Pharmacokinetics of Oral Cephalosporins: Cephradine and Cephalexin

E. FINKELSTEIN *, R. QUINTILIANI ‡, R. LEE §, A. BRACCI *, and C. H. NIGHTINGALE *x

Received November 18, 1977, from the *Department of Pharmacy, State University of New York at Buffalo, Amherst, NY 14260, the ‡Division of Infectious Diseases, Department of Medicine, Hartford Hospital, Hartford, CT 06100, and the §Department of Medicine, State University of New York at Buffalo, Buffalo, NY 14214. Accepted for publication February 8, 1978.

Abstract □ A crossover experiment was utilized to compare the pharmacokinetics of a 1-g dose of cephalexin tablets, cephalexin capsules, or cephradine capsules in nine normal human volunteers. These antibiotics were administered as three formulations: two 500-mg capsules of cephradine every 6 hr for five doses, two 500-mg capsules of cephalexin every 6 hr for five doses, and one 1000-mg tablet of cephalexin every 6 hr for five doses. Pharmacokinetic parameters in the experimental groups showed no statistical differences ($p > 0.1$), indicating that these drugs are equivalent pharmacokinetically.

Keyphrases □ Cephradine—pharmacokinetics compared to cephalexin, capsules and tablets, in humans □ Cephalexin—pharmacokinetics compared to cephradine, capsules and tablets, in humans □ Pharmacokinetics—cephradine and cephalexin compared, capsules and tablets in humans □ Antibacterials—cephradine and cephalexin, pharmacokinetics compared, capsules and tablets, in humans □ Cephalosporins—cephradine and cephalexin, pharmacokinetics compared, capsules and tablets, in humans

Cephalexin and cephradine are cephalosporin antibiotics available for oral administration. These agents have extremely similar spectra of microbiological activity and chemical structures. They are approved for the treatment of infections caused most commonly by sensitive strains of *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae, Escherichia coli, Proteus mirabilis,* and *Klebsiella pneumoniae.* The usual therapeutic dose of these agents is 1–4 g/day, although doses of 6 g/day have been recommended (1–3).

Relatively few studies have appeared on the absorption and excretion characteristics of these drugs in 1-g doses in a single or multiple dosage regimen. This scarcity of information and the lack of any crossover studies, plus the fact that cephalexin is now available as a 1-g tablet, prompted a comparative study of these agents in doses of 4 g/day (4–12).

EXPERIMENTAL

Nine apparently normal, healthy volunteers, 23–38 years of age, underwent clinical-pathologic screening for liver, kidney, and hematologic function. This screen included serum electrolytes, creatinine, blood urea nitrogen, bilirubin, Coomb's test, complete blood count, serum glutamic-oxaloacetic transaminase, alkaline phosphatase, and creatinine clearance. All volunteers with a history of penicillin or cephalosporin allergy were excluded. No subject was receiving any other medications during this experiment.

A crossover design was utilized, with each subject undergoing a total of three experiments:

1. Two 500-mg capsules of cephradine[1] every 6 hr for five doses.
2. Two 500-mg capsules of cephalexin[2] every 6 hr for five doses.
3. One 1000-mg tablet of cephalexin[3] every 6 hr for five doses.

Cephalexin tablets, cephalexin capsules, or cephradine capsules were administered in a random fashion. At least 1 week separated all experiments. All subjects fasted overnight for 8 hr prior to each experiment and through the initial 2 hr of the testing. Water was provided in the following quantities: 200 ml initially, 200 ml at 1 hr, and *ad libitum* after 2 hr for the remainder of the sampling period.

Blood samples (1 ml) were collected through an indwelling butterfly catheter every 15 min for 1.5 hr and then every 30 min until the next dose was given. This schedule was followed for the first and final doses of each experiment. Urine was collected at hourly intervals between the first and second doses. Following the second dose, the total urine output during each dosing interval was collected. Once again, hourly urine output was collected following the final dose in the same manner as after the initial dose. The total urine output for the remainder of the 24 hr following the final dose also was collected.

Serum was separated from whole blood and frozen at −5°. Urine volume was measured, and an appropriate sample was frozen for analysis. Serum and urine concentrations were measured by a disk diffusion assay using *Bacillus subtilis* as the test organism (13). Serum and urine data were analyzed for appropriate pharmacokinetic parameters using a one-compartment open model with first-order absorption (14, 15). A nonlinear least-squares regression analysis computer program was used to fit the data (16).

