Disintegration–Dissolution Analysis of Percent Dissolved–Time Data

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Abstract □ A simple, graphical method is described for the disintegration–dissolution analysis of cumulative percent dissolved–time data. The technique is based on a biexponential equation with the assumption of first-order disintegration and dissolution according to a simple dissolution model. The dissolution data obtained for six commercial tablets and capsules adequately fit the developed equation. The described method is simple and can handle initial data points that are usually ignored by other techniques.

Keyphrases □ Disintegration–dissolution—analysis of percent dissolved–time data □ Dissolution model—method for analysis of percent dissolved–time data □ Pharmacokinetics—method for analysis of percent dissolved–time data

Most techniques used to interpret the percent dissolved–time data of tablets and capsules are based on semilogarithmic plots in which the early data points that precede the dissolution lag time are not considered (1–4). Kitazawa *et al.* (5, 6) utilized the initial data points and calculated the dissolution rate constants of uncoated tablets from the two straight lines obtained by plotting the dissolution data semilogarithmically against time. It was assumed that when the two lines intersect, the surface area greatly increases, causing a sudden increase in the dissolution rate. This assumption, however, is questionable since the change in the surface area is likely to be continuous. Furthermore, the early data points that most frequently form a curve above the terminal line (1) may be a function of both dissolution and disintegration. Drug release from conventional tablets or capsules usually involves two sequential time-dependent processes, disintegration (or content deaggregation for capsules) and dissolution, which occur simultaneously until disintegration is completed.

Drug release from a tablet having a rather idealized formulation was analyzed previously according to a disintegration–dissolution model; however, the mathematics involved are complicated and require computer programs, which may not be available or suitable for routine analysis of dissolution data (7, 8). This paper describes a simple graphical method for disintegration–dissolution analysis of percent dissolved–time data for commercial tablets or capsules in which all data points obtained were utilized and the dissolution and disintegration rate constants were estimated.

THEORETICAL

When a tablet or capsule dissolves, it first disintegrates (capsule disintegration implies shell dissolution and content deaggregation) into small particles which, in turn, due to their large surface area, release the drug into the dissolution liquid. A more detailed scheme comprising an additional step in which the drug dissolves directly from the tablet surface also was reported (9); however, the amount released through this step is very small and need not be considered.

If one assumes that disintegration and dissolution are first-order processes and that A, A_p, and A_s represent the amounts of drug in the dosage form, small particles, and solution, respectively, at any given time, $A \xrightarrow{k_d} A_p \xrightarrow{k_s} A_s$, the following differential equations can be written:

$$\frac{dA}{dt} = -k_d A \qquad \text{(Eq. 1)}$$

$$\frac{dA_p}{dt} = k_d A - k_s A_p \qquad \text{(Eq. 2)}$$

$$\frac{dA_s}{dt} = k_s A_p \qquad \text{(Eq. 3)}$$

where k_d and k_s are apparent first-order rate constants for disintegration and dissolution, respectively.

The Laplace transforms of Eqs. 1–3 are:

$$s\bar{A} - A_0 = -k_d\bar{A} \qquad \text{(Eq. 4)}$$

$$s\bar{A}_p = k_d\bar{A} - k_s\bar{A}_p \qquad \text{(Eq. 5)}$$

$$s\bar{A}_s = k_s\bar{A}_p \qquad \text{(Eq. 6)}$$

where the bar above the function and the s represent the Laplace transform for the function and A_0 is the amount of drug in the dosage form at time zero. Rearrangement of Eq. 4, substitution for $\bar{A}$ in Eq. 5, and rearrangement yield:

$$\bar{A}_p = \frac{k_d A_0}{(s + k_d)(s + k_s)} \qquad \text{(Eq. 7)}$$

Substituting for $\bar{A}_p$ in Eq. 6 and rearranging produce:

$$\bar{A}_s = \frac{k_s k_d A_0}{s(s + k_d)(s + k_s)} \qquad \text{(Eq. 8)}$$

which, when solved using Laplace transform table (8) and rearranged, gives:

$$A_0 - A_s = \frac{k_d A_0}{k_d - k_s} e^{-k_s t} - \frac{k_s A_0}{k_d - k_s} e^{-k_d t} \qquad \text{(Eq. 9)}$$

