USP Dissolution IV: Comparison of Methods

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Abstract □ The hydrodynamics of four dissolution apparatus—*viz.*, the USP basket, the USP paddle, the stationary basket–spinning filter, and the USP disintegration apparatus, were characterized. At higher velocities, the relationship between the intrinsic dissolution rate constant and linear velocity was parabolic rather than linear.

Keyphrases □ Dissolution—hydrodynamics of four different types of apparatus compared □ Apparatus, dissolution—hydrodynamics of four different types compared □ Hydrodynamics—four different types of dissolution apparatus compared

There has been an abundance of literature regarding dissolution apparatus in the past 15 years. A good survey of methods was given by Pernarowski (1) who noted over 150 different apparatus designs. Since many dissolution curves are obtained under these conditions, methods are needed whereby one could grossly correlate data obtained by one method to those obtained by another. One purpose of this study was to suggest such an approach.

A direct approach is, of course, to standardize a test and to make it "official." This approach was attempted in NF XIV and USP XVIII and XIX. Nevertheless, results obtained with different pieces of apparatus or different operators frequently differ. One purpose of this study was to suggest an approach for normalization of results obtained with the same apparatus design but different pieces of equipment.

The drive toward standardization in recent years has tentatively narrowed down to the following three methods: the USP basket apparatus (2), the paddle apparatus (3), and the stationary basket–rotating filter method (4).

Dissolution theories based on Noyes–Whitney (5), Nernst–Brunner (6), and Hixson–Crowell (7) treatments result in "intrinsic dissolution rate constants," k (centimeters per second). These constants equal D/h, where D is the diffusion coefficient (square centimeters per second) and h is the thickness of the diffusion layer about the dissolving particle. Within the limitation of these approaches, the layer thickness is a function of the hydrodynamics of the system (8–10). Therefore, one would not expect identical dosage forms to give identical dissolution curves in the three apparatus.

However, a rank-order correlation between dissolution rates and liquid velocities would be expected. To establish this correlation, it was necessary to establish that there is a relationship between the dissolution rate constant and liquid velocity (8).

In this study, this concept was carried further. Directly measured liquid velocities were compared with dissolution rate constants to establish a functionality over a wider range of velocities. This information then was used to establish the velocity in various spots by the inverse technique—*viz.*, by measuring the dissolution rate constants of oxalic acid in various spots of the apparatus.

Table I—USP Basket Positions

Position	R, cm	H, cm	θ[a]
1	0–1	2	—
2	5	2	90°, 180°, 270°
3	3.15	−0.9	90°, 180°, 270°
4	0–1	0	—
5	3	2	180°
6	5	11	90°, 180°, 270°
7	0.7–1	2	—
8	1–1.31	2	—

[a] Three angles denote that three tablets were placed in individual positions as indicated.

EXPERIMENTAL

Oxalic acid tablets were prepared at 4535 kg (10,000 lb) force on a hydraulic press, using a flat-faced tablet punch and die with a flat steel plate as the lower retainer. The tablets were 1.13 cm in diameter and 0.33 cm in height and weighed 0.500 g. When tablets were to be suspended in the liquid, a piece of nylon string was placed on the retaining plate, producing a tablet on a string, which could then be suspended in the liquid at a desired position. In certain cases (paddle method), the positioning was done *via* a glass capillary.

The following methods were studied: USP rotating basket (50, 100, and 150 rpm); USP proposed paddle method (3) (50, 100, and 150 rpm); rotating filter–stationary basket method (4); and USP disintegration apparatus (2). The dimensions of the vessel used for USP basket and paddle methods are shown in Fig. 1*a* and Table I. A polar cylindrical coordinate system as shown in Fig. 1*b* was used.