RESULTS AND DISCUSSION

Nightingale *et al.* (14) suggested that cephalexin and cephradine be considered interchangeable. This suggestion was made after the pharmacokinetic evaluation of low maintenance dose (0.25–0.50 g) data. This study was undertaken to provide pharmacokinetic data for cephalexin tablet and capsule dosage forms and cephradine in large maintenance doses (1.0 g) in a well-controlled, crossover design.

The results (Fig. 1 and Tables I–III) illustrate that the serum con-

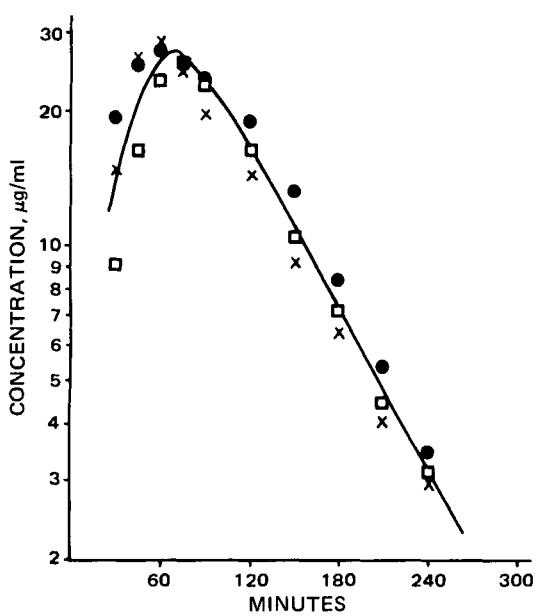

Figure 1—*Mean serum cephradine and cephalexin concentrations as a function of time. Key:* ●, *cephradine capsules;* ×, *cephalexin capsules; and* □, *cephalexin tablet.*

[1] Anspor capsules, 500 mg, lot 576A71, Smith Kline and French Laboratories, Philadelphia, Pa.
[2] Keflex Pulvules, 500 mg, lots 0DD32B and 0CN35B, Eli Lilly and Co., Indianapolis, Ind.
[3] Keflex tablets, 1 g, lot 9SH65A, Eli Lilly and Co., Indianapolis, Ind.

0022-3549/78/1000-1447$01.00/0

Table I—Serum Cephradine Concentrations [a]

Subject	Minutes after Dose												
	15	30	45	60	75	90	120	150	180	210	240	270	300
BL	—	11.7	14.1	18.9	19.9	23.6	19.3	12.9	8.2	4.4	2.9	2.1	—
EM	—	3.5	12.3	21.6	22.6	25.0	20.1	16.1	7.6	5.5	3.9	2.5	1.7
CN	1.7	17.4	22.6	24.4	19.1	19.0	12.6	8.5	5.6	3.5	2.0	—	—
EF	6.6	30.6	35.6	31.6	26.6	23.2	17.8	10.8	6.4	3.4	1.9	—	—
TI	—	9.3	21.0	26.7	26.5	22.0	14.5	8.3	4.6	3.0	1.7	—	—
AM	12.4	44.5	44.2	40.1	32.0	26.7	17.9	10.9	7.7	4.7	3.1	—	—
AB	—	9.8	19.2	21.6	26.5	25.1	22.4	20.2	12.7	9.1	5.6	—	—
JO	—	36.3	43.9	41.5	34.8	30.5	21.6	9.9	8.6	4.9	3.1	—	—
GL	—	10.1	16.7	20.6	21.0	24.3	24.0	20.0	13.0	9.5	6.5	—	—
Mean	6.95	19.3	25.5	27.4	25.5	24.4	18.9	13.1	8.2	5.3	3.4		
SD	5.37	14.3	12.4	8.4	5.4	3.2	3.7	4.6	2.9	2.4	1.7		

[a] Data expressed as micrograms per milliliter.

