New Compartment- and Model-Independent Method for Rapid Calculation of Drug Absorption Rates

WIN L. CHIOU

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Abstract □ A simple and rapid method for the absorption rate calculation for drugs exhibiting linear pharmacokinetics is proposed. The method employs the novel instantaneous midpoint-input principle, which assumes that all drug absorbed during a given interval, regardless of the complexity of the absorption kinetics, is absorbed instantaneously at the midpoint of the interval. The drug amount absorbed is calculated by comparing the net plasma level resulting from the absorption during that interval with the plasma drug level obtained after intravenous dosing at the midpoint of the absorption interval. The method does not assume any compartments or models commonly used in pharmacokinetic studies. In examples with markedly different pharmacokinetic properties, the new method yielded accurate results almost identical to those obtained with the standard Wagner–Nelson and Loo–Riegelman methods. The method often is accurate to two to four significant figures in absorption rate calculations. For first-order absorption, the new method appears to be less subject to the influence of timing of the first blood sample. Theoretically, information on only a small portion of the intravenous plasma level–time profile is sufficient for the analysis. Data on plasma levels shortly after intravenous dosing and the terminal biological half-life are not always needed. Thus, the method might be particularly useful for drugs with long or uncertain biological half-lives. Theoretically, the method also can be applied to urine or saliva data. The method assumes the same drug disposition kinetics between the intravenous and absorption studies.

Keyphrases □ Drug absorption—compartment- and model-independent calculation for drugs with linear pharmacokinetics □ Pharmacokinetics, linear—compartment- and model-independent drug absorption calculation □ Absorption—compartment- and model-independent calculation for drugs with linear pharmacokinetics □ Instantaneous midpoint–input principle—drug absorption, linear pharmacokinetics

Calculation of the drug absorption rate from various dosage forms or administration routes is important in biopharmaceutical and pharmacokinetic studies. Many methods for calculating the absorption rate have been reported or reviewed (1–17). The original Wagner–Nelson (1) and Loo–Riegelman (2) methods have been the most widely and successfully used numerical methods in the past decade.

BACKGROUND

The original Wagner–Nelson method (1) is based on the linear one-compartment open model for drug disposition. Since the disposition kinetics of almost all drugs can be described more accurately by multicompartment models (2, 18), its use in many cases can be viewed only as an approximation. Precautions for using this method were discussed previously (2–4).

The Loo–Riegelman method (2) can be used for drugs exhibiting linear multicompartment properties. The method was derived based on multicompartment models in which drug elimination was assumed to take place exclusively from the central compartment (2). Although such an assumption probably is correct for most drugs, for some drugs various degrees of elimination probably also can take place in the tissue or peripheral compartments. However, it was shown subsequently that such an assumption is not necessary for the correct calculation of absorption rates (10, 15). In addition, the pharmacokinetic parameters of the drug in the body are assumed to remain the same during intravenous and absorption studies (2). For intrasubject variation in the terminal biological half-life during intravenous and oral studies, a new elimination rate constant from the central compartment must be used. This new rate constant is calculated based on the assumption that the central compartment volume and the intercompartmental first-order transfer rate constants remain the same (19).

Three approximations are made in the derivation of the final equations used in the original Loo–Riegelman method:

1. The linear trapezoidal rule method is used to estimate the area under the plasma level–time curve for the calculation of the drug amount eliminated from the body during a time interval. Such an approximation method also is employed in the Wagner–Nelson method. The accuracy of the linear trapezoidal rule method for calculating the area under the curve was discussed (15, 20, 21). An improper blood sampling schedule during absorption might result in significant errors in the estimate of the plasma area and, hence, the absorption rate calculation.
2. The plasma level is assumed to change linearly with time in the calculation of the drug distribution rate from the central compartment to the tissue or peripheral compartment. Again, various degrees of under- or overestimation probably occur if an improper blood sampling schedule is employed.
3. The two-term Taylor expansion series is used as a substitution for the exponential term in the equation. Such an approximation occasionally may result in serious errors. As a result, a three-term Taylor expansion series (4) or one without the Taylor series (16) was recommended.

Despite the assumptions and approximations for solving the absorption differential equation, the method has yielded excellent results (16).

This article reports a new, simple, compartment- and model-independent method for the rapid calculation of the absorption rate of drugs exhibiting linear pharmacokinetics. No assumptions regarding specific pharmacokinetic models or the drug elimination site from the body are necessary. Although the development of this method is empirical, it generally is highly accurate when properly used and might be satisfactory for many pharmacokinetic studies. Such use is analogous to the empirical use of the linear trapezoidal rule method for estimation of the area under the curve (20, 21).

THEORETICAL

It was shown (22, 23) that the plasma drug concentration after the constant intravenous infusion period for the one-compartment open model system can be approximated by assuming that the entire infused dose is injected instantaneously into the body as a bolus dose at the midpoint of the infusion period. Errors in such an approximation are negligible or insignificant when the infusion period to biological half-life ratios are low (22). For example, the error is ~0.1% when the ratio is 0.25.