The positions tested with the USP basket method are shown in Table II and Figs. 2 and 3. It was determined earlier (11) that agitation in the USP basket method does not ensure homogeneity of the liquid. The method used here was as follows. A volume of 900 ml of 0.1 N HCl was placed in the dissolution vessel, which was located in a constant-temperature bath at 25°. One-half hour at 25° was allowed for temperature calibration, and the tablets (3) were placed at the desired position(s). A timer was started simultaneously. After t sec, the tablet was removed and

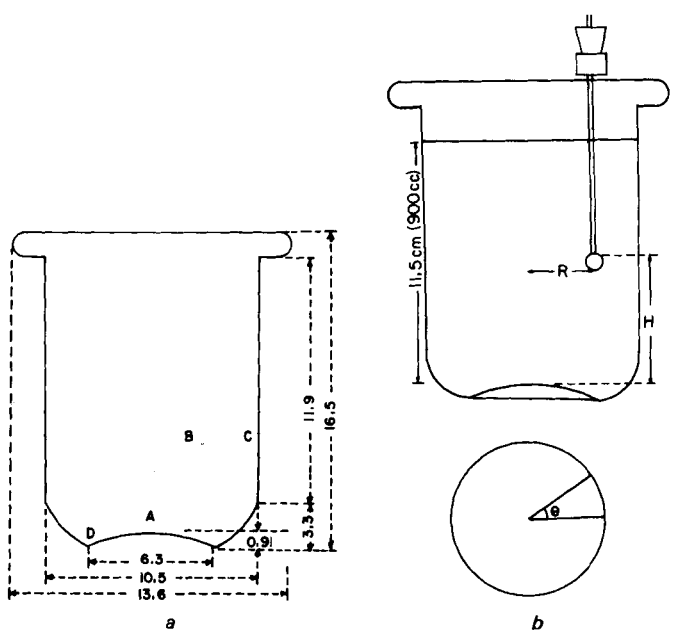

Figure 1—*Dimensions* (a) *and descriptive coordinates* (b) *of the vessel used in the USP apparatus.*

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Table II—Positions of Tablets in the Paddle Apparatus

Position	R, cm	H, cm	θ^a
1	3.15	−0.9	90°, 180°, 270°
2	0–1	0	—
3	5	4.5	90°, 180°, 270°
4	3	4.5	180°
5	5	11	90°, 180°, 270°

[a] Three angles denote that three tablets were placed in individual positions as indicated.

the entire content of the dissolution vessel was determined by spectrophotometry at 255 nm.

The experiment was then repeated for various time periods, t, to produce a dissolution curve of concentration, C (milligrams per milliliter), *versus* t (seconds). This method is obviously more cumbersome than taking samples at a particular place in the liquid at various times (and maintaining the same bulk liquid throughout the experiment), but the external liquid is not homogeneous in the early phases of dissolution in the USP basket method (11).

With the proposed USP paddle method, the tablets were held in position by capillary glass tubes. A special means of introducing the tablet was needed when it was underneath the paddle; two curved capillaries with a string running through both allowed the tablet to be pulled into position rapidly. The adequacy of the agitation in the paddle method was first determined (11) by sampling and assaying the entire content at several time and position points. The sampling positions used are shown in Fig. 3. Dissolution rates were determined in the positions shown in Fig. 4.

To validate the velocities obtained for dissolution data, the following crude, but direct, method was used. Scarlet red dye[1] was dissolved in cyclohexyl chloride, which has a density matching that of water at 25°. A drop of this solution was introduced at the various test points, and the

