Specificity of the Relationship between Rate of Dissolution and Disintegration Time of Compressed Tablets

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Dissolution rates and disintegration times of 76 lots of tablets were determined employing the U.S.P. disintegration apparatus without plastic disks. The time for 50% of the drug to dissolve ($t_{50\%}$) or the amount of drug in solution at a specific time was used as criteria of the rate of dissolution. Disintegration times were also obtained with plastic disks. The drugs included a steroid, a sulfonamide, an antidiabetic agent, and an aspirin-phenacetin-caffeine combination. In some cases there was a quantitative relationship between $t_{50\%}$ and one or both of the disintegration times. In other cases there was none. Where a quantitative relationship existed, the slopes of the lines relating the variables varied widely and depended upon the drug(s) involved, and in one case upon the presence of a pharmaceutical adjuvant. With two of the series of tablets, one could not differentiate between lots on the basis of their disintegration times determined with plastic disks. However, in one of these series disintegration times were determined without plastic disks, and in both the $t_{50\%}$ values clearly identified lot-to-lot variation. Questions are raised regarding the use of plastic disks in the official disintegration test and the validity of applying uniform disintegration standards to large groups of drugs in tablets. An explanation for the correlation between *in vivo* availability of certain drugs administered as tablets to human subjects and their disintegration times is presented.

SIXTY YEARS ago Hance (1) defined solubility as applied to compressed tablets to indicate the "power to disintegrate rather than the power to form solutions." This is regrettable terminology. Sperandio, *et al.* (2), pointed out that disintegration of a tablet does not necessarily mean that the drug has dissolved; the tablet is merely broken up into smaller particles when it disintegrates. Nair and Bhatia (3) showed that changing the screen in the U.S.P. disintegration apparatus from a No. 10 mesh to a No. 20 mesh screen could markedly alter observed disintegration times. Parrott, *et al.* (4), stated that "while the disintegration time of a tablet does influence the rate of drug release to the body, a most important aspect is the rate of release from the primary drug particle since solution of the drug is essential in order for absorption to take place."

Nelson (5) and Levy (6) pointed out that rapid disintegration of tablets has been equated by some workers with rapid availability of the drug for absorption. In his excellent review of the history of committee and official action on tablet disintegration tests, Vliet (7) quoted from the April 1949 Contact Committee meeting minutes as follows: "in setting up a list of recommended disintegration times, it was felt that the primary purpose of such a limit is to insure to the user of the tablet that ultimate availability of the medication and in such reasonable time as the nature of the medication might warrant." With a series of sugar-coated tablets containing riboflavin and another series containing sodium *p*-aminosalicylate, Chapman, *et al.* (8, 9), showed that the availability of these drugs for absorption was predictable from the disintegration time of the tablets determined by a modified U.S.P. XIV disintegration test. The modifications involved employing a 3-L. instead of a 1-L. beaker, using rubber disks which exerted a rubbing action on the tablets, and using a simulated gastric juice, pH 1.6, for the first half-hour followed by simulated intestinal juice, pH 8.0. Subsequently, Endicott and Kirchmeyer (10) presented a literature study and new experimental data as evidence that tablets requiring considerably more than 1 hour to disintegrate *in vitro* by the U.S.P. XV method may still be satisfactory drug sources in the human body. With a series of five commercial aspirin tablets, Levy (6) showed that their disintegration times had no relation whatsoever to rate of absorption or to biological availability of the aspirin in human subjects. However, the amount of aspirin in solution after 10 minutes, which was measured in a standardized *in vitro* test and used as a criterion of the rate of dissolution, did correlate linearly with the amount of salicylate excreted during the first hour following administration of the tablets.

Perhaps the reason for this discrepancy in

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results lies in the specificity of any correlation between either rate or extent of availability *in vivo* and either rate of dissolution or disintegration time determined by a particular *in vitro* method. Assuming that the rate and/or the extent of availability of a certain drug administered in tablets to human subjects will correlate with the *in vitro* rates of dissolution, then the *in vivo* data will also correlate with results of some disintegration test providing the specific dissolution test correlates with the specific disintegration test.

This hypothesis requires experimental proof. In this communication evidence is presented that the nature of the drug, the tablet formulation, and the method of manufacture will determine whether a correlation exists between any two of the variables: rate of dissolution, disintegration time determined without disks, and disintegration time determined with disks. If such a correlation exists, these same factors will also influence the quantitative relationship between the variables. In future communications data will be presented which also support the concept of specificity in correlations between *in vivo* availability and either rate of dissolution or disintegration time determined by particular methods.

Suggestions have been made (6, 11, 12) that the U.S.P. tablet disintegration test be replaced by a dissolution test, and opinions were recently requested (13) on this subject. Before such a change is made, or even seriously considered, it appears to be desirable to test the above hypothesis. If each drug incorporated into a given series of compressed tablets is an individual problem then the attempt to establish uniform standards for large numbers of drugs in many types of compressed tablets is spurious.

EXPERIMENTAL

Tablets.—All tablets were from experimental lots prepared in the process of developing satisfactory formulas for possible commercial use. Series of 12 lots of compressed tablets containing an anti-inflammatory steroid, seven lots of compressed tablets containing a sulfonamide, seven lots of compressed tablets containing an antidiabetic agent, and 16 lots of compressed tablets and one lot of granulation containing a combination of aspirin, phenacetin, and caffeine were studied. Details pertaining to the exact formulation and their methods of manufacture would add nothing to the test results and the conclusions drawn and, hence, are omitted. In one series, the tablets containing the sulfonamide, the presence of one ingredient, sodium chloride, influenced the nature of the statistical correlations presented. This was taken into consideration in interpreting the results.

Dissolution and Disintegration Tests Determined without Plastic Disks.—The disintegration time, without plastic disks, was always determined during the same test in which the fluid was being sampled to obtain rate of dissolution.[1] Hence, all original dissolution data refer to test conditions employing the U.S.P. XV tablet disintegration apparatus. The buffers used in these tests are shown in Table I. When performing such tests, care must be taken that the dissolution medium does not become saturated with the drug before all the dose is released from the tablet or tablets being tested. It is most desirable to arrange the dissolution test so that when all the drug has been released from the sample, the fluid is only 25%, or less, saturated with respect to the drug. If this is the case, then the plots of amount or per cent of drug in solution against time will not be influenced appreciably by this factor, but rather reflect the nature of the tablet itself. The approximate per cent saturations of the buffers with the drugs at the end of the tests are shown in Table I.