In absorption studies, the plasma drug concentration of the first blood sample shortly after dosing, $C^{o}_{pt_1}$, also might be approximated satisfactorily by assuming that all drug absorbed up to the first sampling time, t_1, is absorbed instantaneously at the midpoint of the absorption period (*i.e.*, $0.5t_1$). The drug amount absorbed into the general circulation up to t_1 then can be calculated by comparing the $C^{o}_{pt_1}$ value with the theoretical plasma drug concentration, $C^{iv}_{p0.5t_1}$, at the midpoint of the absorption period (*i.e.*, $0.5t_1$) after an intravenous bolus dose. The drug amount absorbed between the first (t_1) and second (t_2) blood sampling periods can be estimated by the same principle after correction for the plasma level contribution, $C^{o}_{pp_1}$, at t_2 from the drug absorbed prior to t_1. Again, to calculate $C^{o}_{pp_1}$, all drug absorbed prior to t_1 is assumed to be absorbed instantaneously at $0.5t_1$. This can be done as follows: $C^{o}_{pp_1}$ = fraction of dose absorbed during the first absorption period × $C^{iv}_{p(t_2-0.5t_1)}$, where $C^{iv}_{p(t_2-0.5t_1)}$ is the theoretical plasma concentration at $(t_2 - 0.5t_1)$ when the same extravascular dose is given intravenously as a bolus. The same principle then can be used to calculate the drug amounts absorbed during other sampling intervals. The known or estimated absorption lag time should be corrected for the calculation of absorption periods.

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Table I—Comparisons of the Absorption Rates Calculated by the Loo–Riegelman Method and the New Method for Example 1

Hours	C_p[a]	C_p[b]	Cumulative Fraction Absorbed			
			Reported[c]	Calculated[d]	Theoretical[e]	Calculated[f]
0.5	3.0	3.36	0.165	0.1654	0.1853	0.1852
1.0	5.2	5.48	0.316	0.3167	0.3364	0.3357
1.5	6.5	6.77	0.437	0.4378	0.4594	0.4587
2.0	7.30	7.48	0.540	0.5401	0.5596	0.5584
2.5	7.60	7.83	0.618	0.6184	0.6412	0.6404
3.0	7.75	7.92	0.687	0.6865	0.7077	0.7077
3.5	7.70	7.85	0.742	0.7410	0.7619	0.7619
4.0	7.60	7.68	0.790	0.7882	0.8060	0.8060
5.0	7.10	7.19	0.854	0.8529	0.8713	0.8711
6.0	6.60	6.64	0.901	0.8990	0.9146	0.9143
7.0	6.00	6.10	0.926	0.9245	0.9433	0.9430
9.0	5.10	5.16	0.958	0.9575	0.9750	0.9747

[a] Based on data reported in Ref. 2. [b] Based on data generated by the first-order input equation using Eq. A8 in the *Appendix* where $K = 0.41\ hr^{-1}$. [c] Based on data reported in Refs. 2 and 4. [d] Based on the new method. [e] Based on $(1 - e^{-K_a t})$, where $K_a = 0.41\ hr^{-1}$. [f] Based on the newly generated C_p data shown in Column 3 of this table and the new method for absorption rate calculations.

The proposed method also can be described mathematically:

$$f_1 = \frac{C^o_{pt_1}}{C^{iv}_{p0.5t_1}} \qquad \text{(Eq. 1)}$$

where f_1 is the dose fraction absorbed up to t_1, expressed in terms of the fraction of the intravenous bolus dose. If the same dose is used in both intravenous and oral absorption studies, then the f_1 value will equal exactly the fraction of the oral dose absorbed into the general circulation up to t_1. The dose fraction absorbed during each subsequent period can be calculated by:

$$f_2 = \frac{C^o_{pt_2} - C^o_{pp_1}}{C^{iv}_{p0.5(t_2-t_1)}} \qquad \text{(Eq. 2)}$$

$$f_3 = \frac{C^o_{pt_3} - (C^o_{pp_1} + C^o_{pp_2})}{C^{iv}_{p0.5(t_3-t_2)}} \qquad \text{(Eq. 3)}$$

$$f_n = \frac{C^o_{pt_n} - \sum_{i=1}^{n-1} C^o_{pp_i}}{C^{iv}_{p0.5(t_n-t_{n-1})}} \qquad \text{(Eq. 4)}$$

The $C^o_{pp_i}$ value for the calculation of absorption in each period (Eq. 1, 2, or 4) is different, although the same symbol is used in these equations. For example, for the calculation of f_n in Eq. 4, the values are: $C^o_{pp_1} = f_1 C^{iv}_{p(t_n-0.5t_1)}$, $C^o_{pp_2} = f_2 C^{iv}_{p(t_n-0.5t_1-0.5t_2)}$, $C^o_{pp_3} = f_3 C^{iv}_{p(t_n-0.5t_2-0.5t_3)}$, and $C^o_{pp_{n-1}} = f_{n-1} C^{iv}_{p(t_n-0.5t_{n-2}-0.5t_{n-1})}$.

