334 (80); high-resolution mass spectrum: calc. for $C_{27}H_{23}NO_4$, 425.1627; found *m/e* 425.1615.

8,8-Diethylcanadine (XIX)—A XVIII solution (0.1 g, 0.25 mmole) in ethanol (20 ml) was treated with excess sodium borohydride (0.4 g). Workup and recrystallization from methanol furnished 0.096 g (96%) of XIX as tan plates, mp 168–169°; UV: $\lambda_{max}^{ethanol}$ 233 (log ϵ 4.31) and 288 (3.81) nm; mass spectrum: *m/e* M^+ 395 (5), 367 (100), 335 (10), 220 (35), and 175 (40); high-resolution mass spectrum: calc. for $C_{24}H_{29}NO_4$, 395.2096; found *m/e* 395.2125.

8-Benzylcanadine (XXI)—Sodium borohydride reduction of XX (1 g, 2.3 mmoles) in ethanol yielded 0.98 g (99%) of the known XXI, mp 165–166° (methanol) [lit. (5) mp 163–165°].

REFERENCES

(1) M. Shamma, "The Isoquinoline Alkaloids," Academic, New York, N.Y., 1972, pp. 268–314.

(2) M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research, 1972–1977," Plenum, New York, N.Y., 1978, pp. 209–259.

(3) R. D. Haworth, W. H. Perkin, Jr., and H. S. Pink, *J. Chem. Soc.*, **1925**, 1709.

(4) A. C. Santosy and P. Adkilen, *J. Am. Chem. Soc.*, **54**, 2923 (1932).

(5) J. R. Gear and I. D. Spenser, *Can. J. Chem.*, **41**, 783 (1963).

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Comparative Studies on Eight Dissolution Methods Using 21 Commercial Chloramphenicol Tablets and a Nondisintegrating Benzoic Acid Tablet

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Received April 25, 1978, from the *Division of Drug, National Institute of Hygienic Sciences, 1-18-1, Kamiyoga Setagaya-ku, Tokyo, Japan.* Accepted for publication November 17, 1978.

Abstract □ Eight dissolution methods (beaker, rotating basket, oscillating basket, solubility simulator, rotating flask, and column) were evaluated using 21 commercial film-coated chloramphenicol (I) tablets and a nondisintegrating benzoic acid (II) tablet. The relative agitating intensities obtained from different dissolution methods were compared through the relative zero-order nondisintegrating tablet dissolution rate constants. Correlation coefficients between I dissolution rate parameters (lag time, T_{20}, T_{50}, and T_{80}) were determined. Significant correlation was observed for the lag time among seven methods, and all pairwise regression lines passed through zero except one. The regression line slopes reflected the relative destructive force intensities produced by each dissolution method on the coated I tablet films. The seven dissolution methods could be classified into two main groups according to correlations of four dissolution rate parameters. This classification criterion agreed well with that based on the agitation method. However, dissolution methods may not be interchangeable even though they belong to the same dissolution method group.

Keyphrases □ Dissolution testing systems—eight systems compared, chloramphenicol tablets and powder, benzoic acid tablet □ Dissolution rates—chloramphenicol tablets and powder, benzoic acid tablet □ Chloramphenicol—dissolution rates, tablets and powder, eight testing systems compared □ Benzoic acid—dissolution rate, tablet, eight testing systems compared

Since the dissolution rate was first recognized as a significant factor in determining *in vivo* drug bioavailability, many methods for testing solid dosage form dissolution have been reported (1, 2). These methods differ in hydrodynamic properties, agitating intensities, and mechanical destructive forces to the intact drug. There are three basic dissolution testing devices (2, 3): the stirred-tank reactor with a mechanical agitator such as Levy's beaker method (4) or the rotating-basket method (5), the rotating vessel reactor such as the rotating flask (6) or the solubility simulator[1], and the stream reactor such as the column method (7–9).