In the case of the series of tablets of the anti-inflammatory steroid, one test was performed per lot of tablets, but each test involved five tablets. For two of the lots a repeat test was run. For all other tablet lots only one tablet was tested at a time, but two separate tests were performed on each lot. Tablets were chosen randomly from the lots for the dissolution-disintegration tests with the exception of the tablets containing aspirin-phenacetin-caffeine. In the latter case, tablets of the lot were chosen which had individual weights and thicknesses as closely as possible to the average weight and thickness of the particular lot.

Without stopping the agitation of the U.S.P. tablet disintegration apparatus, aliquots of the dissolution medium were withdrawn at different times through pipets which were wound with glass wool at their tips. When the filtered aliquots had cooled to room temperature they were either transferred directly to 1-cm. silica cells or repipetted and appropriately diluted with the same buffer used as dissolution medium. The filtered aliquots or their dilutions were scanned in a Cary recording spectrophotometer, model 11, over the wavelength region 210 to 400 mμ. The absorbances at the wavelength of maximum absorption of the unknown and standard were used to calculate the concentration of drug. In calculating the amount of drug released at a given time, corrections were applied for the amounts of drug in previously withdrawn aliquots. In the case of the aspirin-phenacetin-caffeine combination, the percentage of drug released at a given time, t, was calculated from the expression

$$\% \text{ drug released} = A_t/A_{t_\infty} \times 100 \quad \text{(Eq. 1)}$$

[1] Apparently, Klein (14), in 1932, was the first investigator to determine the rate of dissolution of a compressed tablet. A year later, Elliott (15), using the same apparatus, which he called a Solvometer, published plots of amount of drug dissolved against time following tests on compressed tablets of five different drugs; he attempted "to show the influence exerted upon the rate of solution by two important variables —temperature and surface in contact with the liquid." Elliott's tablets apparently had essentially constant surface areas since he found the rates of solution were constant until about nine-tenths of the tablets were dissolved. Prior to Klein and Elliott, Noyes and Whitney (16), in 1897, derived their law governing rate of dissolution by studying dissolution from constant surface cylinders of pure benzoic acid in water. Subsequent to Klein and Elliott's investigations, Parrott, Wurster, and Higuchi (17) studied dissolution from spherical tablets of pure benzoic acid. Nelson (18) studied dissolution from cylindrical tablets of pure compounds. To our knowledge, Chapman, Crisafio, and Campbell (9) were the first investigators to determine rates of dissolution at the same time that the distintegration time was being determined; they obtained curved plots similar to some of those illustrated in this paper.

TABLE I.—BUFFERS, NUMBER OF TABLETS PER TEST, NUMBER OF TESTS PER LOT OF TABLETS, AND APPROXIMATE PER CENT SATURATION OF BUFFER WITH DRUG IN THE DISSOLUTION AND DISINTEGRATION TESTS

	Rate of Dissolution and Disintegration Tests without Plastic Disks				Disintegration Tests with Plastic Disks	
Type of Drug in Tablets	Buffer Used[a]	No. of Tablets per 750 ml. of Buffer Held in 1-L. Beaker	No. of Tests per Lot	Approximate % Saturation of Buffer with Drug When Tablet(s) all Dissolved	Fluid Used	No. of Tablets (Vol. Fluid)
Anti-inflammatory steroid	HCl-NaCl, pH 1.3 (μ = 0.1)	5	1	22.7	U.S.P. XVI, pH 1.2[b]	6 (1 L.)
Sulfonamide	Phosphate, pH 7.2	1	2	11.5	...	...
Antidiabetic agent	Tris(hydroxymethyl)-aminomethane-HCl pH 7.2	1	2	12 to 15	Water	6 (1 L.)
Phenacetin-aspirin-caffeine combination	HCl-NaCl, pH 1.3 (μ = 0.1)	1	2	*ca.* 6% aspirin *ca.* 8% phenacetin *ca.* 1% caffeine	HCl-NaCl, pH 1.3 (μ = 0.1)	6 (750 ml.)

[a] Buffers and dissolution media were maintained at 37.5 ± 2° during the tests. [b] Simulated gastric fluid T.S. U.S.P. XVI.

where A_t and A_{t_∞} were the absorbances at 230 mμ at time t and at a time when all the aspirin, phenacetin, and caffeine in the tablet had dissolved, respectively. It was shown that when aspirin, phenacetin, and caffeine were mixed in the same ratio as they existed in the tablet, a single absorption maximum at 230 mμ was obtained, whereas the individual components gave absorption maxima at 227, 243, and 272 mμ, respectively.

The other ingredients in the tablets introduced less than 1% error; this is well within the error of the ultraviolet spectrophotometric method. Greater errors were introduced by evaporation and mechanical loss of the dissolution media during prolonged tests. This error amounted to as much as about 10% in the apparent total amount of the antidiabetic agent released from a tablet. However, these tests were carried out for a period of 4 hours or more. Loss of fluid during the first hour was measured. The volumes of fluid lost during the first half-hour and one hour under the conditions employed were about 30 and 40 ml., respectively, or 4 and 5%, respectively, of the initial 750 ml. volume. Hence, the maximum error introduced in any value obtained at a half-hour was 4% and at one hour was 5% of the amount or per cent of drug released at these times. Tests performed on all tablets, other than the antidiabetic agent, were essentially complete after 1 hour. The $t_{50\%}$ values used in the correlations were in the ranges 1 to 14 minutes for the anti-inflammatory steroid and the sulfonamide tablets, and 1 to 38 minutes for the aspirin-phenacetin-caffeine tablets.

Disintegration Times Determined with Plastic Disks.—Disintegration times were determined for the anti-inflammatory steroid, antidiabetic agent, and phenacetin-aspirin-caffeine series of tablets using the U.S.P. XVI tablet disintegration apparatus and the official plastic disks. The fluids used in the individual tests are shown in Table I.

Lack of correlation between rate of dissolution (determined without plastic disks) and disintegration time (determined with plastic disks) in the case of the anti-inflammatory steroid cannot be attributed to the small differences between the buffers used in the two tests. The solubility and rate of dissolution of this particular anti-inflammatory steroid are independent of the pH and such small changes in ionic strength.

Data from the Literature.—Some correlation coefficients were calculated from the data of Chapman, Crisafio, and Campbell (8, 9).