EXPERIMENTAL

Since this method was developed empirically, its validity must be examined using many examples with different disposition kinetic characteristics under various conditions such as first-order and zero-order absorptions.

Example 1—Loo and Riegelman (2) discussed a detailed theoretical example to illustrate the application of their method for a two-compartment open model system. Their absorption profile was reanalyzed using the proposed method. Close agreement between the two methods would support the applicability of the new method. Based on their microscopic rate constants (2) and other relevant data, the following biexponential plasma level equation may be obtained if the entire dose is injected instantaneously into the general circulation:

$$C_p = 12.37e^{-0.684t} + 7.857e^{-0.0725t} \qquad \text{(Eq. 5)}$$

where t is in hours.

Table II—Comparisons of Absorption Rates of Sulfisoxazole Calculated by the Proposed Method with the Theoretical Values following First-Order Absorption Kinetics

Hours	C_p[a], mg/liter	Cumulative Dose Fraction Absorbed	
		Calculated	Theoretical[b]
0.5	65.58	0.2925	0.2928
1.0	98.20	0.4994[c]	0.5000
1.5	113.29	0.6457	0.6464
2.0	118.95	0.7491[d]	0.7499
2.5	119.45	0.8222	0.8232

[a] Plasma levels after absorption study. [b] Based on $(1 - e^{-K_a t})$, where $K_a = 0.693\ hr^{-1}$. [c] With the assumption that the first blood sample was obtained at 1.0 hr, the calculated dose fraction absorbed would be 0.4977. [d] With the assumption that the first blood sample was obtained at 2 hr, the calculated dose fraction would be 0.7349.

The first-order absorption rate constant used in their simulation was $0.41\ hr^{-1}$. Some detailed absorption rate calculations based on this new method are illustrated in the *Appendix*, and the analysis results are summarized in Table I.

Example 2—The following mean biexponential equation was obtained after a bolus intravenous injection of 2000 mg of sulfisoxazole to seven normal subjects (24):

$$C_p = 108.43e^{-1.393t} + 152.13e^{-0.12t} \qquad \text{(Eq. 6)}$$

where C_p is in micrograms per liter and t is in hours.

Theoretical plasma drug concentrations at various times using a first-order absorption rate constant of $0.693\ hr^{-1}$ were generated in part with a programmable calculator. The dose used for absorption simulation also was 2000 mg. The plasma level data up to 2.5 hr after dosing are summarized in Table II.

The absorption simulation data generated throughout this discussion are based on a compartment- and model-independent approach. This approach is in contrast with the more commonly used compartmental approach. The general equation of the plasma level profile after a first-order input with an initial one-unit dose into a system where drug disposition kinetics following the intravenous bolus injection of the same unit of dose can be described by a polyexponential equation ($C_p = \Sigma_{i=1}^{n} A_i e^{-K_i t}$) is shown in the *Appendix*.

Example 3—The following mean biexponential equation was obtained after a bolus intravenous injection of 615 mg of ampicillin to nine subjects (25):

$$C_p = 120.4e^{-2.40t} + 12.12e^{-0.39t} \qquad \text{(Eq. 7)}$$

where C_p is in milligrams per liter and t is in hours.

The plasma level profile (Table III) during the early absorption phase was generated based on an initial dose of 615 mg and a first-order absorption rate constant of $2.0\ hr^{-1}$.

Example 4—The mean plasma level profile following the intravenous rapid injection of 10 mg of diazepam to four subjects (26) can be expressed by the following triexponential equation:

$$C_p = 0.23e^{-4.62t} + 0.15e^{-0.41t} + 0.062e^{-0.0225t} \qquad \text{(Eq. 8)}$$

where C_p is in milligrams per liter and t is in hours.

Based on the same intravenous dose absorbed with a first-order rate constant of $0.693\ hr^{-1}$, the plasma level data during the first 2.5 hr after dosing are summarized in Table IV.

Example 5—The drugs described in Examples 1–4 were infused at a unit intravenous bolus dose (the same intravenous dose used individually in each example) per hour to the same subjects. Theoretical plasma

Table III—Comparisons of Absorption Rates of Ampicillin Calculated by the New Method with Theoretical Values following First-Order Absorption Kinetics

Hours	C_p[a], mg/liter	Cumulative Dose Fraction Absorbed	
		Calculated	Theoretical[b]
0.25	39.27	0.3898	0.3935
0.50	46.99	0.6263	0.6321
1.0	35.02	0.8510	0.8647

[a] Plasma levels after absorption study. [b] Based on $(1 - e^{-K_a t})$, where $K_a = 2.0\ hr^{-1}$.