Multiplying both sides of Eq. 9 by $100/A_0$ yields:

$$100 - f_s = \frac{100 k_d}{k_d - k_s} e^{-k_s t} - \frac{100 k_s}{k_d - k_s} e^{-k_d t} \qquad \text{(Eq. 10)}$$

where $f_s = (A_s/A_0) \times 100$ is the cumulative percent dissolved at time t.

If disintegration is more rapid than dissolution (*i.e.*, $k_d > k_s$), which is generally the case (7), a semilogarithmic plot of $(100 - f_s)$ *versus* time results in a biexponential curve with a terminal linear segment whose slope is equal to $-(k_s/2.303)$. The apparent first-order disintegration rate constant (k_d) can be estimated from the plot using the method of residuals (10).

EXPERIMENTAL

Materials—Anhydrous theophylline[1], isoniazid[2], tetracycline hydrochloride[1], and ampicillin[3] were used for the preparation of standard curves as obtained. All tablet and capsule formulations tested (A[4], B[5], C[6], D[7], E[8], and F[9]) were purchased commercially.

Dissolution Studies—Dissolution tests were performed using a two-blade stirrer apparatus at 25 or 50 rpm. This apparatus was similar to the USP XIX apparatus, except that the basket assembly was replaced

[1] Sigma Co., St. Louis, Mo.
[2] BDH Ltd., Poole, England.
[3] The Upjohn Co., Kalamazoo, Mich.
[4] Isoniazid Tablets (50 mg), Hoffmann–La Roche, Basle, Switzerland.
[5] Theophylline Tablets (125 mg), Riker Laboratories, Northridge, Calif.
[6] Acetaminophen Tablets (500 mg), APM Co., Sult, Jordan.
[7] Ampicillin Capsules (250 mg), Wyeth Laboratories, Philadelphia, Pa.
[8] Tetracycline Hydrochloride Capsules (25 mg), Lagap SA, Lugano, Switzerland.
[9] Tetracycline Phosphate Capsules (250 mg), Bristol Italiana, Rome, Italy.

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Table I—Apparent First-Order Rate Constants and Preexponential Coefficients for Dissolution and Disintegration

Formulation Code	Dosage Form	Q_s[a]	k_s, min^{-1}	Q_d[a]	k_d, min^{-1}
A	Tablet	160.0	0.089	69.2	0.321
B	Tablet	246.4	0.250	143.0	0.461
C	Tablet	168.6	0.165	81.1	0.456
D	Capsule	127.6	0.0859	25.0	0.365
E	Capsule	120.3	0.0619	22.1	0.413
F	Capsule	259.7	0.103	166.8	0.203

[a] Q_s and Q_d are the preexponential coefficients for dissolution and disintegration, respectively [$Q_s = 100k_d/(k_d - k_s)$ and $Q_d = 100k_s/(k_d - k_s)$].

Table II—Experimentally Determined Disintegration Times (DT_{exp}) and Values Estimated According to Eq. 11 (DT_{calc})

Formulation	DT_{exp}, min ($n = 6$)	DT_{calc}, min	DT_{exp}/DT_{calc}
A	14.0[a] (1.47)[b]	13.0	1.08
B	10.4 (0.55)	9.02	1.15
C	6.77 (2.9)	9.12	0.74
D	11.4 (1.09)	11.4	1.0
E	9.92 (5.6)	10.1	0.98
F	24.6 (2.09)	20.5	1.2

[a] Mean. [b] Standard deviation.

by a 30-cm long glass shaft with one end attached to the motor and the other end equipped with a 7.6-cm glass blade connected in the center to the shaft. The dissolution medium, 900 ml of distilled water, was maintained at 37 ± 0.1°. The tablet or capsule was dropped directly into the vessel, and stirring and timing were initiated. At the indicated intervals (Fig. 1), 1-ml samples were withdrawn through a filtration unit[10] and analyzed spectrophotometrically at the maximum for each drug after suitable dilution.