RESULTS AND DISCUSSION

Tablets of Anti-inflammatory Steroid.—Plots of per cent drug in solution against time in minutes are shown in Fig. 1. From these plots the time required for 50 and 100% of the anti-inflammatory steroid contained in the tablets to dissolve was estimated. These times are shown in Table II. The range of disintegration times and the average disintegration time obtained during the dissolution tests are also shown in Table II. The time required for 50% of the drug to dissolve ($t_{50\%}$) is plotted

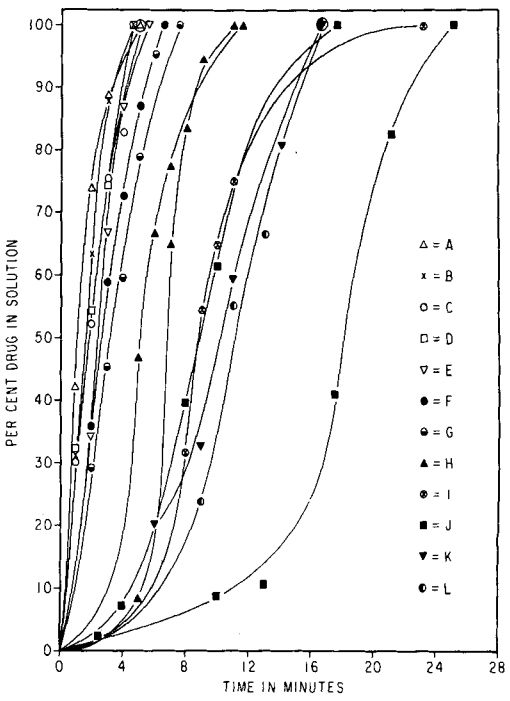

Fig. 1.—Plots of per cent drug in solution against time in minutes for tablets containing the anti-inflammatory steroid.

TABLE II.—ESTIMATED TIMES REQUIRED FOR 50 AND 100% OF THE DRUG TO DISSOLVE, AVERAGE DISINTEGRATION TIMES OBSERVED DURING DISSOLUTION TESTS, AND DISINTEGRATION TIMES BY U.S.P. PROCEDURE FOR TABLETS CONTAINING THE ANTI-INFLAMMATORY STEROID

Lot	Estimated Time Required for 50% of Drug to Dissolve,[a] min.	Estimated Time Required for 100% of Drug to Dissolve,[a] min.	Disintegration Time[a] Determined without Plastic Disks during Dissolution Test, min. Range	Average	Av. Disintegration Time of Six Tablets when Plastic Disks Were Used in U.S.P. Test, min.
A	1	4	2 to 4	3	4
B	1.5	4.5	2 to 4	3.6	5
C	1.5	5	3 to 4	3.6	2
D	2	4.5	3 to 4	3.6	3
E	2	5.5	4 to 5	4.6	4
F	2.5	6.5	3 to 6	4.4	5
G	3	7.5	5 to 7	6	5.5
H[b]	5	11.5	5 to 11	7	
H[b]	7	11	5 only	5	6.5
I	9	23	8 to 23	12	7.5
J[b]	9	17.5	8 to 17.5	12	6
J[b]	18	25	16 to 25	21	
K	10	16.5	5 to 16	11	5.5
L	11	16.5	9 to 16	13	6.5

[a] Based on five randomly selected tablets. [b] Repetitive tests with same lot were performed on separate days.

against the average disintegration time determined during the dissolution tests without plastic disks in Fig. 2. There is a highly significant linear correlation ($P < 0.001$) between the two quantities. The slope of the least squares lines is approximately unity, but there is a significant negative intercept. Since $t_{50\%}$ is a reasonably good criterion of the rate of dissolution, it may be concluded that for this series of 12 lots of tablets of the anti-inflammatory steroid that the rate of dissolution of these tablets is linearly correlated with the average disintegration time obtained under the test conditions. However, use of plastic disks, as in the official U.S.P. disintegration test, masks significant differences between the lots of these tablets. There is no correlation between disintegration times obtained for this series of tablets with the U.S.P. procedure and any criterion of the rate of dissolution such as $t_{50\%}$. These results are different than those reported at the November 1954 Contact Committee meeting (7). At that time it was reported that there was very little difference in time with and without disks, using tablets that disintegrated readily.

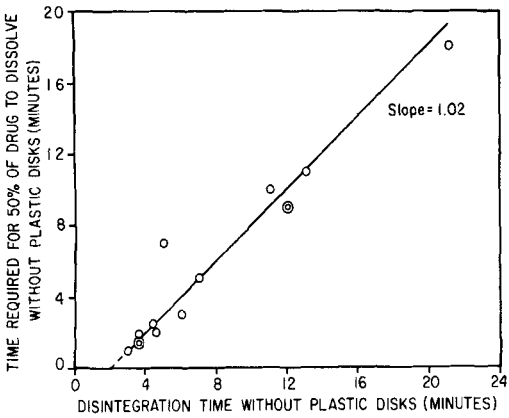

Fig. 2.—Correlation of time required for 50% of drug to dissolve with disintegration time for tablets containing an anti-inflammatory steroid. Each point represents the time required for 50% of the drug contained in five tablets to dissolve and the average disintegration time of the same five tablets observed during the dissolution test.

Tablets Containing the Sulfonamide.—Typical plots of per cent drug in solution against time in minutes are shown in Figs. 3 and 4. Figure 4 is a plot of part of the same data as shown in Fig. 3, but the time scale has been expanded to show more clearly differences between lots in the first 15 minutes of the dissolution tests. From these and similar plots the average time required for 25, 50, 75, and 90% of the sulfonamide contained in the tablets to dissolve was estimated. These times are shown in Table III together with the average of the disintegration times of the two tablets of each lot observed during the dissolution tests. The $t_{50\%}$ value for each individual tablet is plotted against the corresponding disintegration time observed