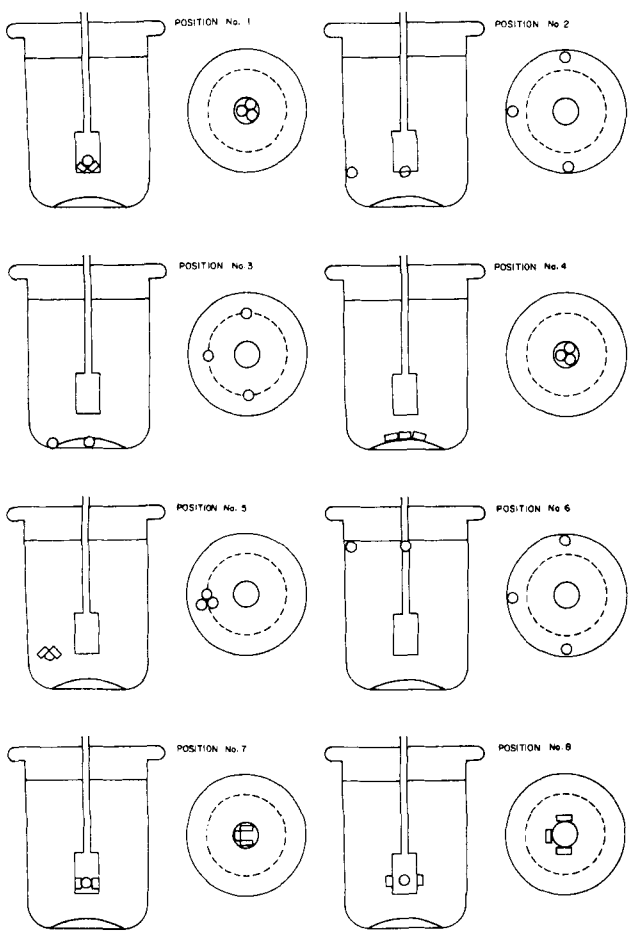

Figure 2—*Positions tested in the USP basket study.*

[1] Sudan IV.

Table III—Intrinsic Dissolution Rate Constants, k, and Corresponding Liquid Velocities, v, for Four Dissolution Methods

Method	Position	Condition, rpm	10^3k, cm/sec[a]	v, cm/sec[b]
USP basket	1	50	1.3 ± 0.06	4.1
	2	50	0.93 ± 0.04	2.4
	3	50	0.71 ± 0.10	1.6
	4	50	0.80 ± 0.10	1.9
	5	50	0.95 ± 0.05	2.5
	6	50	0.92 ± 0.02	2.4
	7	50	1.8 ± 0.2	6.9
	8	50	1.85 ± 0.5	7.2
	1	100	1.7 ± 0.07	6.3
	2	100	0.95 ± 0.08	2.5
	3	100	0.92 ± 0.02	2.4
	4	100	1.17 ± 0.06	3.5
	5	100	1.00 ± 0.03	2.7
	6	100	0.90 ± 0.08	2.3
	7	100	1.7 ± 0.15	6.3
	8	100	2.40 ± 0.07	10.8
	1	150	2.2 ± 0.20	9.4
	2	150	1.05 ± 0.05	2.9
	3	150	1.02 ± 0.04	2.8
	4	150	1.50 ± 0.06	5.1
	5	150	1.19 ± 0.05	3.6
	6	150	0.95 ± 0.02	2.5
	7	150	2.8 ± 0.3	13.8
	8	150	3.30 ± 0.14	17.9
	1 (bottom)	50	1.9 ± 0.2	7.5
	2	50	1.6 ± 0.2	5.7
	3	50	2.1 ± 0.1	8.7
	4	50	1.90 ± 0.03	7.5
	5	50	1.8 ± 0.1	6.9
	6 (free bottom)	50	1.8 ± 0.1	6.9
	1 (bottom)	100	2.90 ± 0.04	14.7
	2	100	2.4 ± 0.1	10.8
	3	100	3.6 ± 0.3	20.6
	4	100	3.5 ± 0.3	19.7
	5	100	3.0 ± 0.2	15.4
	6 (free bottom)	100	2.5 ± 0.1	11.6
	1	150	4.1 ± 0.3	25.3
	2	150	3.1 ± 0.2	16.3
	3	150	4.2 ± 0.2	26.3
	4	150	3.8 ± 0.3	22.5
	5	150	3.5 ± 0.2	19.7
	6 (free bottom)	150	3.3 ± 0.2	17.9
Rotating filter	Inside basket	300	2.00 ± 0.03	8.1
	Bottom rim	300	1.9 ± 0.2	7.5
	Inside basket	600	2.9 ± 0.2	14.6
	Bottom rim	600	3.0 ± 0.3	15.4
USP disintegration	Inside tubes	—	2.9 ± 0.2	14.6
	Bottom of beaker	—	1.4 ± 0.2	4.6

[a] Limits shown are 95% confidence interval. [b] According to Eq. 4a in the form: $\ln v = 1.587 \ln k + 11.957$.