Table II—Serum Cephalexin Capsule Concentrations [a]

Subject	Minutes after Dose												
	15	30	45	60	75	90	120	150	180	210	240	270	300
BL	—	23.3	33.7	30.4	24.1	20.9	16.4	9.6	7.2	4.2	2.8	1.7	—
EM	—	7.0	20.0	26.1	29.0	—	24.0	12.9	10.0	6.8	4.6	4.0	2.3
CN	—	21.1	27.9	22.2	19.3	16.0	9.0	6.5	3.3	3.0	—	—	—
EF	—	21.1	32.8	32.8	24.6	18.1	9.7	6.1	3.1	2.1	—	—	—
TI	—	14.3	29.5	33.9	26.3	22.2	16.3	10.2	7.5	4.8	2.2	1.8	—
AM	—	13.3	17.7	23.4	20.8	17.2	10.9	7.5	5.3	3.5	2.6	—	—
AB	—	12.2	—	29.0	25.9	24.8	18.9	15.0	10.4	6.5	3.9	—	—
JO	—	17.6	35.5	32.7	25.4	16.1	9.9	5.9	4.0	1.8	—	—	—
GL	—	2.5	13.3	23.9	—	20.6	14.2	7.4	5.3	3.4	1.7	—	—
Mean	—	14.7	26.3	28.3	24.4	19.5	14.4	9.0	6.3	4.0	3.0		
SD	—	6.9	8.3	4.5	3.1	3.2	5.0	3.2	2.7	1.7	1.1		

[a] Data expressed as micrograms per milliliter.

Table III—Serum Cephalexin Tablet Concentrations [a]

Subject	Minutes after Dose											
	15	30	45	60	75	90	120	150	180	210	240	270
BL	6.9	13.6	20.8	20.5	23.0	17.8	11.9	5.7	3.9	2.1	—	—
EM	—	7.1	14.6	22.4	24.3	20.8	16.0	12.1	8.3	5.6	3.1	2.2
CN	—	2.5	12.3	21.0	22.5	20.0	14.4	10.8	7.7	4.2	2.9	1.8
EF	—	19.7	28.5	28.6	25.2	23.6	14.1	9.0	6.2	4.7	2.7	—
TI	—	4.9	12.3	32.7	28.7	22.7	19.2	11.3	8.1	6.1	4.4	2.7
AM	—	21.8	30.1	27.4	23.6	22.2	14.5	9.5	6.2	3.9	2.7	—
AB	—	—	—	—	—	—	—	—	—	—	—	—
JO	—	1.2	7.8	19.8	36.3	32.5	19.6	10.8	7.6	3.6	2.2	—
GL	—	1.3	4.2	12.9	20.2	21.0	18.9	12.5	8.3	4.9	3.7	2.4
Mean	—	9.0	16.3	23.2	25.5	22.6	16.1	10.2	7.0	4.4	3.1	
SD	—	8.3	9.4	6.2	5.0	4.4	2.9	2.2	1.5	1.2	0.7	

[a] Data expressed in micrograms per milliliter.

Table IV—Peak Serum Concentration [a]

Subject	Cephradine Capsules		Cephalexin Capsules		Cephalexin Tablet	
	First Dose	Fifth Dose	First Dose	Fifth Dose	First Dose	Fifth Dose
CN	25.2[b]	23.7	27.9	27.9	17.6	27.6
EF	33.0	38.2	35.2	31.3	33.1	29.5
AM	47.2	48.2	24.3	27.9	25.0	36.4
JO	46.8	41.9	32.1	38.9	33.0	39.5
GL	28.8	28.8	24.5	31.1	23.8	22.3
TI	27.3	26.7	36.2	31.6	33.0	33.7
EM	29.0	26.7	30.6	27.7	30.9	21.6
BL	23.7	26.5	32.7	36.3	24.2	26.2
AB	33.5	27.8	23.9	35.5	—	—
Mean	32.7	32.0	29.7	30.9	27.6	29.6
SD	8.7	8.6	4.8	3.2	5.8	6.5

[a] Paired Student *t* tests were used to compare first- and fifth-dose peak serum concentrations in each of the three experimental groups. No statistical differences were found ($p > 0.1$). [b] Data expressed in micrograms per milliliter.

centration *versus* time profiles of these drugs at higher doses (1 g) are remarkably similar. No accumulation, as evidenced by lack of an increasing peak serum concentration, was observed after multiple dosing (Table IV). This result was not surprising since the half-lives of these drugs (approximately 45 min) are relatively short in relation to the dosing interval (6 hr).