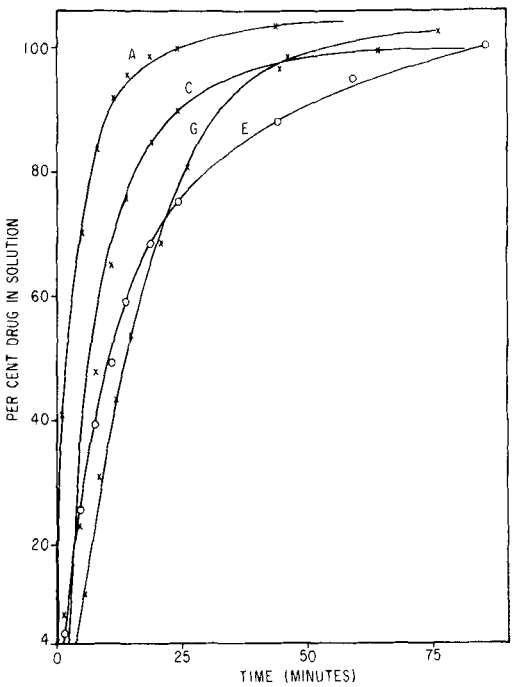

Fig. 3.—Plots of per cent drug in solution against time in minutes for some of the tablets containing the sulfonamide.

during the dissolution test in Fig. 5. The points in Fig. 5 fall into two different populations. In each population there is a highly significant linear correlation between $t_{50\%}$ and disintegration time. The line with slope of 1.82 includes the two tablets of lots A, B, D, and E; all tablets in this series contained sodium chloride as an ingredient. The line with slope of 1.10 includes the two tablets of each of lots C, F, and G; all tablets in this series contained no sodium chloride. These results indicate that correlations between rate of dissolution (using $t_{50\%}$ as a criterion of rate) and disintegration time are highly specific and may be dependent not only upon the type of drug but also upon the nature of pharmaceutical adjuvants in the tablets.

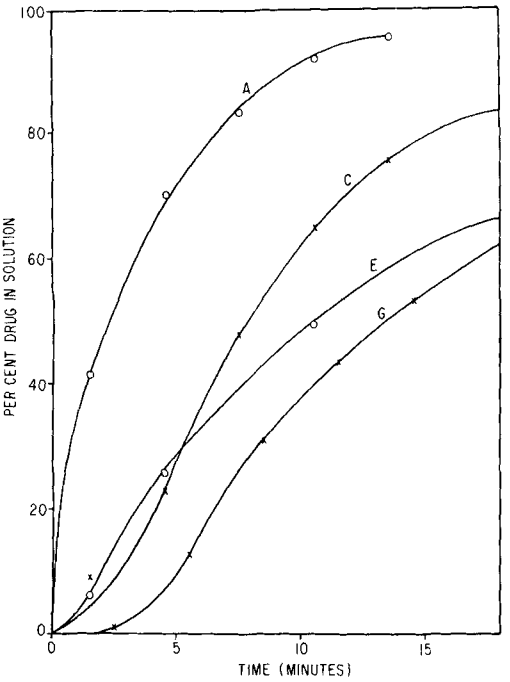

Fig. 4.—Plots of per cent drug in solution against time in minutes for some of the sufonamide tablets; data for first 15 min. only are plotted.

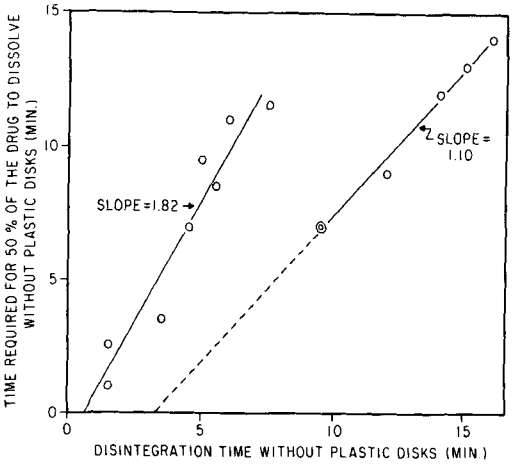

Fig. 5.—Correlation of time required for 50% of drug to dissolve with disintegration time for tablets containing a sulfonamide. Each point represents a single tablet. The line with slope of 1.82 resulted from testing two tablets of each of lots A, B, D, and E; all tablets in this series contained sodium chloride as an ingredient. The line with slope of 1.10 resulted from testing two tablets of each of lots C, F, and G; all tablets in this series contained no sodium chloride.

Tablets Containing the Antidiabetic Agent.—Plots of apparent milligrams of drug in solution against time in hours for all the tablets tested are shown in Figs. 6 and 7. Two tablets of each of the seven lots were tested. The data for the more rapidly dissolving tablets of each lot are plotted in Fig. 6; the data for the more slowly dissolving tablet of each lot are plotted in Fig. 7. The data were not converted to percentages in this case since insufficient assays were performed in some cases to obtain the 100% values. Errors were introduced due to loss in volume of dissolution medium by evaporation during the prolonged dissolution tests. For this reason the word "apparent" has been used.

TABLE III.—AVERAGE TIME REQUIRED FOR THE DIFFERENT PERCENTAGES OF DRUG TO DISSOLVE AND AVERAGE DISINTEGRATION TIME WITHOUT DISKS FOR DIFFERENT LOTS OF SULFONAMIDE TABLETS[a]

Lot	Av. Time Required for the Indicated Percentage of Drug to Dissolve, min. 25%	50%	75%	90%	Av. Disintegration Time without Disks, min.
A	1.0	2.0	5.0	9.5	1.5
B	1.5	5.0	13.5	30.5	4.0
C	5.0	8.0	13.0	24.0	9.5
D	4.5	10.0	19.5	34.5	6.0
E	4.5	10.5	23.5	48.0	6.0
F	6.5	11.0	19.0	30.0	13.5
G	7.5	13.5	23.0	32.5	15.0

[a] Time estimated to nearest 0.05 minute.

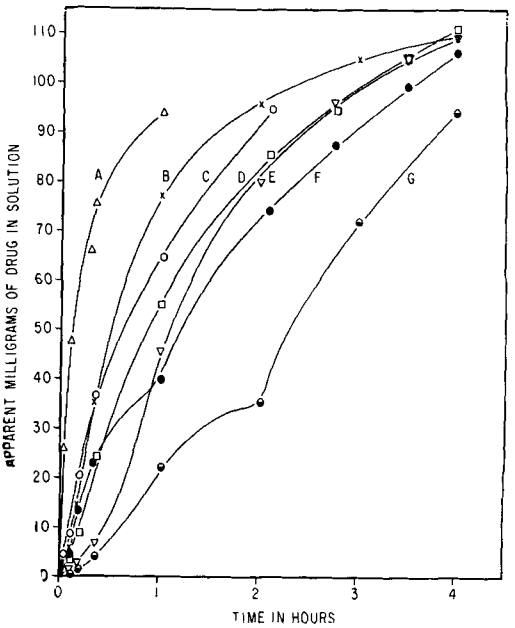

Fig. 6.—Plots of apparent milligrams of drug in solution against time in hours for the more rapidly dissolving tablet of each pair of tablets of each lot of tablets of antidiabetic agent tested.