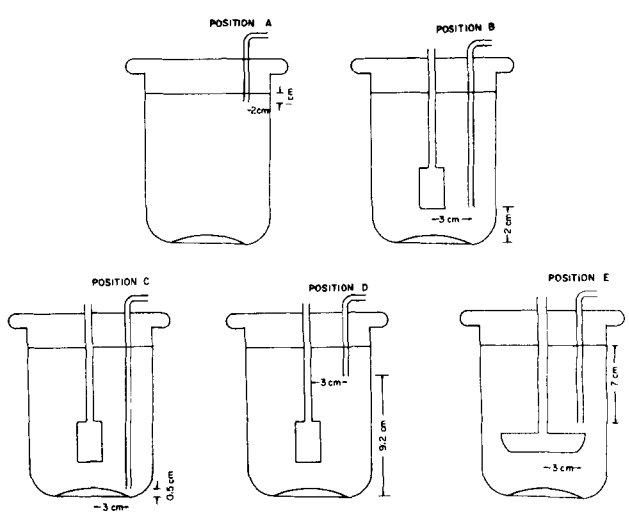

Figure 3—*Sampling positions in the USP basket apparatus (A–D) and paddle method (E).*

Table IV—Observed and Calculated Velocities and Dissolution Rate Constants for Four Dissolution Methods

Method	Position	Condition, rpm	Velocity, cm/sec		ln $v°$	10^3k, cm/sec	$7 + \ln k$
			Observed, $v°$	Calculated			
USP basket	8	50	4.6	5.2	1.53	1.85	0.71
	8	100	9.9	10.5	2.29	2.40	0.97
	8	150	16.1	15.7	2.78	3.3	1.29
Rotating filter		300	7.1	6.2	1.96	2.0	0.79
		600	8.4	8.4	2.13	1.9	0.43
USP paddle	1	50	8.2	—	2.10	1.9	0.73
	1	100	14.5	—	2.67	2.9	1.16
	3	50	8.1	—	2.09	2.1	0.83
	3	100	15.7	—	2.75	3.6	1.37
	4	50	9.4	—	2.24	1.9	0.73
	5	50	6.6	—	1.89	1.8	0.68
	5	150	18.8	—	2.93	3.5	1.35
USP disintegration	Inside tubes	—	—	16.1	2.78	2.9	1.16
	Outside tubes	—	—	6.4	1.85	1.4	0.43

time required for one rotation was noted. Many trials are needed to get the correct path, since the path followed by the drop must be as close to a circle as possible.

With the stationary basket–rotating filter apparatus (4), the adequacy of mixing was first determined as already described. The dissolution rates were then determined with the tablet inside the basket and with the tablet outside the basket (on the bottom close to the rim) at 300 and 600 rpm.

With the USP disintegration apparatus, the adequacy of mixing was first ascertained as already described. The dissolution rates were then determined with the tablets in the tubes (three tablets were placed, one each, in alternating tubes) and with the tablets outside the tube–basket assembly. A volume of 800 ml of 0.1 *N* HCl was used in a 1000-ml beaker (10-cm diameter). At the lowest part of the downstroke, the mesh was 2.5 cm above the bottom. Samples of 4 ml were used for assay.

In all described experiments, at least eight time points were used to calculate the dissolution rate constants.

The dissolution of two dosage forms—*viz.*, 50-mg nitrofurantoin tablets and capsules[2], was then determined in the four apparatus with the prescribed procedures. With the capsules, two antifloating devices were used[2]: a copper coil (with four coilings) of the outer dimensions of the capsule into which the capsule fits snugly, and a 6-mesh steel basket 2 cm in diameter. (This basket can be separated into two halves and is held together by a clip.)