Table IV—Comparisons of Absorption Rate Analysis of Diazepam (Three-Compartment Model) Calculated by Two Methods with the Theoretical Values following First-Order Absorption Kinetics (K_a = 0.693 hr^{-1})

Hours	C_p[a], mg/liter	Fractional Absorption Rate during Each Study Period		Cumulative Dose Fraction Absorbed		
		Theoretical[b]	Calculated[c]	Theoretical[d]	Calculated[c]	Calculated[e]
0.5	0.082204	0.2928	0.3050	0.2928	0.3050	0.2767
			(4.17)		(4.17)[f]	(−5.55)[f]
1.0	0.1106	0.2072	0.2085	0.5000	0.5135	0.4874
			(0.63)		(2.7)	(−2.53)
1.5	0.1223	0.1464	0.1451	0.6464	0.6586	0.6339
			(−0.89)		(1.89)	(−1.95)
2.0	0.1253	0.1035	0.1018	0.7499	0.7604	0.7388
			(−1.64)		(1.4)	(−1.74)
2.5	0.1233	0.0733	0.07189	0.8232	0.8323	0.8132
			(−1.92)		(1.1)	(−1.22)
1.0	0.1106	0.5000	0.5361[g]	0.5000	0.5361[g]	0.4497[g]
			(7.22)		(7.22)	(−10.1)

[a] Plasma levels after absorption study. [b] Calculated from Column 5 of this table. [c] Based on the new method. [d] Based on $(1 - e^{-K_a t})$. [e] Based on Loo–Riegelman method. [f] Percent over- or underestimation of the absorption of the new method as compared to theoretical results. [g] Based on the first blood sample collected 1 hr after dosing.

level data at various times after the beginning of infusion were generated by the programmable calculator based on a compartment- and model-independent equation (see *Appendix*).

RESULTS AND DISCUSSION

The results of the absorption rate calculation using the standard Loo–Riegelman method (2, 4) and the proposed method for Example 1 are summarized in Table I. The values for cumulative dose fractions absorbed from 0.5 to 9.0 hr after dosing obtained from the two methods were essentially identical (up to three significant figures for some data). Since absorption was assumed to follow first-order kinetics with a rate constant, K_a, of 0.41 hr^{-1}, the cumulative dose fraction, F_t, absorbed at various times can be determined theoretically by:

$$F_t = 1 - e^{-K_a t} \qquad \text{(Eq. 9)}$$

These theoretical values are summarized in Table I; compared to them, the absorption rates calculated by the two methods were underestimated. Recalculation of theoretical plasma level data based on Eq. A2 in the *Appendix* revealed slight discrepancies between the reported values (2, 4) and the newly generated values (Table I). Using these new plasma level data and the proposed absorption rate calculation, the calculated cumulative dose fractions (Table I) absorbed at various times were essentially identical (identical values up to four significant figures for data at 3, 3.5, and 4 hr) to the theoretical values. These results were encouraging during early evaluation of the new method.

The total area under the plasma level–time curve from Eq. 5 calculated by the integration method was essentially identical to the total area from the absorption study reported (4) (126.46 *versus* 126.44), indicating the correctness of Eq. 5. In the absorption rate analyses, 97.5% of the dose theoretically was absorbed at 9 hr after dosing.

The results of the absorption study on sulfisoxazole (Example 2), which exhibited two-compartment properties, are summarized in Table II. The excellent accuracy of the new method also was demonstrated in this example. The first blood sample, obtained 1 or 2 hr after dosing, gave calculated fractions of the dose absorbed of 0.4977 and 0.7349, respectively. These values compared well with the corresponding theoretical values: 0.5000 and 0.7491.

The results for ampicillin (Example 3) are shown in Table III. This drug was selected due to its relatively large contribution of the distribution phase (21.5% of the total area, AUC_∞). A high degree of accuracy also was observed with the new method.

The results of the absorption rate analysis of diazepam in Example 4 are summarized in Table IV. Despite its three-compartment characteristics, errors of the absorption rate estimate for each sampling period and the cumulative absorption calculated by the new method were insignificant, except for the first 0.5-hr point where absorption was overestimated by 4.17%. The overestimation for the 0.5–1.0-hr period was only 0.63%, and the underestimations for the next three sampling periods were <2% (Table IV). The accuracy of the new method was improved considerably if the first blood sample was obtained at an earlier time. For example, the overestimation was reduced to only 1.48% when the 0.25-hr plasma level (0.05382 mg/liter) was used for calculation.

The Loo–Riegelman method without the Taylor expansion series also was employed to calculate the diazepam absorption rate discussed in Example 4. The results are summarized in Table IV. The Loo–Riegelman method underestimated absorption up to 0.5 hr by 5.55%, which was slightly greater (based on absolute percent) than the 4.17% underestimation based on the new method. In this example, the new method always overestimated the cumulative absorption values (up to 2.5 hr) while the Loo–Riegelman method always underestimated them. However, the absolute percentages of over- or underestimation by these two methods were practically the same (Table IV). The accuracy of both methods for calculating the diazepam absorption rates was demonstrated by the fact that, at 2.5 hr after dosing when 82.32% of the dose had been absorbed, the new method overestimated the absorption by 1.1% while the Loo–Riegelman method underestimated it by 1.22% (Table IV).

The new method also had essentially the same accuracy as the Wagner–Nelson method on theoretical compounds with one-compartment characteristics.

