissolution testing, erythromycin decomposition was rapid as evidenced by the decrease of its peak height and appearance of a new peak at about 12.5 min. Dissolution of the drug increases with increased acidity. However, acidity and temperature promote decomposition of erythromycin. On the basis of these considerations, the dissolution test method developed used pH 6.6 phosphate buffer at room temperature for the dissolution medium.

The dissolution studies were performed in a USP Apparatus 2 (4), equilibrating 500 ml of 0.05 *M* pH 6.6 phosphate buffer at 22°. The paddle was rotated at 50 rpm and 500 mg of erythromycin stearate (dispersing it with a micro spatula to ensure that it is wetted) or an erythromycin stearate tablet was added to the medium. A 5.0-ml aliquot was withdrawn after 60 min. The test sample was filtered through a membrane filter[1] and assayed immediately for erythromycin by the HPLC method (3). Under these test conditions, no decomposition of erythromycin was detected on the chromatograms. (The HPLC assay was used to obtain the data reported below; however, any convenient method could be employed after establishment of the validity of the test conditions.) Decomposition of erythromycin becomes evident after prolonged residence (several hours) in the dissolution medium; hence the injunction to assay the test sample immediately after completion of the test.

Table I—Dissolution of Erythromycin Stearate Bulk Drug and Corresponding Tablets

Curve No.[a]	Percent Dissolution After 1.0 Hr		
	Bulk Drug	500-mg Tablet	250-mg Tablet
4	49	44	
6	72	70	
7	75	70	
—	78	—	80
8	82	78	
9	92	88	

[a] Dissolution curves from Fig. 1.

Ten lots of erythromycin stearate from two domestic and six foreign sources were found to vary from 27 to 100% dissolution in 1 hr. A plot of the dissolution rate as a function of time is shown for these lots in Fig. 1. In general, dissolution of the bulk drug was similar to that of the tablets made from it. The dissolution rates of bulk drug and corresponding tablets are shown in Table I.

Bioavailability studies showed that the tablets made from bulk drugs of 72 and 78% dissolution were acceptable, while those made from bulk drug of 49% dissolution were unacceptable. For this reason, 70% dissolution for the bulk drug has been arbitrarily set as acceptable.

Erythromycin stearate is a mixture of the stearate salt of erythromycin with varying amounts of free stearic acid, medium stearate, and water. The chemical and physical properties that affect its dissolution have not been elucidated; attempts to correlate dissolution with particle size, shape, and crystal forms of the drug have failed. However, the test method proposed affords a facile empirical means for selecting suppliers.

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Jose Philip [x]
Robert E. Daly
Product Development Laboratories
Warner Lambert Pharmaceutical Research
Warner Lambert Company
Morris Plains, NJ 07950

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[1] Metricel Membrane filter, 0.45 μm; Gelman Instrument Co., Ann Arbor, MI 48106.