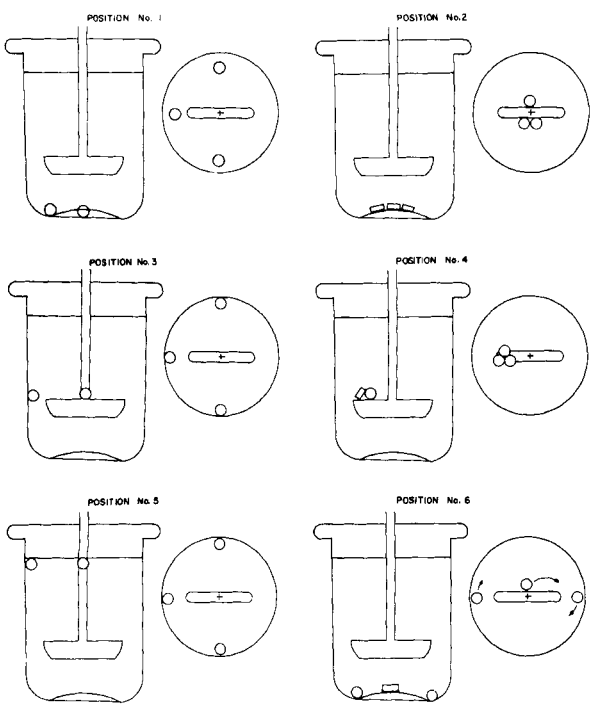

Figure 4—*Tablet positions in the USP paddle method.*

[2] Supplied by the Biopharmaceutics Laboratory, Food and Drug Administration, Washington, D.C.

The rotations per minute were checked and verified in all cases by means of a strobe light.

RESULTS AND DISCUSSION

The intrinsic dissolution rate constants were obtained from concentration *versus* time curves by the method of Lai and Carstensen (12) (Table III). The method is a modification of the Hixson–Crowell law; but where the Hixson–Crowell law assumes the particles to be isometric, the modified method (12) takes into account the change in the shape factor as a function of time.

Carstensen and Dhupar (8) studied the k values *versus* v in a rather narrow column; v was kept fairly low to avoid turbulence. In the study reported here, the dissolution apparatus had large diameters and larger k (and v) values. Because of the larger diameter, the higher v values do not necessarily imply turbulent flow conditions. Table IV lists the velocities obtained experimentally by the dye method and the k values. The linearity found between k and v at low v values (8) fails at higher v values (Fig. 5).

The first point then is to establish a correlation between v and k at these higher velocities. Therefore, the experimentally found velocity values were compared with theoretical figures. For the USP basket and spinning filter methods, this comparison was done as follows. If v denotes the laminar velocity of an incompressible fluid in steady motion between two infinitely long concentric rotating cylinders of radii R_1 and R_2 (where $R_2 > R_1$) at a point that is r cm removed from the concentric axis, it can be shown (13) that:

$$v = Ar + (B/r) \qquad \text{(Eq. 1)}$$

If the outer cylinder is stationary while the inner cylinder moves so that the surface velocity is Ω, then Eq. 1 is subject to the following boundary conditions:

$$\Omega = AR_1 + (B/R_1) \qquad \text{(Eq. 2}a\text{)}$$

$$0 = AR_2 + (B/R_2) \qquad \text{(Eq. 2}b\text{)}$$

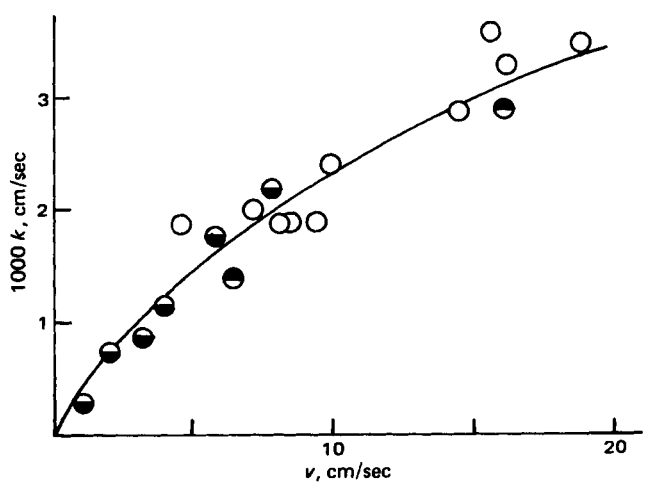

Figure 5—*Dissolution data from USP basket and paddle and rotating filter method* (○), *USP disintegration apparatus* (◓), *and data reported by Carstensen and Dhupar* (8) (◒).