Several investigators compared the relative agitating intensities or hydrodynamic properties of selected dissolution devices by using a nondisintegrating model tablet (10–12). Bathe *et al.* (3) studied dissolution rates by beaker, rotating-basket, and flow column methods under eight different conditions. However, detailed comparisons of disintegrating tablet dissolution methods have not been made.

In the present study, eight representative dissolution testing methods were compared and evaluated. They can be divided into three categories: (*a*) stirrer-tank reactor type (beaker, rotating basket, and oscillating basket), (*b*) rotating-vessel reactor type (rotating flask and solubility simulator[1]), and (*c*) stream reactor type (column). Disintegrating tablets—21 chloramphenicol (I) brands available in Japan—and nondisintegrating tablets—benzoic acid (II)—were used as markers. The two drugs were selected because of their moderate solubilities in acidic solutions (2–4 mg/ml).

EXPERIMENTAL

Materials—Twenty-one different sugar-coated I tablets were obtained from 16 manufacturers in Japan. Tablets A–E each contained 50 mg of I while Tablets F–U each contained 250 mg of I. A powder of I[2] was included for comparison. Nondisintegrating and uncoated tablets containing 100 mg of II[3] were used.

[1] Sartorius-Membranfilter GmbH, Göttingen, West Germany.
[2] Yamanouchi Pharmaceutical Co., Tokyo, Japan.
[3] Supplied by Dr. Ikeda and Dr. Nishimura, Sankyo Co., Tokyo, Japan.

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Table I—Benzoic Acid Dissolution Rate Constants from Nondisintegrating Tablet under Sink Condition

Method	K_d, mg/min	Relative K_d
a	0.896	1.00
b (in)[a]	0.221	0.25
b (out)[b]	0.288	0.32
c-I (in)	1.012	1.13
c-I (out)	0.294	0.33
c-III (in)	1.132	1.26
c-III (out)	0.500	0.56
d	0.974	1.09
e	0.123	0.14
f	0.339	0.38

[a] Tablet was placed in the basket. [b] Tablet was placed out of the basket.

Dissolution Methods—*Beaker: Method a*—A cylindrical flat-bottom vessel for the disintegration test (JP IX) was used. One liter of the dissolution medium kept at 37° was stirred at 120 rpm with a three-bladed impeller (4.5 × 1.5 cm), which was held 4.5 cm from the vessel bottom. The tablets were placed at the vessel bottom during dissolution.

Rotating Basket: Method b—The test was carried out according to USP XIX specifications at 120 rpm.

Oscillating Basket: Method c—The disintegration test (JP IX) device was used, with the basket-rack assembly attached under three different conditions: (*a*) without the disk (c-I), (*b*) with the disk as specified in JP IX (c-II), and (*c*) with the disk located so that it touched the vessel bottom at the lowest point on the downward stroke (c-III). Tablets were placed into one of six open-ended glass tubes. The medium volume was 1 liter.

Rotating Flask: Method d—A 2-liter round-bottom flask was used as the vessel into which 150 g of glass beads (8-mm diameter) and 75 g of butyl rubber pieces (15 × 15 × 5 mm) were added with 900 ml of the medium. The flask was attached to a device for rotation[4] and immersed into the water bath maintained at 37° at 165° angle against the horizontal axis. The flask rotation speed was 18 rpm. The medium was sampled continuously through steel tubing attached to the flask.

Solubility Simulator: Method e—The thermostated (37°) solubility chamber (100 ml), which contained 170 g of glass beads (8-mm diameter) and 100 ml of the medium, was rotated horizontally at 1.2 rpm. A fixed sample volume was automatically removed from the chamber through a membrane filter at definite intervals. As the sample was taken, an identical fresh dissolution medium volume flowed into the chamber. The sampling volume and interval were set at 2.5 ml and 2.5 min, respectively.

Column: Method f—An ultrafiltration[5] cell with support screens[6] on both ends was used. The membrane filter was not used because the high-speed upward flow of the medium caused the dispersed particles to clog the upper filter. Dissolution medium was circulated through the column at 35 ml/min. The effluent was returned to a sink, which was stirred by the same procedure as in Method a. The total dissolution medium volume was 1 liter.

