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PHARMACEUTICAL TECHNOLOGY

Comparison of Dissolution Profiles of Tablets and Capsules from the USP, Levy, and Magnetic Basket Methods

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Abstract □ Single-batch lots of pentobarbituric acid tablets and sodium butabarbital capsules were dissolved in the USP, Levy beaker, and three different size magnetic basket dissolution apparatuses. Each method was compared using an analysis of variance and other statistical tests to ascertain if significantly different dissolution profiles were produced. Variation in terms of standard deviation of drug released by the different methods was also compared. The five different dissolution methods produced significantly different dissolution profiles at various selected times for both the tablets and capsules studied. However, differences in variations produced by the different dissolution methods upon repeated dissolution of either tablets or capsules seemed to be of the same order.

Keyphrases □ Dissolution profiles (pentobarbituric acid tablets and sodium butabarbital capsules)—comparison of USP, Levy beaker, and three different size magnetic basket apparatuses, statistical analysis □ Tablets, dissolution (pentobarbituric acid)—comparison of USP, Levy beaker, and magnetic basket apparatuses, statistical analysis □ Capsules, dissolution (sodium butabarbital)—comparison of USP, Levy beaker, and magnetic basket apparatuses, statistical analysis

The adoption by the compendia of an official dissolution apparatus (1) has produced much controversy for and against that method. Many new methods and adaptations of older methods have been reported (2). Usually each method has been presented with *in vitro* data to substantiate its effectiveness in following tablet and/or capsule dissolution as well as its ability to differentiate between common manufacturing variables. Many suggestions have been made to "improve" or replace the official method or to establish more than one official method. Some *in vitro* comparisons of the different dissolution methods also have been reported (3). However, little has been done to determine if the methods themselves actually produce significantly different dissolution profiles or if the variations seen in the dissolution apparatuses are of such magnitude as to produce overlapping curves that are essentially similar.

Table I—*F* Values for Pentobarbituric Acid Tablets at Selected Times

Minutes	*F* Value: Repeated Tablets	*F* Value: Different Dissolution Methods	$F(4,16)_{0.99}$
8	0.462	15.29	4.77
12	1.38	36.25	4.77
18	0.987	21.86	4.77
30	0.391	7.13	4.77

This study compared several different dissolution methods to determine if they produced significantly different dissolution profiles for a drug from the same dosage form. Variation in terms of standard deviation of drug released as produced by the different dissolution methods was compared, as well as the significant changes in drug availability caused by changing the impeller speed for both capsule and tablet dosage forms.

EXPERIMENTAL

Materials—Each tablet was formulated to contain 25 mg pentobarbituric acid[1], 236 mg fast-flow lactose[2], 43.5 mg microcrystalline cellulose[3], 35 mg starch[4], and 10.5 mg stearic acid[5]. Tablets were compressed using a 16-station rotary tablet press[6] equipped with an induced die feeder. Standard concave punches,

[1] Abbott Laboratories.
[2] Foremost Dairy, San Francisco, Calif.
[3] FMS Corp., Newark, Del.
[4] Ruger Chemical Co., Irving, N.J.
[5] Fisher Chemicals, Fairlawn, N.J.
[6] Model 216-RP, Cherry-Burrell.

Table II—Average[a] Percent Dissolved and Standard Deviation of Pentobarbituric Acid Tablets for the Different Dissolution Methods at Selected Times

Dissolution Method	8 min		12 min		18 min		30 min	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Levy beaker	22.35	12.81	39.75	12.84	61.25	12.02	84.50	10.31
Small basket	24.13	5.42	32.31	4.39	42.18	4.93	59.24	5.64
Regular basket	30.55	5.85	47.22	15.36	59.36	15.61	74.08	13.27
Larger basket	50.28	16.52	59.24	4.11	74.30	3.76	91.18	2.53
USP method	70.51	14.61	91.96	3.76	92.13	1.85	95.64	3.31

[a] Each mean is the average of five tablets.