Table V—Dissolution Parameters of Nitrofurantoin Tablets and Capsules

Method	K, 10^3, sec^{-1} Tablet	K, 10^3, sec^{-1} Capsule	v, cm/sec	Position
USP basket				
50 rpm	0.025	0.050	7	7, 8 average
100 rpm	0.033	0.080	8	7, 8 average
150 rpm	0.026	0.084 0.075	16	7, 8 average
Paddle: cage				
50 rpm	0.012 0.018	0.025 0.045	7.5	1 (bottom)
100 rpm	0.03	0.13	14.7	1 (bottom)
150 rpm	0.25	0.27	17.9	1 (bottom)
Paddle: coil				
50 rpm	0.022	0.012	7.5	1 (bottom)
100 rpm	0.075	0.13	14.7	1 (bottom)
150 rpm	0.20	0.24	17.9	1 (bottom)
USP disintegration	0.97	0.043	14.6	In tube
Rotating filter				
300 rpm	0.047 0.023	0.015	8.1	In basket
600 rpm	0.058	0.30 0.25	14.5	In basket

The last equation assumes that no slip occurs. This principle is directly applicable to the rotating basket. It also applies to the rotating filter method because the filter can be viewed as the inner cylinder and the beaker can be viewed as the outer cylinder (R_2 = 5 cm). If one assumes that the major contribution of medium movement at the site of the basket is due to the filter body (R_1 = 2.5 cm), as demonstrated in Fig. 6, while the major contribution of the medium movement at the bottom rim is due to the filter base (R_1 = 4.5 cm), then Eq. 1 can be solved for these two positions at various numbers of rotations per minute of the filter.

Solving for tablets inside the basket at 300 rpm gives $v = (53.25/r) - 2.13r$; at 600 rpm, $v = (106.5/r) - 4.26r$. Obtaining A and B values for the bottom rim gives $v = (200/r) - 8r$ at 300 rpm and $v = (400/r) - 16r$ at 600 rpm.

If one takes 3.75 as r for the basket and 4.5 cm as r for the bottom rim position (Fig. 6), the medium velocity at the two positions can be predicted. The predicted values are given in Table IV.

Table IV also lists the observed velocities obtained using the dye method in the paddle apparatus. To estimate the velocities in the USP dissolution apparatus, the following simplified model was used. If the entire rack (Fig. 6) of the disintegration apparatus does not cause any displacement of medium, then the average relative velocity of the rack moving through the medium is 6.4 cm/sec (calculated from the fact that the rack moves at a rate of 32 cpm and moves 6 cm in half of a cycle). During the downstroke, the solid portion of the base (Fig. 7) of the rack displaces 256 ml in 0.94 sec. This volume of medium has to move through the tubes and through the side of the rack.

The beaker is 10 cm in diameter while the base of the rack is 9 cm in diameter, giving an area of 15 cm^2 between the rack base and the side wall of the beaker. The total cross section of the six tubes is 21 cm^2 less 8 cm^2 due to the wire mesh, *i.e.*, a total of 13 cm^2. Therefore, the 256 ml of medium has to travel through about 28 cm^2 in 0.94 sec, creating an upward medium velocity of 9.7 cm/sec, while the rack moves downward at 6.4 cm/sec; *i.e.*, the relative velocity is 16.1 cm/sec between the base of the rack and the medium. The reverse would happen during the upward stroke, resulting in the same relative velocity.