Rate Determination—Dissolution was determined for a single tablet in each procedure. Except in Method e, the dissolution medium was circulated through a flowcell (5-mm cell length) by a microtube pump[7] at 3.0 ml/min, and the medium absorbance was determined spectrophotometrically at two wavelengths[8]. In Methods a and b, the sampling tubing, with a glass filter at its end, was placed on the side and midheight

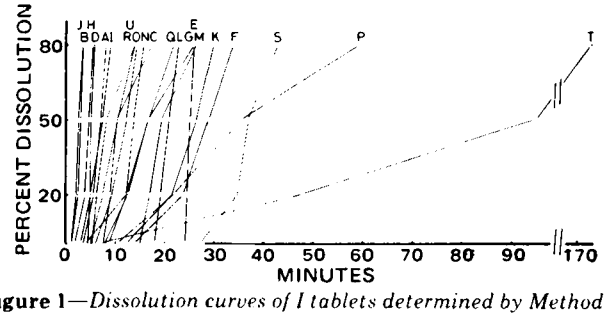


Figure 1—*Dissolution curves of I tablets determined by Method a.*

[4] Japan Servo Co., Tokyo, Japan.
[5] Millipore xx 42 025 00.
[6] Millipore xx 30 025 10.
[7] Tokyo Rikakikai Co., Tokyo, Japan.
[8] Hitachi 156.

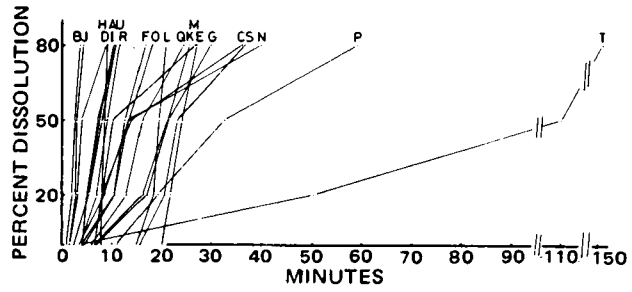


Figure 2—*Dissolution curves of I tablets determined by Method b.*

in the dissolution vessel. In Methods c and d, the filter was attached to the oscillating basket-rack bottom or to the round-bottom flask bottom and immersed into the medium.

In all methods except Method e for I tablets, the asymptotic absorbance was used as the value of 100% dissolution. In Method e, the drug absorbance in the medium removed from the chamber was determined and the cumulative amount dissolved was calculated. The asymptotic value was then substituted as the amount of 100% dissolution.

The I tablet dissolution rates were represented by four parameters: lag time (T_0), T_{20}, T_{50}, and T_{80}, where T_{20}, T_{50}, and T_{80} represent 20, 50, and 80% dissolution times, respectively. In II tablets, the absolute dissolved II amount was determined; the dissolution rate constant (milligrams per minute) was obtained from the slope of the earlier straight line of the dissolution curve. In all experiments, the dissolution medium was simulated gastric fluid without enzymes (JP VIII).

Disintegration and Hardness Measurements—Disintegration measurements were carried out according to JP IX. Hardness was measured by a hardness tester[9]. The disintegration time and hardness values reported are the average values of six tablets.

RESULTS

Dissolution Rate Constant of Nondisintegrating II Tablets—The drug dissolution rate can be represented by the Noyes–Nernst equation (13):

$$J = SK(C_s - C) \qquad \text{(Eq. 1)}$$

where J, S, K, C_s, and C represent the dissolution rate, surface area available to dissolution, dissolution rate constant, solubility, and drug concentration in the medium, respectively. According to the diffusion layer theory (14), the dissolution rate constant is a function of two parameters:

$$K = \frac{D}{h} \qquad \text{(Eq. 2)}$$

where D and h represent the diffusion coefficient and diffusion layer thickness, respectively. When $C_s \gg C$, Eq. 3 is obtained from Eqs. 1 and 2:

$$J = \frac{DS}{h} C_s = K_d \qquad \text{(Eq. 3)}$$

Thus, if the dissolution rate is measured under sink condition, the dissolution process follows apparent zero-order kinetics. When the same nondisintegrating tablet is tested using different dissolution methods, the differences in K_d should reflect only variations in h as a function of the dissolution method because D, S, and C_s are held constant. From