It previously was established that the pharmacokinetics of cephalexin and cephradine (14, 15) are described most appropriately by two-compartment model analysis. Greene *et al.* (15) extensively studied the pharmacokinetics of cephalexin after one- and two-compartment model analysis and concluded that, for practical purposes, the pharmacokinetics could be described adequately by a one-compartment model. Comparison of the data reported in Table V shows that the pharmacokinetic parameters of cephalexin are not appreciably different from those reported by Greene *et al.* (15) after extensive two-compartment analysis. Accordingly, it was decided to analyze the data using a one-compartment model.

Table V—Pharmacokinetic Parameters [a]

Parameter	Cephradine Capsules[b]	Cephalexin Capsules	Cephalexin Tablet
AUC, μg-min/ml	3711.7 ± 671.8	3165.9 ± 561.5	3080.7 ± 417.9
Peak time, min	69.3 ± 22.0	60.4 ± 11.5	66.2 ± 14.5
Peak concentration, μg/ml	32.7 ± 8.1	30.6 ± 3.6	28.5 ± 14.5
Lag time, min	19.7 ± 5.7	22.3 ± 3.7	23.2 ± 8.2
$t_{1/2}$ elim., min	46.3 ± 4.5	46.2 ± 6.0	48.1 ± 7.1
$t_{1/2}$ abs., min	16.6 ± 6.3	12.4 ± 7.4	15.0 ± 4.0
Urinary recovery, %	85.5 ± 9.5	90.6 ± 8.7	89.6 ± 10.8
V_d, liters	18.4 ± 3.2	22.2 ± 4.4	22.7 ± 3.2[c]

[a] Paired Student *t* tests were used to compare all pharmacokinetic parameters between experimental groups. [b] Data expressed as mean ± *SD*. [c] $p < 0.01$ cephradine capsules *versus* cephalexin tablet.

Table VI—Cumulative Urinary Excretion [a]

Hours	Cephradine Capsules	Cephalexin Capsules	Cephalexin Tablet
First dose			
0–1	239.6 ± 90.2	284.0 ± 124.7	163.0 ± 96.8
1–2	599.1 ± 101.6	685.1 ± 140.6	535.0 ± 134.0
2–3	737.1 ± 128.8	795.9 ± 138.5	726.5 ± 113.3
3–4	801.3 ± 135.6	876.5 ± 153.6	804.6 ± 105.7
4–5	831.8 ± 148.0	915.5 ± 161.9	844.2 ± 111.5
5–6	845.1 ± 151.5	945.3 ± 161.5	863.7 ± 111.0
Fifth dose			
0–1	223.4 ± 108.7	266.6 ± 65.0	178.9 ± 96.0
1–2	586.2 ± 155.6	655.6 ± 101.3	602.2 ± 103.1
2–3	762.3 ± 139.0	839.2 ± 103.8	778.6 ± 125.0
3–4	858.4 ± 139.1	926.8 ± 111.1	889.4 ± 146.5
4–5	901.4 ± 143.2	972.2 ± 127.3	953.2 ± 184.7
5–6	921.4 ± 142.7	997.5 ± 137.4	988.7 ± 197.8
6–24	949.0 ± 148.5	1032.5 ± 139.8	1022.3 ± 200.2

[a] Data expressed as mean ± *SD* in milligrams.

Table VII—Urinary Recovery [a]

Dosing Interval	Cephradine Capsules	Cephalexin Capsules	Cephalexin Tablet
First	845.1 ± 151.5	945.3 ± 161.5	863.7 ± 111.0
Second	779.8 ± 104.5	797.6 ± 159.8	864.0 ± 178.1
Third	867.5 ± 91.1	798.1 ± 153.1	858.3 ± 158.4
Fourth	859.4 ± 162.6	951.9 ± 206.1	874.1 ± 161.7
Fifth	949.1 ± 148.5	1032.5 ± 139.8	1022.3 ± 200.2

[a] Data expressed as mean ± *SD* in milligrams.

Table VIII—Clearance Values [a]

	Cephradine Capsules		Cephalexin Capsules		Cephalexin Tablet	
Subject	Renal	TBC[b]	Renal	TBC	Renal	TBC
GL	217.8	234.3	518.3	416.0	415.0	359.7
JO	213.8	235.8	370.0	344.5	473.5	323.0
AB	155.5	241.8	264.3	268.3	—	—
AM	166.5	213.5	345.8	364.5	247.3	293.3
BL	231.2	315.0	255.7	268.8	370.5	412.0
EM	186.2	294.8	293.8	261.3	246.0	330.0
EF	235.5	264.5	188.7	350.0	182.2	288.8
CN	368.7	352.8	256.2	372.7	388.3	359.7
TI	379.0	346.7	283.7	284.8	247.7	270.1
Mean	239.3	277.7	308.5	325.7	321.3	329.7
SD	81.0	51.7	94.8	56.0	103.3	46.5

[a] Data expressed as milliliters per minute. [b] TBC = total body clearance.