These results clearly demonstrate the accuracy and applicability of the new simple method for the calculation of absorption rates of compounds with markedly different pharmacokinetic properties under first-order absorption. In Examples 1 and 4, both the new method and

Table V—Comparisons of Results of Absorption Rate Calculations Based on the Loo–Riegelman Method and the New Method for Example 1 if Only One Plasma Level at Various Times after Absorption Study Is Used

Time for First Sample, hr	C_p	Fraction Absorbed		Theoretical Fraction Absorbed
		Based on Loo–Riegelman Method	Based on New Method	
1	5.484	0.3283	0.3351	0.3364
		(−2.37)[a]	(−0.357)[a]	
2	7.481	0.5172	0.5521	0.5596
		(−7.58)	(−1.34)	
3	7.921	0.6135	0.6900	0.7077
		(−13.3)	(−2.50)	
4	7.681	0.6529	0.7723	0.8060
		(−19.0)	(−4.18)	
5	7.191	0.6613	0.8179	0.8713
		(−24.1)	(−6.13)	
6	6.638	0.6534	0.8392	0.9146
		(−28.6)	(−8.24)	

[a] Percent deviation from the theoretical value.

Table VI—Results of the Zero-Order Absorption Rate Analysis of a Hypothetical Drug in Examples 1 and 5 Calculated by the New Method

Hours	C_p	Cumulative Theoretical Fraction of Unit Intravenous Dose Absorbed	Fraction of Unit Intravenous Dose Absorbed Calculated by New Method
0.25	4.786	0.2500	0.2500
0.50	9.095	0.5000	0.5003
0.75	14.85	0.7500	0.7506
1.00	16.54	1.0000	1.0004

Table VII—Results of the Zero-Order Absorption Rate Analysis of Sulfisoxazole and Ampicillin Calculated by the New Method and the Loo–Riegelman Method

Drug	Hours	C_p, mg/liter	Theoretical Cumulative Fraction of Unit Intravenous Dose Absorbed	Fraction of Unit Intravenous Dose Absorbed	
				Calculated by New Method	Calculated by Loo–Riegelman Method
Sulfisoxazole	0.5	112.9	0.5000	0.5036 (0.72)[a]	0.4976 (−0.49)[a]
	1.0	201.9	1.0000	1.0062 (0.62)	0.9970 (−0.303)
	1.5	277.0	1.5000	1.5077 (0.513)	1.4968 (−0.216)
	2.0	343.5	2.0000	2.0091 (0.455)	1.9971 (−0.146)
Ampicillin	0.25	25.52	0.2500	0.2533 (1.32)	0.2454 (−1.85)
	0.50	40.56	0.5000	0.5065 (1.30)	0.4932 (−1.36)
	0.75	49.76	0.7500	0.7597 (1.29)	0.7425 (−1.00)
	1.00	55.65	1.0000	1.0127 (1.27)	0.9925 (−0.75)

[a] Percent difference from the theoretical value.

the standard Loo–Riegelman method yielded essentially the same results, indicating the similar accuracy of both methods.

In absorption rate studies, the first blood sample occasionally is not collected soon after dosing. Evaluation of the effect of the time of the first blood sample on the accuracy of the new method was important. This effect was evaluated thoroughly using the data in Example 1. Results of comparisons using the first plasma level at 1, 2, 3, 4, 5, or 6 hr are summarized in Table V. This example shows that the new method is much less subject to the influence of the timing of the first sample. For example, with samples at 4, 5, and 6 hr, the new method gave underestimations in absorption of 4.18, 6.13, and 8.24%, respectively, while the Loo–Riegelman method gave underestimations of 19.0, 24.1, and 28.6%, respectively. For diazepam (Example 4), the new method resulted in a 7.22% overestimation, and the Loo–Riegelman method (without the Taylor expansion series) yielded a 10.1% underestimation if the first sample at 1 hr was used. The results for the new method are encouraging since the majority of drug absorption kinetics reported in the literature appear to follow the first-order process. Frequent blood sampling and the use of interpolated plasma level data between adjacent observed points were recommended for obtaining greater accuracy when applying the Loo–Riegelman method to oral data (15).

The accuracy of the new method under zero-order absorption was evaluated also. Extremely accurate (identical up to three or four significant figures in many cases) results were obtained for the hypothetical drug discussed in Example 1, ampicillin, and sulfisoxazole (Tables VI and VII). For sulfisoxazole and ampicillin, the results from the Loo–Riegelman method without the Taylor approximation were equally accurate (Table VII). For diazepam, which exhibited triexponential decay after intravenous dosing, the new method overestimated the absorption (Table VIII) in the first 2.5 hr of simulation. The overestimation was the greatest (6.5%) in the first 0.5 hr of study and decreased gradually (only 1.2% between 2.0 and 2.5 hr). The overestimation was reduced to only 2.2% when the first blood sample was taken at 0.25 hr after the beginning of the zero-order absorption. Considering the variability in the biological system and the accuracy of the dose administered and the plasma levels analyzed, these overestimations can be regarded as insignificant. However, the Loo–Riegelman method yielded more accurate results in this example (Table VIII). For example, it resulted in only a 3.43% underestimation when the first sample at 0.5 hr was used for calculation.