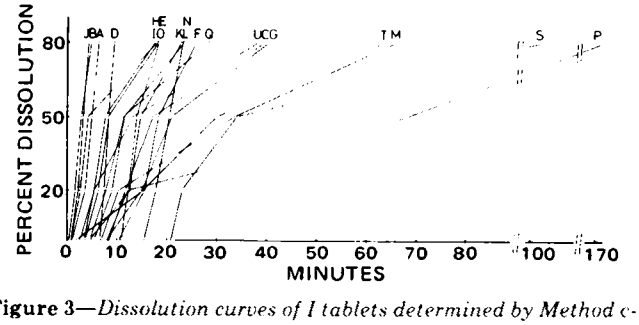


Figure 3—*Dissolution curves of I tablets determined by Method c-I.*

[9] Kiya Seisakusho, Tokyo, Japan.

Table II—Correlation Coefficients between the Dissolution Parameters

Parameter		Disintegration Time	a	b	c-I	c-II	c-III	d	e
Hardness	Lag	0.453	0.367	0.169	0.341	0.407	0.584	0.281	0.330
	T_{20}		0.573[a]	0.461	0.429	0.156	0.426	0.345	0.425
	T_{50}		0.372	0.198	0.197	0.217	0.457	0.274	0.436
	T_{80}		0.242	0.095	0.040	0.100	0.436	0.229	0.456
Disintegration Time	Lag		0.415	0.265	0.507	0.628[a]	0.563[a]	0.514	0.578[a]
	T_{20}		0.367	0.255	0.639[a]	0.738[a]	0.850[a]	0.711[a]	0.678[a]
	T_{50}		0.215	0.100	0.171	0.617[a]	0.900[a]	0.652[a]	0.680[a]
	T_{80}		0.096	0.050	0.006	0.326	0.835[a]	0.594[a]	0.607[a]
a	Lag			0.870[a]	0.796[a]	0.722[a]	0.863[a]	0.872[a]	0.686[a]
	T_{20}			0.911[a]	0.800[a]	0.564[a]	0.583[a]	0.702[a]	0.582[a]
	T_{50}			0.959[a]	0.558[a]	0.783[a]	0.341	0.325	0.421
	T_{80}			0.972[a]	0.405	0.709[a]	0.375	0.203	0.310
b	Lag				0.826[a]	0.693[a]	0.756[a]	0.905[a]	0.606[a]
	T_{20}				0.652[a]	0.416	0.375	0.539[a]	0.542[a]
	T_{50}				0.439	0.705[a]	0.177	0.148	0.382
	T_{80}				0.409	0.694[a]	0.323	0.084	0.315
c-I	Lag					0.823[a]	0.850[a]	0.878[a]	0.685[a]
	T_{20}					0.841[a]	0.861[a]	0.840[a]	0.749[a]
	T_{50}					0.598[a]	0.381	0.089	0.312
	T_{80}					0.681[a]	0.325	0.002	0.119
c-II	Lag						0.880[a]	0.864[a]	0.776[a]
	T_{20}						0.914[a]	0.730[a]	0.663[a]
	T_{50}						0.739[a]	0.565[a]	0.562[a]
	T_{80}						0.629[a]	0.448	0.332
c-III	Lag							0.832[a]	0.652[a]
	T_{20}							0.780[a]	0.730[a]
	T_{50}							0.674[a]	0.660[a]
	T_{80}							0.637[a]	0.595[a]
d	Lag								0.831[a]
	T_{20}								0.679[a]
	T_{50}								0.336
	T_{80}								0.208

[a] Significant ($p < 0.05$).

these considerations, the zero-order dissolution rate constant emerges as the parameter reflecting the relative dissolution method agitation intensity. Table I shows the II dissolution rate constants. The relative values were normalized against the value obtained by Method a.