Disintegration Test—Disintegration times were determined in the same apparatus used for the dissolution studies with a minor modification. This modification consisted of a slightly concave, round, 10-mesh stainless steel screen placed in the vessel horizontally and anchored on the wall so that the distance between the screen center and the vessel bottom was 1 cm. The disintegration test was carried out under the same conditions as in the dissolution studies. The distance between the blade and the screen center (2 cm) was identical to that used in the dissolution test. The disintegration time was defined as the time when the disintegrated particles passed through the screen or suspended in the dissolution fluid. The described method permits the determination of disintegration time under the same conditions as in dissolution tests, as well as observation of the disintegration process.

Estimation of Disintegration Time from Dissolution Data—Theoretically, as Eq. 10 indicates, the disintegration time is equal to infinity. However, since the percent remaining for disintegration after six disintegration half-lives is equal to 1.56%, which is negligible, it may be assumed that the disintegration time $DT_{calc} = 6t_{1/2d}$ or:

$$DT_{calc} = 6\left(\frac{0.693}{k_d}\right) = \frac{4.158}{k_d} \qquad \text{(Eq. 11)}$$

The values of DT_{calc} calculated from Eq. 11 coincided well with those estimated from the semilogarithmic plots, where DT_{calc} was taken as the time when the straight-line segment of the curve commences.

RESULTS AND DISCUSSION

Figure 1 demonstrates the dissolution profiles obtained for the tablet and capsule formulations tested. The selection of these commercial products for evaluation of the described method was arbitrary.

The apparent first-order dissolution and disintegration rate constants (k_s and k_d, respectively) were estimated by plotting log $(100 - f_s)$ *versus* time and the slope of the terminal linear segment is equal to $-(k_s/2.303)$. The apparent first-order disintegration rate constant was determined

[10] Millipore.

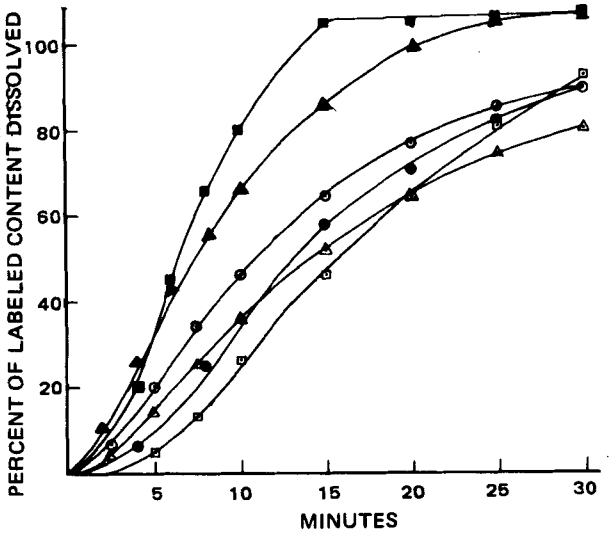

Figure 1—*Dissolution profiles for the formulations tested (mean of six determinations). Key: ●, A; ■, B; ▲, C; ○, D; △, E; □, F; solid symbols, tablets; and open symbols, capsules.*

by plotting the residual $(100 - f_s)$ against time semilogarithmically and the slope of the resulting straight line equal to $-(k_d/2.303)$. The values of k_s and k_d obtained are provided in Table I.

As demonstrated in Figs. 2 and 3, the fit was adequate; however, better fit may have been obtained if the analysis was carried out using nonlinear regression analysis. For Formulation B, dissolution was rapid and fewer data points were used.