TABLE IV.—AVERAGE POTENCIES, DISINTEGRATION TIMES WITH AND WITHOUT PLASTIC DISKS, AND ESTIMATED APPARENT MILLIGRAMS OF DRUG IN SOLUTION AT VARIOUS TIMES DURING THE DISSOLUTION TESTS FOR TABLETS OF THE ANTIDIABETIC AGENT

Lot	Average Potency, mg. drug/tab.	Av. Disintegration Time when Disk Used, min.	Dissolution Tests on Individual Tablets: Tablet No.	Disintegration Time without Disks, min.	Estimated Apparent mg. of Drug in Solution at Indicated Time, hr.: 0.25 hr.	0.50 hr.	1 hr.	2 hr.	3 hr.	4 hr.
A	97.0	0.5	1	0.5	76	81	94	..	...	...
			2	1	30	41	70	78	...	...
B	98.2	0.7	1	90	27	51	77	96	104	109
			2	90	23	36	58	83	97	106
C	89.6	2	1	50	16	30	57	89	...	...
			2	50	26	45	71	92	...	...
D	101.5	4	1	167	14	27	48	77	93	102
			2	130	14	34	55	82	98	111
E	101.8	3	1	140	5	12	46	80	100	109
			2	170	3	7	25	70	91	102
F	100.3	1.5	1	20	21	29	40	73	91	106
			2	21	15	22	29	42	52	60
G	102.9	3	1	490	3	7	16	33	54	72
			2	360	3	7	22	35	72	93

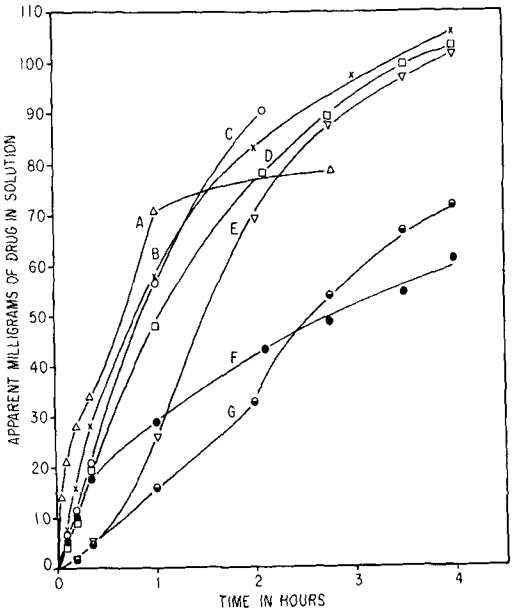

Fig. 7.—Plots of apparent milligrams of drug in solution against time in hours for the more slowly dissolving tablet of each pair of tablets of each lot of tablets of antidiabetic agent tested.

However, such loss in volume of fluid and subsequent error in the amount of drug in solution was not appreciable during the first hour of the tests. From the plots shown in Figs. 5 and 6, the apparent milligrams of drug in solution at 0.25, 0.50, 1, 2, 3, and 4 hours were estimated; these values are shown in Table IV. The disintegration times of the individual tablets observed during the dissolution tests and the average disintegration time obtained using the U.S.P. procedure are also shown in Table III.

Similar to the $t_{50\%}$ value, the apparent milligrams of drug in solution at a given time should be a useful criterion of the rate of dissolution. However, no suitable correlation of the amount of drug in solution at a given time and the disintegration time of the tablet observed during the dissolution test was obtained with this series of tablets. Although there was some tendency for the more rapidly dissolving tablets to disintegrate and to pass through the screen of the apparatus sooner than the more slowly dissolving tablets, there were exceptions and no suitable quantitative correlation could be found. The U.S.P. XVI disintegration test gave results which masked the differences between lots of tablets. This can be seen by comparing the U.S.P. disintegration times shown in Table IV with the dissolution data shown in the same table or with the plots shown in Figs. 6 and 7.

Tablets Containing Aspirin-Phenacetin-Caffeine.—Typical plots of per cent drug in solution against

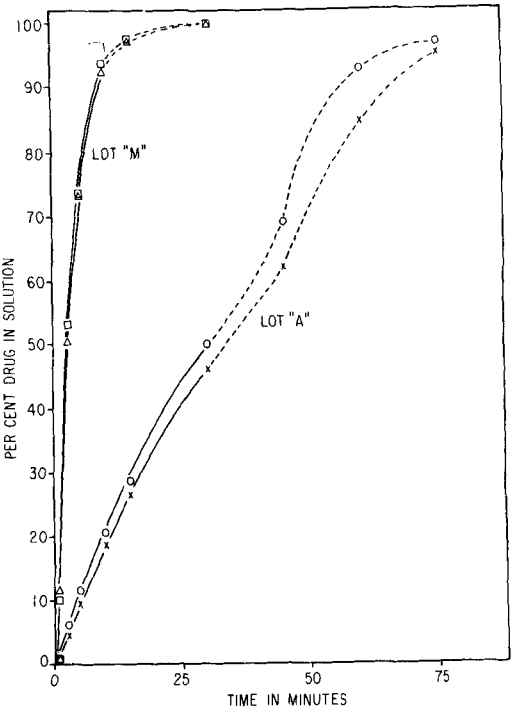

Fig. 8.—Plots of per cent drug in solution against time in minutes for the most rapidly dissolving lot (M) and the most slowly dissolving lot (A) of the tablets containing aspirin-phenacetin-caffeine.

time in minutes are shown in Fig. 8. Of the 16 lots of tablets and 1 lot of granulation tested, tablet lot M was the most rapidly dissolving and tablet lot; A was the most slowly dissolving lot (see Table V). The initial portion of the dissolution curves for this series was found to give excellent pseudo first-order plots. For example, the points joined by solid lines in Fig. 8 are replotted in Fig. 9. The slopes of the linear segments were obtained by the method of "least squares." From these slopes, or pseudo first-order rate constants, the half-lives were calculated. Since there was usually a brief lag time before the tablet started to release drug to solution at a pseudo first-order rate, the half-life does not correspond exactly with the time required for 50% of the drug to dissolve. The latter values were also estimated from the type of plots shown in Fig. 8. The relationship between the time required for 50% of the drug to dissolve and the half-life calculated from the pseudo first-order rate constant is shown in Fig. 10. The slope of the "least squares" line through the origin in Fig. 9 is 1.07; this indicates that, in general, the $t_{50\%}$ value is slightly greater than the half-life.