I Tablet Dissolution—Figures 1–7 show the dissolution curves measured by Methods a–e. The curves were constructed by linking the four points used for further treatment: lag time, T_{20}, T_{50}, and T_{80}.

The I dissolution rates were compared pairwise. Correlation coefficients are reported in Table II. Significant correlations ($p < 0.05$) for all four parameters were found for Method a *versus* b and c-II, b *versus* a, c-I *versus* c-II, c-III *versus* c-II, d and e, and disintegration time *versus* c-III and e. The I tablet disintegration and hardness values are listed in Table III.

Table III—Disintegration Times and Hardness of Chloramphenicol Tablets

Tablet	Disintegration Time, min	Hardness, kg
A	9.2	9.9
B	4.4	13.1
C	10.2	5.9
D	4.2	14.8
E	5.5	10.6
F	16.9	14.0
G	14.5	>20[a]
H	5.9	11.1
I	7.9	>20
J	2.5	5.8
K	18.6	16.4
L	19.2	16.6
M	5.5	16.4
N	9.7	16.0
O	12.7	>20
P	7.8	11.7
Q	12.2	>20
R	7.9	13.9
S	13.4	>20
T	7.8	>20
U	3.4	10.7

[a] More than 20 kg.

Interpretation of Lag Time—The dissolution lag time was the time required for the mechanical destruction of the coated tablet film. Thus, a shorter lag time represents a stronger destructive force. Significant correlations among the seven dissolution methods were observed regarding lag time (Table II). Except for the pairwise comparisons involving Method e, the least-squares regression lines passed through the origin. In these cases, the regression line slope obtained with lag time apparently reflected the relative destructive force intensity to the coated tablet film. Table IV shows the regression line slopes calculated for all combinations except those involving Method e. Thus, a slope of 1.64 for Method a *versus* b indicated that Method b gave 1.64 times the destructive force of a.

DISCUSSION

Agitating Intensity—The K_d values from nondisintegrating tablets (Table I) reasonably reflected the relative agitation intensities produced by the different dissolution methods. Method d had the lowest agitating intensity, and Method c-III (in) had the highest among the methods tested. Methods c-III, d, and e gave relatively sharp sigmoidal dissolution curves for all tablets, while Methods a, b, c-I, and c-II gave sigmoidal curves with smaller slopes, especially after 50% dissolution. Although Method e produced the mildest intensity, it gave comparatively sharp dissolution curves (Fig. 6). This finding suggests that the agitating intensity, as represented by the II dissolution rate from a nondisintegrating tablet, was not the rate-determining factor for disintegrating tablets.