The estimation of k_d and k_s also can be achieved by plotting log (dA_s/dt) (rate of dissolution) *versus* time using the method of residuals given by:

$$\frac{dA_s}{dt} = \frac{k_s k_d A_0}{k_d - k_s}\left(e^{-k_s t} - e^{-k_d t}\right) \qquad \text{(Eq. 12)}$$

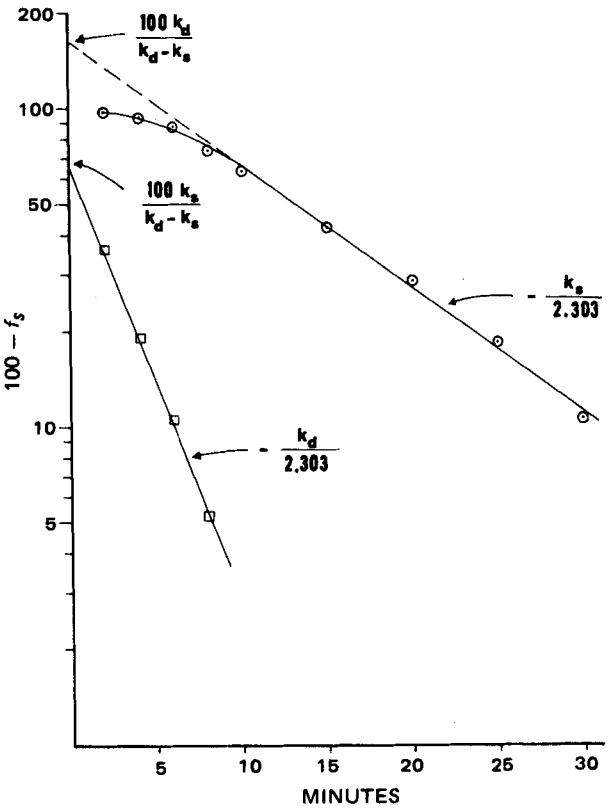

Figure 2—*Semilogarithmic plot of 100 minus cumulative percent dissolved (100 − f_s) against time for Tablet A. Key: ○, actual values; and □, residual values.*

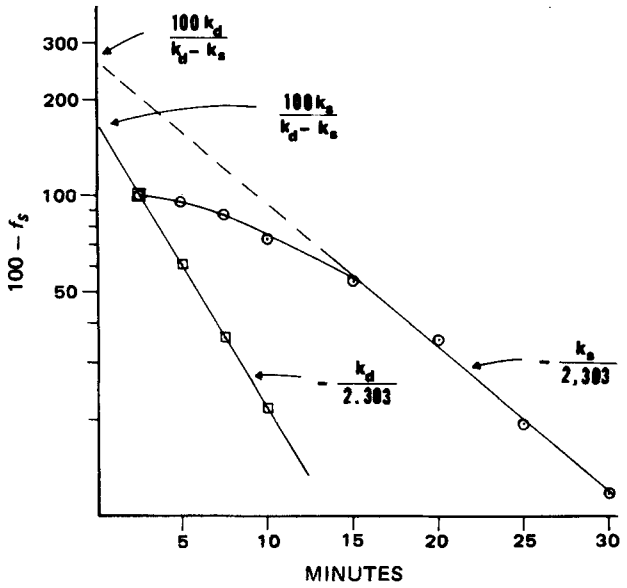

Figure 3—*Semilogarithmic plot of 100 minus cumulative percent dissolved (100 − f_s) versus time for Capsule F. Key: ○, actual values; and □, residual values.*

which can be derived by solving Eq. 7 to yield:

$$A_p = \frac{k_d A_0}{k_d - k_s}\,(e^{-k_s t} - e^{-k_d t}) \qquad \text{(Eq. 13)}$$

and substituting for A_p in Eq. 3. To estimate k_d accurately using Eq. 12, dissolution tests should be carried out automatically so that a sufficient number of early (dA_s/dt) points can be used in the plotting.

The values of DT_{exp} were in good agreement with those of DT_{calc} (Table II). These data confirm that the method proposed, in addition to its simplicity, is capable of reliably characterizing both dissolution and disintegration. In fact, if the percent dissolved–time data are well described by Eq. 10, the amount of drug in small particles at any given time (A_p) can be determined by employing Eq. 12, which permits the prediction of the disintegration time course. Such an approach is being investigated.