However, the reported half-life for absorption, lag time, and volume of distribution should be considered as "apparent" parameters. A comparison of the model-independent parameters such as the peak concentration, time of peak concentration, clearance, area under the curve (*AUC*), elimination half-life, and urinary recovery allows one to determine if any differences exist in the pharmacokinetics of these drugs.

The data for the first and fifth doses of each patient were analyzed separately. Since no accumulation was noted after multiple dosing, the first and fifth dose parameters from each patient were averaged. The data from each experiment were compared and evaluated using paired Student *t* tests. Mean data for all subjects are shown in Table V.

No significant differences in the absorption or elimination half-life, *AUC*, peak serum concentration, time of peak, or lag time for absorption were observed. Analysis of the volume of distribution (V_d) data revealed a statistical difference between cephalexin tablets and cephradine capsules. No differences were found between either the cephalexin capsules and tablets or the cephalexin capsules and cephradine capsules. Since cephradine and cephalexin have similar protein binding (~10%) (14), one would expect similar V_d values as observed with the capsule data. No differences in the V_d values are expected due to dosage form effects. Although a statistical difference in V_d was found between cephalexin tablets and cephradine capsules, from a practical point of view the difference is not of sufficient magnitude to alter any pharmacokinetically derived dosage regimens and, therefore, is insignificant.

Cumulative urinary excretion data after the first and fifth doses (Table VI) illustrate that greater than 50% of both cephalexin and cephradine was excreted during the first 2 hr. Urinary recovery during each dosing interval is shown in Table VII. The amount recovered during any dosing interval was virtually identical for each experimental group. Since these drugs are eliminated unchanged in the urine (14), the percentage of the

total dose excreted can be used as indication of bioavailability. The data in Table V show that the percentage of the total dose recovered after 48 hr was similar for each drug and dosage form and that all were approximately 90–100% bioavailable. These findings are consistent with the results of other investigators (4–6, 12).

Renal clearances were calculated for each subject from the hourly urinary excretion rate data and the serum concentration at the midpoint of the collection period. Total body clearance was calculated from the volume of distribution and the elimination rate constant. Since no metabolites have been identified in humans for either cephalexin or cephradine (14), the renal and total body clearances would be expected to be identical. This expectation was found to be true (Table VIII). Renal and total body clearances of cephalexin and cephradine were also similar. Since both cephalexin and cephradine are eliminated by glomerular filtration and tubular secretion (14), clearances of greater than 125 ml/min were expected. This result is confirmed in Table VIII where it can be seen that the clearance values for these drugs are approximately 300 ml/min.

The present investigation, although not designed to investigate dose-dependent pharmacokinetics, firmly establishes in a carefully controlled manner that no difference exists in any measured parameter (Tables I–VIII) between cephradine and cephalexin in 1-g doses. This finding is consistent with previous pharmacokinetic analysis at low doses (0.25–0.50 g) (14). Rattie *et al.* (10) demonstrated that a linear relationship between dose (0.25–1.0 g) and both peak concentration and *AUC* exists for cephradine. Pfeffer *et al.* (9) reported that a linear relationship in peak concentration and *AUC* exists for cephalexin at doses of 0.25 and 0.5 g. The reported pharmacokinetic parameters from these studies are similar to the present findings; therefore, dose-dependent kinetics do not appear to exist with these drugs.

Since a 1-g tablet of cephalexin is available commercially, it was important to determine if the tablet and capsule dosage forms were equally bioavailable. Figure 1 and Tables II and III show that both the tablet and capsule yield similar serum concentration–time curves, indicating that no dosage form differences affecting the drug's pharmacokinetics exist. Statistical comparison of the *AUC*, percent of dose excreted, and all other pharmacokinetic parameters shown in Table V indicate that the bioavailability of the tablet and capsule dosage forms is similar. However, greater fluctuations in peak concentration and lag time were seen with the tablet dosage form. In addition, comparison of the cephalexin tablet to the cephradine capsules (Table V) reveals no statistically significant differences in any measured pharmacokinetic parameter.