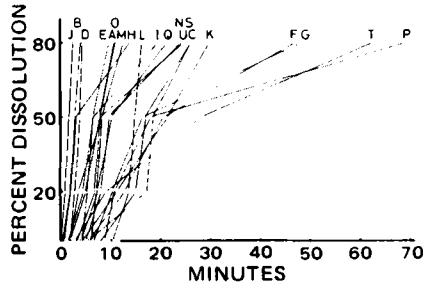


Figure 4—*Dissolution curves of I tablets determined by Method c-II.*

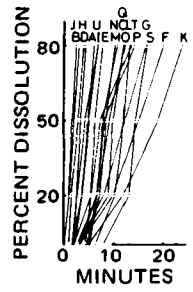


Figure 5—*Dissolution curves of I tablets determined by Method c-III.*

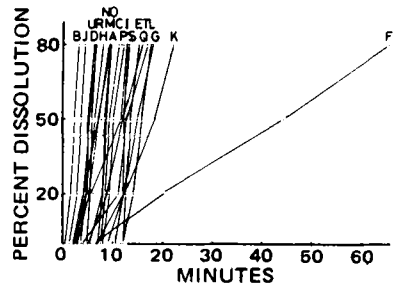


Figure 6—*Dissolution curves of I tablets determined by Method d.*

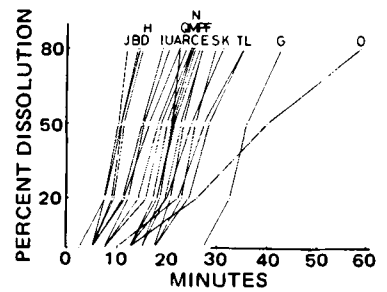


Figure 7—*Dissolution curves of I tablets determined by Method e.*

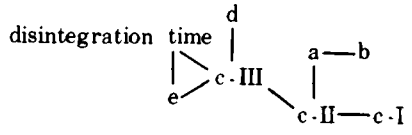
Because Method e used a rotating-vessel type reactor, "mound" formation of particles was prevented in spite of mild agitating intensity.

Tablets T and P showed very slow dissolution rates as determined by Methods a, b, c-I, and c-II but faster rates with Methods c-III, d, and e. The dispersing intensity was highly dependent on the stirring mode. Methods a, b, and c (the stirred-tank reaction type) could not prevent mound formation. On the other hand, the rotating-vessel devices, such as Methods d and e, generated high dispersing intensity in spite of low rotation speed, perhaps because of the unique stirring method.

Destructive Intensity to Coated I Tablet Films—The destructive intensity followed the descending order Method c-III ≥ c-II > d ≥ c-I > b > a (Table IV). Method e was not included in the comparison because of the inaccuracy in the lag time determination due to discontinuous sampling.

Correlation of I Tablet Dissolution Rates—Correlations between hardness and dissolution rates with all four rate parameters (lag time, T_{20}, T_{50}, and T_{80}) were insignificant statistically (Table II). Dissolution rate prediction from hardness is, therefore, impossible in this case. These results differ from those reported for other drugs (15, 16).

The relation among the methods is schematically represented in Scheme I. In this scheme, any two methods having a significant correlation for all four rate parameters were connected with a solid line. The results suggested two conclusions:



Scheme I—Relation among the methods of dissolution

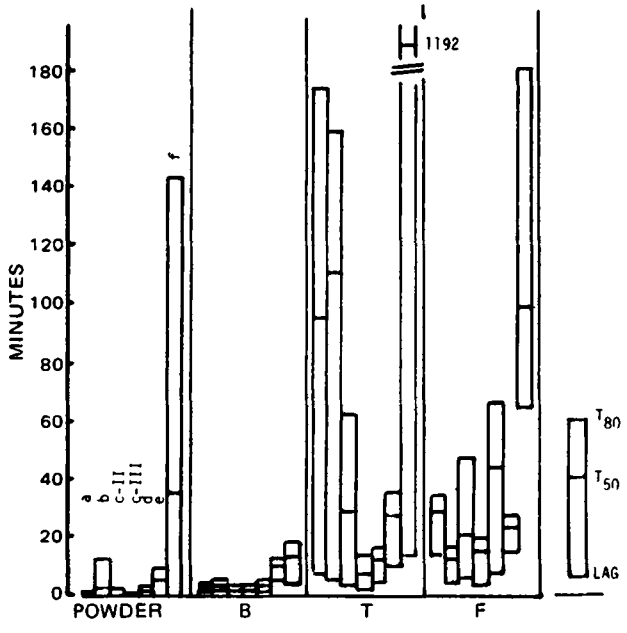


Figure 8—*Schematic representation of the dissolution rates of four samples determined by Method f and other methods.*

Table IV—Regression Line Slope Resulting from Pairwise Comparison of Lag Time Obtained with Different Dissolution Methods

	x-Axis					
y-Axis	a	b	c-I	c-II	c-III	d
a	1.0	1.64	2.50	4.55	3.70	2.00
b	—	1.0	1.61	3.23	2.56	1.20
c-I	—	—	1.0	1.49	2.13	1.32
c-II	—	—	—	1.0	1.20	0.71
c-III	—	—	—	—	1.0	0.50
d	—	—	—	—	—	1.0
Average relative intensity	1.0	1.56	2.33	4.01	4.40	2.40

1. Two different device types were distinguishable: stirred-tank reactors and rotating-vessel reactors. Only Method c-III correlated with both groups.