The oral absorption kinetics of sulfadimethoxine in a steer were reported previously (16). The steer, 190.68 kg, was given an initial oral dose of 12.5 g; blood samples were collected at 4, 8, 12, and 24 hr after dosing. Approximately 5 months later, the same animal, weighing 266.8 kg, received a rapid intravenous injection of 17.502 g. The plasma level profile after intravenous injection was described by a triexponential equation, which corresponded to a three-compartment open model (16). The absorption rates were calculated by the Loo–Riegelman method with and without the Taylor approximation.

Since the body weights of the steer during the oral and intravenous studies were different, an approximation assuming that the intercompartmental distribution rate constants remained constant during the two studies was made (16). In other words, intercompartmental clearances were assumed to increase with increasing body weight, as reflected by changes in the volume of distribution. In applying the proposed method for the absorption rate calculation to this example, only the coefficients of the triexponential plasma level decay equation were inversely corrected for the body weight change (*i.e.*, the volume of the central or initial compartment was proportional to the body weight). Thus, the C_p profile after a 1.0-g intravenous bolus dose at the time of the oral study can be expressed by:

$$C_p = 16.00e^{-9.11t} + 5.281e^{-0.55t} + 15.36e^{-0.0580t} \quad \text{(Eq. 10)}$$

when C_p is in milligrams per liter and t is in hours.

The results of the absorption rate analysis using the new method and the Loo–Riegelman method without the Taylor approximation were similar and encouraging (Table IX); the difference in the cumulative absorption at 24 hr was only 1.56%. The facts that the absorption rate appeared to follow approximately the first-order process (16) and that the first sample was collected only 4 hr after dosing may partially explain why the cumulative absorption at 4 hr calculated by the new method was 8.17% higher than that obtained with the Loo–Riegelman method (in view of the data in Table V). The validity of the new method in the flip-flop absorption condition also was confirmed.

The results of the extensive example analyses clearly demonstrate that the new method might be potentially useful for absorption rate calculations. Its simplicity is shown clearly in the *Appendix*. In contrast to the standard Loo–Riegelman method, the present method does not require the assumption of any pharmacokinetic compartmental model and the calculation of microscopic compartmental constants. Such calculations would be complicated in the classical three-, four-, or five-compartment mammillary model systems (27, 28). The volume of the central compartment (the initial volume of distribution) also is not needed.

Furthermore, the plasma level profile shortly after intravenous dosing theoretically does not need to be known in the new method. For example, the intravenous plasma data before 0.25, 0.75, and 0.125 hr were not necessary in the absorption rate calculations in Examples 1, 2, and 4, respectively. This feature of the new method may be important since drug disposition kinetics immediately or shortly after intravenous dosing often are much more complicated than commonly assumed or understood in conventional pharmacokinetic studies (29). In addition, the apparent value of the volume of the central compartment and the apparent number of compartments in the multicompartment analysis often may be subject to the influence of the frequency and timing of the blood sampling schedule in intravenous studies (30).

Moreover, the new method requires an accurate plasma level profile in the intravenous study for only a short period. For example, the intravenous data up to only 8.75 hr were required for the absorption rate calculation in Example 1. The terminal biological half-life of this hypothetical compound is 9.56 hr. For sulfisoxazole in Example 2, the intravenous data up to 2.25 hr were sufficient for the absorption rate calculation. The terminal half-life of the drug in this example is 5.78 hr. Therefore, if the individual or mean pharmacokinetic parameters (*i.e.*, the disposition function discussed in the *Appendix*) between the intra-

Table VIII—Comparisons of the Zero-Order Absorption Rate Analysis of Diazepam in Examples 4 and 5 Calculated by the Loo–Riegelman Method and the New Method

Hours	C_p, mg/liter	Cumulative Fraction of Unit Intravenous Dose Absorbed: Theoretical	Calculated by New Method	Calculated by Loo–Riegelman Method
0.5	0.1435	0.5000	0.5325 (6.50)[a]	0.4829 (−3.43)[a]
1.0	0.2337	1.0000	1.0472 (4.72)	0.9875 (−1.25)
1.5	0.3092	1.5000	1.5558 (3.72)	1.4897 (−0.686)
2.0	0.3758	2.0000	2.0629 (3.15)	1.9908 (−0.457)
2.5	0.4351	2.5000	2.5690 (2.76)	2.4912 (−0.352)
0.25[b]	0.08520	0.25000	0.2555 (2.2)	0.2459 (−1.64)

[a] Percent deviation from the theoretical value. [b] Data are based on the first blood sample collected at 0.25 hr.

venous and oral studies in the same subject or same panel of subjects may be assumed to be the same, the present method may be applied without knowledge of the terminal biological half-life of the drug as long as the intravenous data during a certain period can be obtained or generated accurately. This feature could be valuable for drugs with long biological half-lives (*e.g.*, greater than several days or weeks). As an approximation for the absorption rate calculation, the needed plasma level data can be obtained directly from a semilogarithmic intravenous data plot.