The $t_{50\%}$ values for this series are plotted against the disintegration times of the tablets observed during the dissolution tests in Fig. 11. The slope of the "least squares" line is 0.56 which is distinctly different from the slope of 1.02 found for the tablets of the anti-inflammatory steroids and the slopes of 1.10 and 1.82 found for the two series of tablets containing the sulfonamide.

The average disintegration time determined on six tablets using plastic disks is plotted against the average disintegration time of two tablets determined without plastic disks in Fig. 12. The slope of the "least squares" line through the origin is 0.67; this indicates that, in general, the effect of the plastic disks, with this series of tablets, was to decrease the disintegration time to about two-thirds of the time obtained without disks. Because of the significant linear correlations shown in Figs. 10, 11, and 12, it is obvious there are also significant linear correlations for this series between either $t_{50\%}$ or half-life and average disintegration time determined with plastic disks.

Tablets Containing Riboflavin.—The data of Chapman, Crisafio, and Campbell (8) were used. A plot of the average disintegration time determined with rubber disks against the average disintegration time determined without rubber disks is shown in Fig. 13. The values for lot 17 were omitted in estimating the regression. Although the slope (0.62) of the "least squares" line in Fig. 13 is similar to that (0.66) found for the aspirin-phenacetin-caffeine combination in our studies, the intercepts of two plots are significantly different. The slopes of the lines forced through the origin are 0.72 for the

TABLE V.—DISINTEGRATION TIMES WITH AND WITHOUT PLASTIC DISKS, TIME REQUIRED FOR DIFFERENT PERCENTAGES OF DRUG TO DISSOLVE, AND HALF-LIVES CALCULATED FROM THE DISSOLUTION DATA FOR TABLETS CONTAINING ASPIRIN, PHENACETIN, AND CAFFEINE

Lot	Av. (and Range) of Disintegration Times when, Disks Used, Min.	Dissolution Tests on Individual Tablets: Tablet No.	Disintegration Time without Disks, min.	Time for the Indicated Percentage to Dissolve, min.: 50%	70%	80%	90%	Half-Life, min.
A	35.3	1	59	34	51	57	64	32.9
	(28 to 41)	2	53	30	46	51	57	29.5
B	33.8	1	55	38	47	52	58	31.6
	(20 to 40)	2	53	32	47	52	58	28.4
C	32.5	1	45	29	42	48	57	23.3
	(28 to 36)	2	59	34	51	58	61	32.5
D	33.2	1	47	27	37	43	52	26.9
	(30 to 35)	2	46	25	37	44	54	24.5
E	27.2	1	44	28	38	42	49	24.1
	(23 to 32)	2	41	22	34	39	47	19.7
F	27.8	1	38	18	..	..	..	18.8
	(25 to 32)	2	38	18	31	37	42	17.5
		3	37	23	34	39	44	22.3
G	24.8	1	35	21	33	37	42	18.7
	(22 to 30)	2	31	19	29	34	40	18.2
H	23.8	1	31	23	34	39	44	21.3
	(20 to 26)	2	31	22	33	38	44	21.3
I	20.7	1	27	15	23	27	33	15.0
	(16 to 28)	2	27	14	21	25	29	12.2
J	13.7	1	21	14	20	24	28	13.9
	(11 to 18)	2	17	10	15	18	23	8.38
K	4.7	1	16	12	16	19	22	13.1
	(3 to 8)	2	14	8	12	14	17	7.25
L	3.3	1	6	6	8	9	13	3.34
	(2 to 4)	2	4	4	6	8	11	2.81
M	2.5	1	2	3	5	6	9	2.53
	(2 to 4)	2	2	3	5	6	9	2.32
N	1.0	1	1	2.5	4	6	8.5	2.87
	(1)	2	1	2.5	5	6	9	2.95
O	1.2	1	1	2	4	6	8.5	2.51
	(1 to 2)	2	1	2	4	6	8.5	2.39
P	1.0	1	1	3	5.5	7.5	10	2.13
	(1)	2	1	2	4	5.5	9	2.45
Granulation	0	1	0	2	4	6	8.5	2.81
		2	0	1.25	3.5	6	8.5	3.02

riboflavin tablet data and 0.67 for the aspirin-phenacetin-caffeine data. This is remarkable correspondence in the effect of the disks in these two series when one takes into consideration the marked differences in the other experimental conditions of the disintegration tests in the two series. It should be mentioned, however, that in the riboflavin tablets series, rubber disks were used whereas in the aspirin-phenacetin-caffeine series, plastic disks were used. In a series of seven sugar-coated tablets of sodium

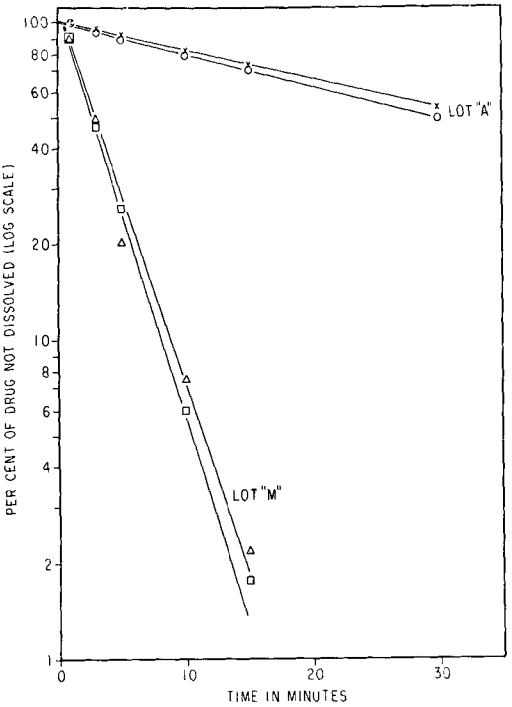

Fig. 9.—Initial pseudo first-order plots for dissolution of tablets containing aspirin-phenacetin-caffeine.