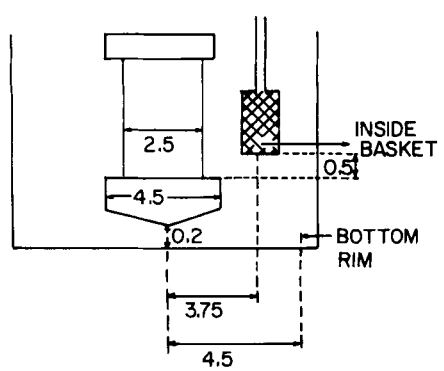

Figure 6—*Dimensions (in centimeters) of rotating filter apparatus.*

Table VI—Mean Deviation of Assays from True Value[a]

Method	Position	Temperature	Number of Determinations, n	Mean Deviation, % (p = 0.95)
Paddle, 50 rpm	Average of all[a]	25°	17	4.2 ± 1.8
Paddle, 100 rpm	Average of all[a]	25°	20	3.1 ± 0.9
Paddle, 150 rpm	Average of all[a]	25°	20	6.0 ± 2.0
Paddle, 50 rpm	Average of all[a]	37°	7	6.7 ± 4.0
Rotating filter[b]	A	25°	9	10 ± 3
Rotating filter[b]	Filter	25°	7	13 ± 3
Rotating filter[b]	E	25°	9	2.8 ± 1.6
USP disintegration		25°	5.3	5.3 ± 2.8

[a] If a sample is taken at random from the liquid during the first 4 min of dissolution, the deviation from the true content will be as shown. [b] Both 300- and 600-rpm figures are included.

There is good correlation between the observed values (*i.e.*, the values from the dye method) and the calculated values in the five cases where comparison is possible (USP basket method and spinning filter method). The first five entries in Table IV give the following least-squares fit:

$$v_{calc} = 0.96v_{obs} + 0.37 \quad (r = 0.989, n = 5) \qquad \text{(Eq. 3)}$$

The slope does not differ significantly from 1.00 (p = 0.01), and the intercept does not differ significantly from zero (p = 0.01). Therefore, it is felt that the dye method yields results in good agreement with theory. At the higher k values that apply here, as mentioned, k is not linear when plotted *versus* v. A plot of ln k *versus* ln v is shown in Fig. 8 and the least-squares fit is:

$$\ln k = (0.63 \pm 0.20) \ln v - (7.53 \pm 0.57) \quad (r = 0.85, n = 15) \qquad \text{(Eq. 4a)}$$

Equation 4*a* may be written as:

$$k = 0.00054(v^{0.63}) \qquad \text{(Eq. 4b)}$$

and the curve shown in Fig. 5 is indeed this correlation. At low v values, the previously reported linear data (8) fit well with Eq. 4*b*. Both the linear model and the one outlined here assume that $k = 0$ at $v = 0$, which cannot be strictly correct since there will always be some finite dissolution rate even under stagnant hydrodynamic conditions.

It is expected from hydrodynamic theory (14) that the diffusion layer thickness, h, relates to the liquid velocity by the relation:

$$h = \Gamma v^{-1/n} \qquad \text{(Eq. 5)}$$

where Γ is a proportionality constant and n has a value between 1 and 2. Since $k = D/h$, it would be expected that:

$$k = \beta v^{1/n} \qquad \text{(Eq. 6)}$$

and Eq. 4*a* substantiates this assumption; β is here a proportionality constant.

It is now possible to list velocities calculated from dissolution rate constants in all positions of the four apparatus tested, and this is done in the last column of Table III.

It was stated previously (15) that, *e.g.*, 100 rpm in the paddle method corresponded to 150 rpm in the basket method which, in turn, corresponded to 600 rpm in the spinning filter method. The spinning filter method yields a velocity of 14–15 cm/sec, the basket method in and at the basket (positions 7 and 8, respectively) yields a velocity of 14–18 cm/sec at 150 rpm, and the paddle method at the bottom (either confined or free, *i.e.*, position 1 or 6, respectively) yields a velocity of 12–15 cm/sec at 100 rpm. This result substantiates such rules in the sense that the dissolution is considered from a point of view that disregards disintegration effects. These effects were discussed elsewhere (16).