Despite these advantages, experimental protocols for studying complete plasma level profiles are recommended. For more accurate determination of absorption kinetics, a sufficient number of blood samples should be collected in absorption studies. The present method also might be used (perhaps as a good approximation) for drugs showing unusual plasma level profiles due to extensive enterohepatic circulation. Similarly, the method probably can be used with some salivary or urinary data obeying linear pharmacokinetic principles. Precautions in using saliva level data for pharmacokinetic studies were discussed previously (31–34).

The most unique assumption made in the proposed method is that all of the drug absorbed during a given interval, regardless of the complexity of the true absorption kinetics, is absorbed instantaneously at the midpoint of the interval. This assumption now has been shown to result in useful and practical applications for the determination of the apparent volume of distribution and total body clearance after a constant-rate intravenous drug infusion (22, 23) and for the absorption rate calculation. The method using such an assumption will be referred to as the instantaneous midpoint-input method.

The absolute accuracy of this new method for absorption rate calculations is a function of many factors such as the absorption rate, the drug disposition function, and the blood sampling schedule. This dependence is similar to the problems of the accuracy of the trapezoidal rule method for the estimation of the area under the curve (21) and the instantaneous midpoint-input method for the estimation of the volume of distribution and total body clearance (22, 23). Many digital computer programs also are available for the calculation of drug absorption rates (3, 4, 35).

APPENDIX

Sample Calculations Using New Method for Example 1—Absorption rate calculations based on the oral data reported in the literature (2, 4) in the first 1.5 hr after dosing are used for illustration. The oral data were taken from Table I. The intravenous data were generated from Eq. 5. They are 18.14, 14.85, and 12.437 at 0.25, 0.75, and 1.25 hr, respectively.

The dose fraction absorbed up to 0.5 hr, $f_{0.5\text{ hr}}$, is:

$$f_{0.5\text{ hr}} = \frac{C^o_{p0.5\text{ hr}}}{C^{iv}_{p0.25\text{ hr}}} = \frac{3.0}{18.14} = 0.1654 \qquad \text{(Eq. A1)}$$

The dose fraction absorbed between 0.5 and 1 hr, $f_{1\text{ hr}}$, is calculated from:

$$\text{contribution from 0 to 0.5 hr } (C^o_{pp0.5\text{ hr}}) = C^{iv}_{p0.75\text{ hr}} \times f_{0.5\text{ hr}} \qquad \text{(Eq. A2}a\text{)}$$

$$= 14.85 \times 0.1654 \qquad \text{(Eq. A2}b\text{)}$$

$$= 2.456 \qquad \text{(Eq. A2}c\text{)}$$

Table IX—Comparisons of Absorption Rate Calculations of Sulfisoxazole in a Steer by the Loo–Riegelman Method and the New Method

Hours	Cumulative Amount Absorbed, mg: Based on Loo–Riegelman Method[a]	Based on New Method
4	3294	3563 (8.17)[b]
8	5445	5679 (4.30)
12	6525	6710 (2.83)
24	7610	7729 (1.56)

[a] Calculated from Ref. 16. [b] Percent overestimation as compared to the value obtained from the Loo–Riegelman method.

and:

$$f_{1\text{ hr}} = \frac{C^o_{p1\text{ hr}} - C^o_{pp0.5\text{ hr}}}{C^{iv}_{p0.25\text{ hr}}} = \frac{5.20 - 2.456}{18.14} = 0.1513 \qquad \text{(Eq. A3)}$$

Therefore, the cumulative dose fraction absorbed up to 1 hr = 0.1654 + 0.1513 = 0.3167.

The dose fraction absorbed between 1.0 and 1.5 hr, $f_{1.5\text{ hr}}$, is calculated from:

$$C^o_{pp0.5\text{ hr}} = C^{iv}_{p1.25\text{ hr}} \times f_{0.5\text{ hr}} = 12.437 \times 0.1654 = 2.057 \qquad \text{(Eq. A4)}$$

$$C^o_{pp1\text{ hr}} = C^{iv}_{p0.75\text{ hr}} \times f_{1\text{ hr}} = 14.85 \times 0.1513 = 2.247 \qquad \text{(Eq. A5)}$$

and:

$$f_{1.5\text{ hr}} = \frac{C^o_{p1.5\text{ hr}} - C^o_{pp0.5\text{ hr}} - C^o_{pp1\text{ hr}}}{C^{iv}_{p0.25\text{ hr}}} \qquad \text{(Eq. A6}a\text{)}$$

$$= \frac{6.5 - 2.057 - 2.247}{18.14} = 0.1211 \qquad \text{(Eq. A6}b\text{)}$$

Therefore, the cumulative dose fraction absorbed up to 1.5 hr = 0.3167 + 0.1211 = 0.4378. For the calculation of absorption between 7 and 9 hr, $C^{iv}_{p1.0\text{ hr}}$ rather than $C^{iv}_{p0.25\text{ hr}}$ should be used.