2. Among similar devices, a significant correlation was not observed among all methods. Thus, dissolution methods are not interchangeable, even if they belong to the same group.

Dissolution Rates Using Method f—Method f was inadequate for disintegrating tablet evaluation due to filter clogging. To avoid this problem, experiments were carried out without the filter. The modified device was similar in nature to that used in Method a for well-dispersed tablets since most disintegrated particles were returned to the impeller-stirred vessel. For poorly dispersed tablets, however, the dissolution rate may be evaluated more accurately with Method f because the drug remained longer in the column. Thus, despite the clogging defect, Method f was used for selected dissolution tests.

Figure 8 shows the dissolution rates of four I samples, *i.e.*, the powder and three commercial tablets, as determined by different methods. Surprisingly, the powder took much longer to dissolve using Method f than with the other methods. This result might have occurred because of the small agitating intensity produced by Method f (Table I) or because the laminar flow produced much less dispersing ability than that achieved with turbulent flow in the other methods. The dissolution lag times observed with Method f were generally longer than those obtained with other methods. This finding suggests that the Method f destructive force to coated film was far less than that of other methods. These data indicate that Method f is suitable for testing the intrinsic dissolution rate of a nondisintegrating drug matrix because of its controlled hydrodynamic flow but is unsuitable for evaluating the drug dissolution rate from disintegrating tablets and capsules.

REFERENCES

(1) J. Swarbrick, "Current Concepts in the Pharmaceutical Sciences: Biopharmaceutics," Lea & Febiger, Philadelphia, Pa., 1970, p. 265.

(2) W. H. Barr, *Pharmacology*, **8**, 55 (1972).

(3) R. V. Bathe, O. Hafliger, F. Langenbucher, and D. Schonleber, *Pharm. Acta Helv.*, **50**, 3 (1975).

(4) G. Levy and B. A. Hayes, *N. Engl. J. Med.*, **262**, 1053 (1960).

(5) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975.

(6) M. Gibaldi and H. Weintraub, *J. Pharm. Sci.*, **59**, 725 (1970).

(7) D. G. Baun and G. C. Walker, *ibid.*, **58**, 611 (1969).

(8) J. E. Tingstad and S. Riegelman, *ibid.*, **59**, 692 (1970).

(9) O. Umezawa and S. Yamamoto, *J. Nippon Hosp. Pharm. Assoc.*, **2**, 73 (1976).

(10) J. Tingstad, E. Gropper, L. Lachman, and E. Shami, *J. Pharm. Sci.*, **63**, 925 (1974).
(11) F. L. Underwood and D. E. Cadwallader, *ibid.*, **65**, 697 (1976).
(12) M. Ikeda and K. Nishimura, "Abstract 91st Annual Meeting of the Pharmaceutical Society of Japan," Fukuoka, Japan, Apr. 1971, p. 323.
(13) A. Noyes and J. Whitney, *J. Am. Chem. Soc.*, **19**, 930 (1897).
(14) W. Nernst, *Z. Phys. Chem.*, **47**, 52 (1904).
(15) S. Kitazawa, I. Johno, Y. Ito, S. Teramura, and J. Okada, *J. Pharm. Pharmacol.*, **27**, 765 (1975).
(16) T. Higuchi, R. A. Narsimha, L. W. Busse, and J. V. Swintosky, *J. Am. Pharm. Assoc., Sci. Ed.*, **42**, 194 (1953).