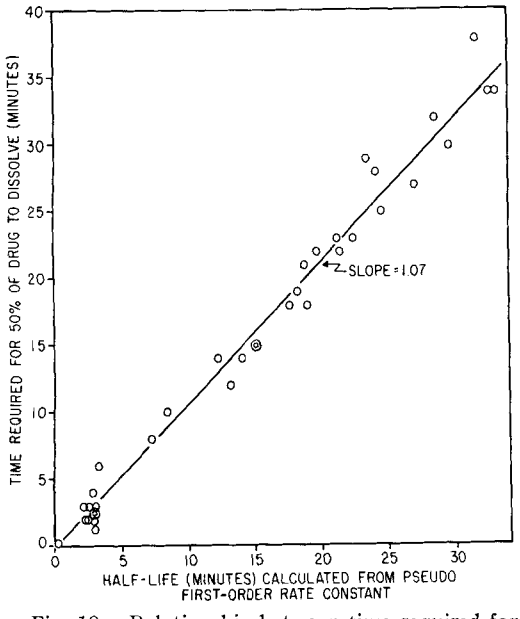

Fig. 10.—Relationship between time required for 50% of the drug to dissolve (estimated from dissolution rate plot such as shown in Fig. 8) and the half-life calculated from the initial pseudo first-order rate constant for tablets containing aspirin-phenacetin-caffeine.

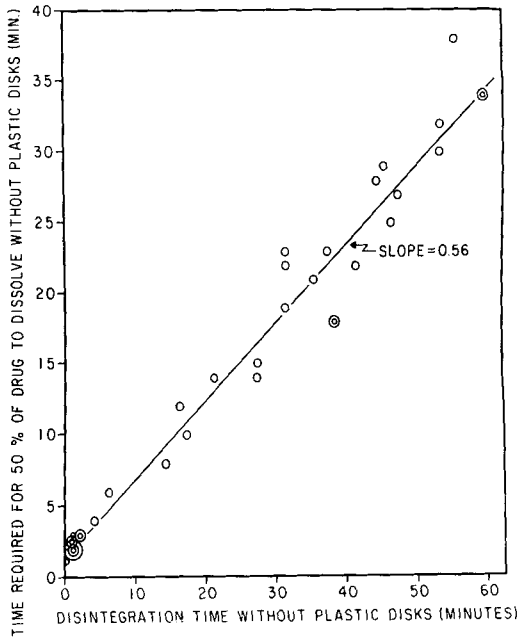

Fig. 11.—Correlation of time required for 50% of the drug to dissolve with disintegration time for tablets containing aspirin-phenacetin-caffeine. Each point represents a single tablet.

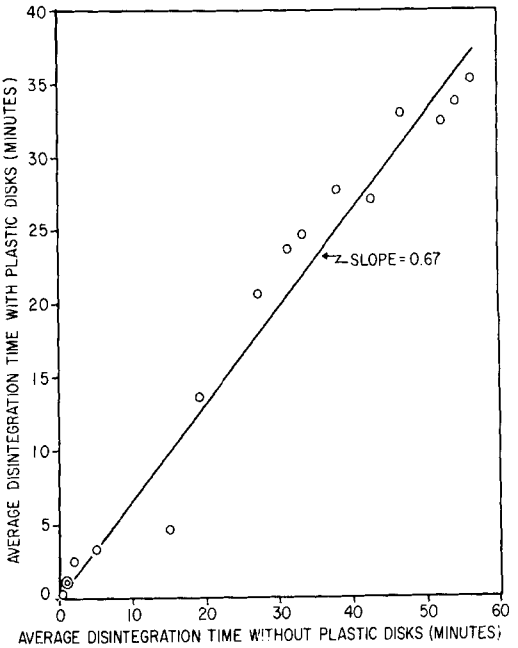

Fig. 12.—Correlation of average disintegration time determined with plastic disks with average disintegration time determined without plastic disks for tablets containing aspirin-phenacetin-caffeine.

p-aminosalicylate, Chapman, *et al.*, showed that results of disintegration tests obtained with rubber disks were significantly different ($P = 0.05$) than results obtained with plastic disks.

Tablets Containing Sodium *p*-Aminosalicylate.—The data of Chapman, Crisafio, and Campbell (9) were used. For five of the tablets studied in this series, the order of excretion rates of NaPAS in human subjects was A > D > E > F > G, whereas the order of *in vitro* dissolution rates reported was A > D > F > E > G. The order of per cent availability of NaPAS based on 8-, 24-, and 32-hr. excretion data was A ≃ D > E > F > G. As an index of the rates of dissolution *in vitro*, we have estimated the time required for 50% of the drug to dissolve ($t_{50\%}$) from their Fig. 2. Plots of the variables, per cent availability *vs.* $t_{50\%}$ and per cent availability *vs.* disintegration time with rubber disks, are shown in Fig. 14A. Plots of $t_{50\%}$ (obtained with method of Chapman, *et al.*) against disintegration time determined with method of Chapman, *et al.*, and with U.S.P. XV fluids plus plastic disks

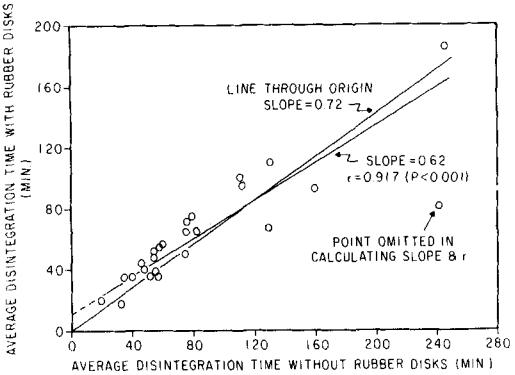

Fig. 13.—Data of Chapman, D. G., Crisafio, R., and Campbell, J. A., THIS JOURNAL, **43**, 297(1954), for sugar-coated tablets containing riboflavin.

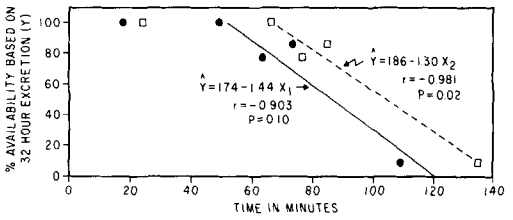

Fig. 14A.—A plot of per cent availability of sodium *p*-aminosalicylate based on 32-hr. urinary excretion against disintegration time in min.; data from Ref. 9.