Previous models (5, 6) are in sharp disagreement with the present method, which assumes that dissolution occurs at a single rate constant throughout the dissolution test. In fact, the early data points that constitute the first dissolution phase according to previous models (5, 6) may not only represent dissolution but disintegration as well. By separating the disintegration component of these points from that of dissolution, a good estimate of the disintegration rate constant (k_d) may be obtained.

The described method provides a comprehensive, practical, and simple tool for the disintegration–dissolution analysis of dissolution rate data where familiar mathematics is employed. The good fit of the data obtained to the developed equation does not imply that drug dissolution and disintegration are first order in nature; it indicates that dissolution data for conventional tablets and capsules may be described by Eq. 10, in which case k_s and k_d can be estimated graphically.

REFERENCES

(1) J. G. Wagner, *J. Pharm. Sci.*, **58**, 1253 (1969).

(2) M. Gibaldi and S. Feldman, *ibid.*, **56**, 1238 (1967).

(3) F. Langenbucher, *J. Pharm. Pharmacol.*, **24**, 979 (1972).

(4) A. El-Yazigi, *Int. J. Pharm.*, **5**, 89 (1980).

(5) S. Kitazawa, I. Johno, Y. Ito, S. Teramura, and J. Okada, *J. Pharm. Pharmacol.*, **27**, 765 (1975).

(6) S. Kitazawa, I. Johno, T. Minouchi, and J. Okada, *ibid.*, **29**, 453 (1977).

(7) K. G. Nelson and L. Y. Wang, *J. Pharm. Sci.*, **66**, 1758 (1977).

(8) *Ibid.*, **67**, 86 (1978).

(9) A. J. Aguiar, J. E. Zelmir, and A. W. Kinkel, *ibid.*, **56**, 1243 (1967).

(10) M. Gibaldi and D. Perrier, "Pharmacokinetics," Dekker, New York, N.Y., 1974, pp. 270, 281.

Synthesis of Alkylaminoalkylamides of Substituted 2-Aminopyrroles as Potential Local Anesthetic and Antiarrhythmic Agents II: β-Amines

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Abstract □ The synthesis, local anesthetic and antiarrhythmic properties, and CNS toxicity of 14 2-(3-alkylaminoalkylamido)-pyrroles are described. Most of the compounds exhibited local anesthetic activity by the guinea pig wheal test, with seven showing comparable or greater activity than lidocaine. Most compounds also exhibited antiarrhythmic activity; three compounds had more potent activity than lidocaine. All compounds exhibiting antiarrhythmic activity also were toxic to the CNS. However, two of the three compounds having greater activity than lidocaine possessed more desirable therapeutic indexes.

Keyphrases □ 2-(3-Alkylaminoalkylamido)pyrroles—synthesis, evaluated for local anesthetic activity in guinea pigs and for antiarrhythmic activity and CNS toxicity in mice □ Anesthetic activity, potential—2-(3-alkylaminoalkylamido)pyrroles synthesized and evaluated for activity in guinea pigs, structure–activity relationships □ Antiarrhythmic activity, potential—2-(3-alkylaminoalkylamido)pyrroles synthesized and evaluated for activity in mice, structure–activity relationships □ Structure–activity relationships—2-(3-alkylaminoalkylamido)pyrroles synthesized and evaluated for anesthetic activity and antiarrhythmic activity and CNS toxicity in guinea pigs and mice

Previous publications reported the synthesis and pharmacological evaluation of several series of 2-(2-alkylaminoalkylamido)pyrroles (I*a*) as potential local anesthetic and antiarrhythmic agents (1–3). Many of these compounds possessed significant activity (1–3), but most compounds with the desired activity were also toxic to the central nervous system (CNS).

Several series of antiarrhythmic agents derived from substituted anilines were reported recently (4–6). The β-amino analog (II*b*) of tocainide (II*a*) was more potent

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