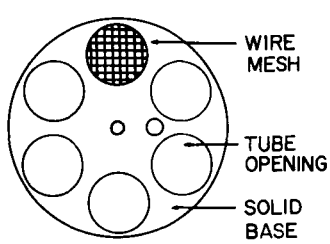

Figure 7—*USP disintegration apparatus rack.*

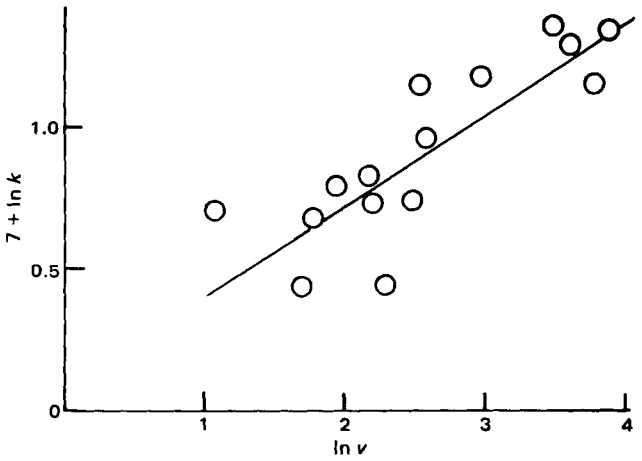

Figure 8—*Dissolution data from dissolution apparatus reported here plotted according to Eq. 4a.*

The effect of liquid velocity on the dissolution of nitrofurantoin from two dosage forms (capsules and tablets) was checked by conducting dissolution tests with all mentioned methods. All (except one) sets of data adhered to a σ^{-}-type plot (17) of the type:

$$\ln(m/m_0) = -Kt + Q \qquad \text{(Eq. 7)}$$

where m is mass undissolved, the zero subscript implies the initial condition, K is a dissolution constant (seconds^{-1}), and Q is a constant. The value of K depends both on dissolution and on how well the dissolution apparatus disintegrates the dosage unit, and Q depends on dissolution only (16). Table V lists K values from the data. There is a correlation between K and v (correlation coefficient of 0.432, which is significant for $n = 29$ at $p = 0.95$), but it is not sufficiently exacting to allow correlation from method to method. The different methods undoubtedly act differently regarding the disintegration of the dosage unit. The fact that the correlation is real, however, makes it a sound basis for calibration or correlation between different pieces of the same apparatus.

The heterogeneity of the dissolution medium reported earlier for the USP basket method (8) is not nearly as pronounced in the other apparatus studied. The paddle apparatus in particular gives good homogeneity (Table VI).

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Quantitative TLC Determination of Propranolol in Human Plasma

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Abstract □ A spectrodensitometric assay was developed for propranolol based on measurement of the absorbance of the drug on silica gel plates irradiated at 288 nm. Quantities as low as 0.010 μg can be detected, and a linear relationship was obtained between 0.010 and 0.400 μg. The percent recovery from plasma spiked with known amounts of the drug was 90.0–102.0. This procedure was used to determine propranolol in the plasma of patients receiving therapeutic doses of the drug.

Keyphrases □ Propranolol—TLC analysis in plasma □ TLC—analysis, propranolol in plasma □ Cardiac depressants—propranolol, TLC analysis in plasma

Propranolol produces a specific blockade of β-adrenergic receptors with minimal intrinsic activity, resulting in an effect on the cardiovascular system. It is capable of suppressing heart rate and contractility and of increasing vasoconstriction in those beds where there may be some degree of masked β-adrenergic vasodilator effect. It is used for the treatment of angina pectoris and in cardiac arrhythmias, hypertrophic subaortic stenosis, pheochromocytoma, and digitalis-induced ventricular tachycardia.

Propranolol is presently receiving much attention in the treatment of essential hypertension associated with a high cardiac output or high plasma angiotensin levels (1, 2).

BACKGROUND

To follow the pharmacokinetics of this drug and to understand the mechanism of its action, plasma propranolol levels are determined. The low levels and the wide variability of plasma propranolol concentrations

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