0.95 cm (0.37 in.), were used. When using an electronic hardness tester[7], the tablets were found to have a 8.6–9.0 range of hardness with an average of 8.8.

Commercially prepared capsules of sodium butabarbital[8] were purchased, since a previous publication (4) showed that capsules manufactured in an automated manner displayed less variance than hand-packed ones. All dissolution runs were done at 37° in 600 ml of a pH 2 buffer mixture consisting of hydrochloric acid and potassium chloride; unless otherwise stated, a propeller speed of 60 rpm was used.

Dissolution Methods—Tablets and capsules were dissolved in the modified Levy beaker (5–7), the official USP dissolution apparatus (1), and the magnetic basket dissolution apparatus (3, 4) using three types of magnetic baskets. The first basket (regular basket) conformed to the original specifications (4). The second (small mesh basket) conformed to the original specifications but used 16-mesh instead of the original 8-mesh stainless steel wire. The third basket (bigger basket) was constructed using 8-mesh wire but having an inner diameter of 12 mm and a length of 38 mm instead of the 11 × 25-mm dimensions of the original basket.

Analysis—The weight of each tablet or capsule was determined prior to dissolution, and the amount dissolved at any time t, reported as a percent of the total drug, was determined at 240 nm using the appropriate blanks. Each dissolution profile is the average of five tablets or capsules to provide a similar basis of comparison between methods.

RESULTS AND DISCUSSION

The dissolution rate profiles for pentobarbituric acid tablets at pH 2.0 are shown in Fig. 1. Although the same formulation and hardness were used in each case, a different dissolution pattern was found for each dissolution method, with the official USP method allowing the most rapid drug release. To evaluate these dissolution or availability profiles, the following questions must be considered:

1. Do the methods studied produce significantly different profiles?
2. In a series of tablets from the same batch, is the variation a function of the methods used or of the tablets themselves?

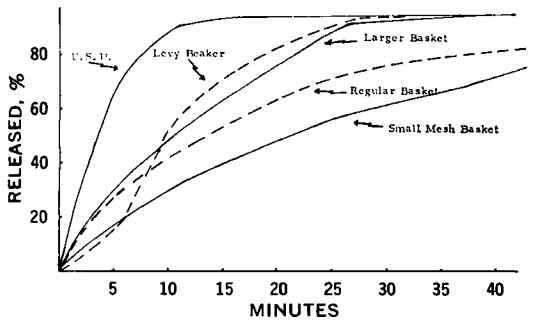

Figure 1—*Comparison of the dissolution rates of pentobarbituric acid tablets using the different dissolution apparatuses.*

[7] Erweka Electronic.
[8] McNeil Laboratories.

These factors can be partially analyzed using a two-way classification of an analysis of variance (ANOV) which, in this case, will compare at a given point in time the difference or nondifference in percent released between dissolution methods and between different tablets. By using data in the form of percent drug released for five different pentobarbituric acid tablets for each of the five different methods, an analysis of variance was calculated at 8, 12, 18, and 30 min and used as representative of the entire dissolution profile. Table I shows that at all of the times studied the calculated F value for the different dissolution methods exceeds the tabular F value at the 0.99 level. This leads to the conclusion that at each of the times studied, a statistical difference was evident between some of the dissolution methods.

Comparison of the individual dissolution methods to determine which apparatuses were producing significantly different release was accomplished using the Newman–Keuls test (8). Analysis of the values of percent pentobarbituric acid released (Table II) indicates that at 8 and 12 min the Levy beaker method was significantly different from the larger basket or the USP method but not from the regular or smaller mesh basket. The smaller mesh basket was also significantly different in the average amount of drug released from the larger basket and USP methods, while the regular basket showed a significant difference only from the USP method.