The results of this study confirm that, from a pharmacokinetic view, these drugs in tablet or capsule form are essentially identical, both at low (0.25 g) and high (1.0 g) oral doses.

REFERENCES

(1) R. J. Fass, R. L. Perkins, and S. Saslaw, *Am. J. Med. Sci.*, **259,** 187 (1970).

(2) J. Klastersky, D. Daneau, and D. Weerts, *Chemotherapy*, **18,** 191 (1973).

(3) V. Macquet and P. L. Lafitte, *Postgrad. Med. J.*, **46S,** 128 (1970).

(4) P. E. Gower and C. H. Dash, *Br. J. Pharmacol.*, **37,** 737 (1969).

(5) R. S. Griffith and H. R. Black, *Clin. Med.*, **75,** 14 (1968).

(6) C. Harvengt, P. DeSchepper, F. Lamy, and J. Hansen, *J. Clin. Pharmacol.*, **13,** 36 (1973).

(7) C. H. O'Callaghan, J. P. R. Toothill, and W. D. Robinson, *J. Pharm. Pharmacol.*, **23,** 50 (1971).

(8) R. L. Perkins, H. N. Carlisle, and S. Saslaw, *Am. J. Med. Sci.*, **256,** 122 (1968).

(9) M. Pfeffer, A. Jackson, J. Ximenes, and J. P. DeMenezes, *Antimicrob. Agents Chemother.*, **11,** 331 (1977).

(10) E. S. Rattie, P. D. Bernardo, and L. J. Ravin, *ibid.*, **10,** 283 (1976).

(11) J. F. Scholand, G. R. Hodges, R. J. Fass, and S. Saslaw, *Am. J. Med. Sci.*, **267,** 111 (1974).

(12) A. Zaki and E. C. Schreiber, *J. Clin. Pharmacol.*, **14,** 118 (1974).

(13) H. P. Bassaris, R. Quintiliani, E. G. Maderazo, R. C. Tilton, and C. H. Nightingale, *Curr. Ther. Res.*, **19,** 110 (1976).

(14) C. H. Nightingale, D. S. Greene, and R. Quintiliani, *J. Pharm. Sci.*, **64,** 1899 (1975).

(15) D. S. Greene, D. R. Flanagan, R. Quintiliani, and C. H. Nightingale, *J. Clin. Pharmacol.*, **16,** 257 (1976).

(16) C. M. Metzler, G. L. Elfring, and A. J. McEwen, "A User's Manual for NONLIN and Associated Programs," Upjohn Co., Kalamazoo, Mich., 1974.

Versatile Kinetic Approach to Analysis of Dissolution Data

PETER VENG PEDERSEN *x and JAMES W. MYRICK ‡

Received December 5, 1977, from the **Department of Pharmacy, School of Pharmacy, University of California at San Francisco, San Francisco, CA 94143,* and the ‡*National Center for Drug Analysis, Food and Drug Administration, St. Louis, MO 63101.* Accepted for publication February 14, 1978.

Abstract □ A new kinetically based dissolution equation is presented that considers dissolution of polydisperse systems and disintegrating solid dosage forms. The equation is applicable under sink as well as nonsink conditions and enables the specific dissolution rate parameter, the dispersion parameter, the disintegration lag time, and a newly introduced parameter, the dissolution availability, to be evaluated simultaneously and directly from percent of label claim dissolved *versus* time data. The equation showed excellent fit to dissolution data for aminophylline tablets. The kinetic significance of the estimated parameters of the equation is discussed. The method of analysis is compared to an approach employing an empirical equation based on a modified Weibull distribution function.

Keyphrases □ Dissolution—kinetically based equation considers polydisperse systems and solid dosage forms, various conditions □ Models, mathematical—kinetically based equation considers dissolution of polydisperse systems and solid dosage forms, various conditions □ Kinetic approach—mathematical model considers dissolution of polydisperse systems and solid dosage forms, various conditions

The extensive literature on dissolution testing of drugs contains many theories and equations to describe observed behavior (1, 2). The equations often have limited application because they are derived for specific experimental conditions such as sink or nonsink conditions or they are based on unrealistic assumptions such as an ideal monodisperse system. Such equations often do not agree adequately with observed dissolution data.

Consequently, there has recently been interest in empirical equations for obtaining a better, more flexible

0022-3549/78/1000-1450$01.00/0