dissolution medium to 40 sec/sampling time. This combination of reduced probe size and minimal contact with the dissolution medium results in minimal disturbance of the hydrodynamics of the medium.

In summary, this design offers these advantages for adaptation to Hanson Easi-Lift dissolution units:

1. The device does not disturb the hydrodynamics of the dissolution test, and the sampling probes are inserted in the solution only while sampling.
2. There is easy access to the dissolution unit because probes and brackets retract.
3. The sampling device is inexpensive to make and could be linked to a variety of dissolution pump-sample collection devices.

This device has proven to be reliable and essentially carryover-free in our laboratory and is in routine use.

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Computation of Model-Independent Pharmacokinetic Parameters During Multiple Dosing

Keyphrases □ Pharmacokinetics—computation of model-independent parameters, multiple dosing

To the Editor:

Pharmacokinetic analysis by means of traditional compartmental methods is slowly giving way to model-independent or noncompartmental approaches. Computational simplicity and, in some cases, more useful information are among the reasons for this trend. Methods that use the area under the drug concentration *versus* time curve (AUC) and the area under the first moment of drug concentration *versus* time curve (AUMC) are available to determine clearance (CL), mean residence time ($\bar{t}$), and apparent volume of distribution at steady state (V_{ss}) from data obtained after a single dose of drug (1, 2).

Often, the need arises to calculate pharmacokinetic parameters after several doses or at steady state; this is particularly true when patients are being treated with the study drug, and doses may not be manipulated for the purposes of the investigation. With the limited exception of the determination of clearance at steady state, noncompartmental methods have not been considered for this purpose.

Following repeated administration of a fixed dose of a drug at fixed intervals, the AUC during a dosing interval at steady state is equal to the total AUC after the first dose (3). Therefore, drug clearance can be calculated at steady state. On the other hand, AUMC during a dosing interval at steady state ($AUMC_{ss}$) is less than the total AUMC after a single dose. Therefore, $\bar{t}$ and V_{ss} cannot be calculated directly from steady-state data.

The inequivalence of $AUMC_{ss}$ and AUMC (single dose) can be demonstrated by considering multiple intravenous bolus doses of a drug with linear multicompartmental characteristics. Drug concentration (C) after a single dose is given by:

$$C = \sum_{i=1}^{n} A_i \exp(-k_i t) \qquad \text{(Eq. 1)}$$

where A_i and k_i are drug specific constants with units of concentration and reciprocal time, respectively; k_i values are independent of dose; $k_1 > k_2 \ldots > k_n$. The total area under the drug concentration–time curve after a single dose (AUC) is obtained by integrating Eq. 1 with respect to time:

$$\text{AUC} = \int_0^\infty C\,dt = \sum_{i=1}^{n} A_i/k_i \qquad \text{(Eq. 2)}$$

The total area under the first moment *versus* time curve after a single dose (AUMC) is given by the following integral:

$$\text{AUMC} = \int_0^\infty Ct\,dt = \sum_{i=1}^{n} A_i/(k_i)^2 \qquad \text{(Eq. 3)}$$

The analogous equations that apply to a dosing interval at steady state are as follows:

$$C_{ss} = \sum_{i=1}^{n} A_i \exp(-k_i t)/[1 - \exp(-k_i \tau)] \qquad \text{(Eq. 4)}$$

$$\text{AUC}_{ss} = \int_0^\tau C_{ss}dt = \sum_{i=1}^{n} A_i/k_i \qquad \text{(Eq. 5)}$$

$$\text{AUMC}_{ss} = \int_0^\tau C_{ss}t\,dt = \sum_{i=1}^{n} \frac{A_i}{(k_i)^2} \times \frac{[1 - \exp(-k_i\tau)] - k_i\,\tau \exp(-k_i\tau)}{1 - \exp(-k_i\tau)} \qquad \text{(Eq. 6)}$$

where τ is the fixed dosing interval. Note that Eqs. 2 and 5 are equivalent.

However, the relationship between $AUMC_{ss}$ and AUMC is given by the following ratio:

$$\frac{\text{AUMC}_{ss}}{\text{AUMC}} = \sum_{i=1}^{n} \frac{A_i}{(k_i)^2} \times \left[1 - \frac{k_i\,\tau \exp(-k_i\,\tau)}{[1 - \exp(-k_i\,\tau)]}\right] \Big/ \sum_{i=1}^{n} A_i/(k_i)^2 \qquad \text{(Eq. 7)}$$

Clearly, attempting to calculate t or V_{ss} by replacing AUMC with $AUMC_{ss}$ would provide incorrect answers, because $AUMC_{ss} < AUMC$.

We wish to propose an alternate, noncompartmental method to calculate pharmacokinetic parameters during repetitive dosing. This method may be called reverse superposition because a single dose curve is derived from data obtained during the second, third, or nth dosing interval. It is not limited to steady state but does require that subsequent doses be given during the postabsorptive, postdistributive phase of the previous dose. Each data point on the single-dose curve is calculated by means of the following equation:

$$C(t) = C_i(t) - C_i(0) \exp(-k_n t) \qquad \text{(Eq. 8)}$$

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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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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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