General Equation for Plasma Level Profile after First-Order Input—If it is assumed that after an instantaneous intravenous injection of a unit drug dose, the plasma level–time profile, $C_{p_{inst}}$, can be described adequately by the following polyexponential equation (disposition function):

$$C_{p_{inst}} = \sum_{i=1}^{n} A_i e^{-K_i t} \qquad \text{(Eq. A7)}$$

the general equation to describe its plasma level profile, C_p, after the same unit drug dose with a first-order absorption rate constant, K_a, can be derived by using the input–output convolution method with the assistance of the Laplace transform technique (36). The general equation derived is:

$$C_p = K_a \sum_{i=1}^{n} \frac{A_i}{K_i - K_a} (e^{-K_a t} - e^{-K_i t}) \qquad \text{(Eq. A8)}$$

In absolute terms, Eq. A7 is incorrect because the plasma drug level at the sampling site immediately after dosing (*i.e.*, time = zero) is zero due to a definite lag time of the drug to be transported from the injection site to the sampling site and the complicated disposition kinetics shortly after dosing (29).

General Equation for Plasma Level Profile after Zero-Order Input—When the zero-order absorption rate is K_0 unit of dose per unit of time, the general equation to show the plasma level profile, C_p, during the zero-order absorption can be derived similarly as:

$$C_p = K_0 \left(\sum_{i=1}^{n} \frac{A_i}{K_i} - \sum_{i=1}^{n} \frac{A_i}{K_i} e^{-K_i t} \right) \qquad \text{(Eq. A9)}$$

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Oxygen Solubilization in Egg Lecithin Dispersed in Distilled Water and Physiological Electrolyte Fluids

R. SAUL LEVINSON *[x], SERAP BUYUKYAYLACI [‡], and LOYD V. ALLEN, Jr. [§]

Received April 10, 1979, from the **Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, NY 11201*, the [‡]*School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47907*, and the [§]*College of Pharmacy, University of Oklahoma, Oklahoma City, OK 73190.* Accepted for publication July 31, 1979.

Abstract □ Gaseous oxygen solubilization in egg lecithin dispersed in distilled water, saline, and a multi-ion physiological electrolyte solution was determined and compared to controls deficient in egg lecithin. Significant oxygen solubilization occurred in the presence of egg lecithin. Oxygen solubilization was significantly greater in saline and in the multi-ion physiological electrolyte solution than in distilled water.

Keyphrases □ Solubilization—of oxygen in egg lecithin dispersed in distilled water and physiological electrolyte fluids □ Lecithin, egg—dispersions in distilled water and physiological electrolyte fluids, oxygen solubilization □ Pulmonary surfactant model systems—egg lecithin dispersions in distilled water and physiological electrolyte fluids, oxygen solubilization □ Model systems, pulmonary surfactant—egg lecithin dispersions in distilled water and physiological electrolyte fluids, oxygen solubilization □ Oxygen—solubilization in egg lecithin dispersions in distilled water and physiological electrolyte fluids

Several studies (1–5) demonstrated that respiratory disease syndrome[1] is a direct result of a pulmonary surfactant deficiency. Mammalian lung surfactant was shown to be primarily dipalmitoyl phosphatidylcholine (I) (6–8). Since I also is the major constituent of egg (*Gallus domesticus*) lecithin (9), egg lecithin dispersions serve as convenient and relatively inexpensive pulmonary surfactant model systems.

[1] Hyaline membrane disease.

Micellar oxygen solubilization in lung surfactant was proposed (10) as a mechanism for oxygen transposition at the alveolar membrane. Other studies (11–14) demonstrated the ability of lung surfactant to solubilize oxygen and other nonpolar gases.

The effect of the presence of electrolytes at physiological concentrations on oxygen solubilization in aqueous egg lecithin dispersions is reported here.

EXPERIMENTAL

Glass reaction vials were cleaned ultrasonically[2] in 2% aqueous detergent[3], rinsed three times with tap water, and rinsed three times with deionized, glass-distilled water[4]. The vials were air dried in a ventilated oven at 200°.

Egg lecithin[5] was weighed accurately to yield 50-ml samples of 0.25, 0.50, 0.75, and 1.00% (w/v) phospholipid in normal saline[6], physiological electrolyte solution[7], and deionized, glass-distilled water. A magnetic

[2] Cole Palmer Co., Chicago, Ill.
[3] Alconox, New York, N.Y.
[4] Deionized through an exchange resin deionizer (Continental Water Service, Oklahoma City, Okla.) and then glass distilled.
[5] Lot 12073, United States Biochemical Corp., Cleveland, Ohio.
[6] Travenol Laboratories, Deerfield, Ill.
[7] Normosol-R, Abbott Laboratories, North Chicago, Ill. Contains sodium, potassium, magnesium, chloride, and bicarbonate ions in isotonic aqueous solution.

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