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Dissolution Systems for Chloramphenicol Tablet Bioavailability

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Abstract □ The relationship between chloramphenicol (I) tablet bioavailability and *in vitro* dissolution rates was examined. The effect of solid food on the I tablet and powder bioavailability was also studied. Five tablets of I were selected for bioavailability testing on the basis of the dissolution rates of 18 I tablets (250 mg) determined by several methods. Compound I, 500 mg, was administered orally to five subjects, following overnight fasting, according to a crossover design. The bioavailability parameters were obtained from urinary I excretion. Among the five formulations studied, only one tablet (F) showed significantly poorer bioavailability. The dissolution rates at pH 1.2 did not give the same rank order as the bioavailability. The dissolution rate of Tablet F showed remarkable pH dependency. The dissolution rates at pH 4 showed good correlation with *in vivo* bioavailability data. The bioavailability of I powder was not affected by solid food. Tablet F, which had poor bioavailability in the fasting state, showed good bioavailability when administered just after the standard breakfast.

Keyphrases □ Chloramphenicol—various dosage forms, bioavailability correlated with dissolution rates □ Bioavailability—chloramphenicol, various dosage forms, correlated with dissolution rates □ Dissolution rates—chloramphenicol, various dosage forms, correlated with bioavailability □ Antibacterials—chloramphenicol, various dosage forms, bioavailability correlated with dissolution rates

The dissolution rates of 21 chloramphenicol (I) tablets manufactured in Japan were reported previously (1). In this paper, the *in vivo* bioavailability of selected I tablets was correlated with *in vitro* dissolution tests. The bioavailability of nine different I tablets available in Japan was determined previously by Watanabe *et al.* (2, 3), who showed significant correlation of *in vivo* bioavailability with disintegration time and dissolution rate as measured by a disintegration apparatus[1] using water as the medium.

The dissolution devices used in that study (beaker, rotating basket, oscillating basket, and disintegration[1] methods) all belonged to the stirred-tank reactor type (1). *In vivo–in vitro* correlation with rotating-flask type dissolution devices was not attempted. These investigators (2, 3) also reported better correlation of *in vitro* dissolution rate and *AUC* (area under plasma level–time curve) following oral administration of I tablets with water as the dissolution medium instead of the pH 1.2 solution recommended in JP IX. Chloramphenicol dissolution in an unbuffered medium could have complicated the system since the pH value changed as the tablet dissolved.

Comparative bioavailability studies of five I tablets are described in this report. These tablets were selected based on dissolution rates of 18 I tablets (250 mg) and I powder determined by seven methods (1). The relationship between *in vivo* bioavailability and *in vitro* dissolution was examined. The effect of food on the I bioavailability was also studied.

EXPERIMENTAL

Materials—The I tablets and powder were the same as those described previously (1), except for Tablets V and V′ which were of the same brand but different lot numbers.

***In Vitro* Studies**—The methods and procedures for determining the dissolution rate were the same as those reported previously (1): beaker (a), rotating basket (b), oscillating basket (c-II and c-III), rotating flask (d), solubility simulator (e)[2], and column (f). The dissolution medium pH was controlled by a pH stat. No corrections were made for acidic dissolution media adjusted at pH 1.2.

Bioavailability Studies—Six healthy adult male volunteers, 55–72 kg and 29–49 years old, participated after being informed about the study and the drug. All subjects received no barbiturates or other enzyme-inducing agents for 30 days before and for the duration of the studies. They also received no other medication or alcoholic beverages for 7 days before and for the duration of the studies.

Study I—The bioavailability of five I tablets was studied using a Latin square. Treatments were separated by 1 week. Subjects fasted for 10 hr prior to dosing and took two I tablets (total of 500 mg) with 300 ml of water. They took 200 ml of water at 2 hr and had lunch at 4 hr after administration. Urine samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, and 28 hr after dosing. The exact sampling times and the volume were recorded.

Study II—The effect of solid food on Tablet F and I powder bioavailability was studied with four subjects using a Latin square. Tablet F or I powder (500 mg) was taken either with 300 ml of water in the fasting state or immediately after a standard breakfast of 100 g of toast, 20 g of butter, 35 g of cucumber, 65 g of boiled egg, 200 ml of milk, and 100 ml of water. The urine collection procedure was the same as that for Study I.

Study III—One subject participated in a study of the relationship

[1] Erweka.

[2] Sartorius-Membranfilter GmbH, Göttingen, West Germany.

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