TABLE VI.—SUMMARY OF SLOPES (s), INTERCEPTS (y_0), LINEAR CORRELATION COEFFICIENTS (r), NUMBER OF OBSERVATIONS (n), AND PROBABILITIES OF SIGNIFICANCE (P) FOR CORRELATIONS BETWEEN DISINTEGRATION TIMES WITH AND WITHOUT DISKS AND RATE OF DISSOLUTION

Ordinate (y) → / Abscissa (x) → / Tablet Series	Linear Regression: Average Disintegration Time with Disks *vs.* Average Disintegration Time without Disks	Linear Regression: Time Required for 50% of the Drug to Dissolve *vs.* Disintegration Time without Disks	Linear Regression: Time Required for 50% of the Drug to Dissolve *vs.* Disintegration Time with Disks
Anti-inflammatory steroid, lots A–L	Relationship curvilinear and not satisfactory for predictive purposes since too scattered	$s = 1.02$ $y_0 = -2.1$ $r = 0.969$ ($n = 14$) $p < 0.001$	No significant relationship
Sulfonamide lots A, B, D, E	Not studied	$s = 1.82$ $y_0 = -1.1$ $r = 0.942$ ($n = 8$) $P < 0.001$	Not studied
Sulfonamide lots, C, F, G	Not studied	$s = 1.10$ $y_0 = -3.6$ $r = 0.995$ ($n = 6$) $P < 0.001$	Not studied
Antidiabetic agent lots A–G	Not significant[a] $P > 0.10$	No significant relationship	No significant relationship[a]
Aspirin-phenacetin-caffeine combination	$s = 0.66$ (0.67) $y_0 = 0.54$ (0)	$s = 0.56$ $y_0 = +1.65$	$s = 0.82$ $y_0 = +1.65$
Lots A–P and granulation	$r = 0.987$ ($n = 17$) $P < 0.001$	$r = 0.984$ ($n = 35$) $P < 0.001$	$r = 0.959$ ($n = 35$) $P < 0.001$
Calculated from literature data			
Sugar-coated tablets containing riboflavin. data of Chapman, *et al.* (8)[b]	$s = 0.62$ (0.72) $y_0 = 11.5$ (0) $r = 0.917$ ($n = 26$) $p < 0.001$	...	...
Sugar-coated tablets containing sodium *p*-aminosalicylate, data of Chapman, *et al.* (9)	...	...	With Rubber Disks $s = 0.83$ $y_0 = -1.75$ $r = 0.995$ ($n = 5$) $p = 0.001$ With Plastic Disks $s = 0.48$ $y_0 = +16.0$ $r = 0.966$ ($n = 5$) $P < 0.001$

[a] It should be noted that with these tablets the disintegration times with and without disks were determined in different fluids. [b] Includes lots J through N and 1 through 22, with the exception of lot 17.

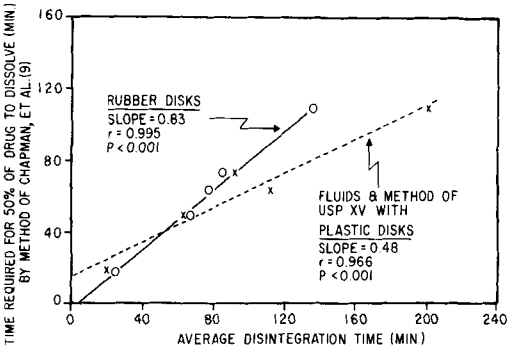

Fig. 14B.—A plot of time required for 50% of the drug to dissolve (determined by method of Chapman, *et al.*), against average disintegration time in min.; data from Ref. 9.

are shown in Fig. 14B. It is of interest that the correlation between $t_{50\%}$ and the disintegration method of Chapman (rubber disks with pH 1.6 and pH 8.0 fluids) gives a highly significant regression coefficient ($r = 0.995$). In this case the dissolution rate was determined during the same test as the disintegration time. One may conclude that the disintegration time determined by the method of Chapman, *et al.* (8, 9), was truly an indication of the rate of dissolution of the sodium *p*-aminosalicylate from the tablets. It is most probably for this reason that there was also a relationship between the per cent availability of the sodium *p*-aminosalicylate in human subjects and the disintegration time.

SUMMARY AND CONCLUSIONS

1. A total of 27 simultaneous dissolution-disintegration tests employing the U.S.P. tablet disintegration apparatus but without plastic disks were performed. These tests involved 12 lots of compressed tablets containing an anti-inflammatory steroid, seven lots of compressed tablets containing a sulfonamide, seven lots of compressed tablets containing an antidiabetic agent, and 16 lots of compressed tablets and one lot of granulation containing a combination of aspirin, phenacetin, and caffeine. A disintegration test employing the same apparatus but with plastic disks was also performed on all of these lots except those containing the sulfonamide.

2. The time required for 50% of the drug to dissolve ($t_{50\%}$) was estimated from each of the amount (or per cent) of drug in solution *vs.* time plots and used as a criterion of the rate of dissolution of the drugs from the tablets.

3. The existence or absence of a quantitative relationship between (*a*) $t_{50\%}$ and the results of the two types of disintegration tests, and (*b*) between results of the two types of disintegration tests were determined. Results are summarized in Table VI.

4. The results indicate there is an extreme specificity in the presence or absence of a relationship between rate of dissolution and disintegration time. In those cases where a quantitative relationship exists, the slopes of the "least squares" lines relating the variables were found to vary widely and depend upon the particular drug(s) involved, and in one case upon the presence or absence of a pharmaceutical adjuvant in the compressed tablet with the drug.

5. With two of the four series of tablets studied, the use of plastic disks in the tablet disintegration test was observed to mask real differences between the lots. In both of these series of tablets, one could not conclude that the tablets differed from lot-to-lot on the basis of their disintegration times determined with plastic disks. However, disintegration times determined without plastic disks and the $t_{50\%}$ values clearly indicated pronounced differences from lot-to-lot in each series. This indicates adoption of plastic disks in the official tablet disintegration test was perhaps hasty and not based upon enough experimental data.

6. These results raise questions as to the validity of uniform disintegration tests and disintegration time limits applied to large groups of drugs in compressed tablets. There will most probably be similar specificity of any correlation between either rate or extent of availability of drugs from tablets *in vivo* and either rate of dissolution or disintegration time determined by a particular test method. If this hypothesis is borne out by future experimentation, then limits of disintegration time or dissolution rate of individual drugs should be based on *in vivo-in vitro* correlations which, in turn, would be specific for the drug and the particular type or types of tablets to be controlled later by the *in vitro* test.

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