The relationship changed somewhat at 18 min, with the average amount of drug released from the smaller mesh basket differing from the Levy beaker which, in turn, showed a significantly different drug release from that of the USP method. In fact, the release from the smaller mesh basket was low enough at an average of 42.18% to be significantly different from the release seen in the Levy, larger basket, and USP methods. Again the regular basket showed a different release from that seen in the USP dissolution apparatus. At 30 min, as the tablets approached complete dissolution, a smaller difference was seen among the methods. The Levy, regular basket, larger basket, and USP methods showed no difference from each other, while the smaller mesh basket was significantly different from the Levy, larger basket, and USP methods but not from the regular basket method.

It can be seen from this analysis that tablets from the same batch will release a significantly different amount of drug at various times throughout an entire dissolution when different dissolution apparatuses are used.

The variation between different tablets from the same manufactured batch, which is usually reported as standard deviation in the percent released from a series of dissolved tablets, can be attributed to several sources. These differences can usually be

Table III—F Values for Sodium Butabarbital Capsules at Selected Times

Minutes	F Value		$F(4,16)_{0.99}$
	Repeated Capsules	Different Dissolution Methods	
8	0.608	1.23	4.77
10	0.901	0.997	4.77
30	0.680	5.80	4.77
80	0.317	6.45	4.77
100	1.05	5.66	4.77
120	0.905	3.22	4.77

Table IV—Average[a] Percent Dissolved and Standard Deviation of Sodium Butabarbital Capsules for the Different Dissolution Methods at Selected Times

Dissolution Method	8 min		10 min		30 min		80 min		100 min		120 min	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Levy beaker	24.37	16.40	27.41	5.33	52.71	10.06	77.36	13.05	84.47	14.15	88.76	13.57
Small basket	16.56	2.72	21.97	6.78	42.27	3.01	68.49	2.18	71.34	2.18	79.22	4.18
Regular basket	27.12	5.60	31.33	5.14	51.49	6.45	77.18	2.01	84.89	4.77	90.49	5.56
Larger basket	21.74	9.27	22.04	17.67	51.54	9.97	87.17	8.31	84.15	5.93	92.74	5.31
USP method	19.20	5.88	32.17	16.94	65.39	4.91	93.51	6.81	94.45	5.70	94.97	5.38

[a] Each mean is the average of five tablets.

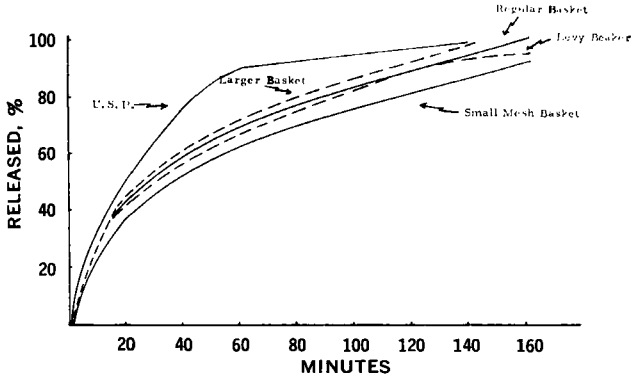

Figure 2—*Comparison of the dissolution rates of sodium butabarbital capsules using the different dissolution apparatuses.*

traced to the manufacturing procedure, variation in the sampling and analytical procedure, and variation produced by the dissolution methods. In this case, since all tablets were from the same manufactured batch and were sampled and analyzed in the same manner, this part of tablet variation should have remained constant during each method. Therefore, differences in tablet variations could be traced to that component contributed by the dissolution method.

Table I shows that the calculated F value from an analysis of variance for the repeated dissolution of tablets in all of the dissolution methods tested is significantly less than the standard F value at 0.99 level of 4.77. This leads to the acceptance of the null hypothesis that all variance between tablets is homogeneous. Further comparison can be made using the mean and standard deviation for each dissolution method at 8, 12, 18, or 30 min (Table II). At each time interval, a varying range of standard deviations was seen, which would seemingly indicate differences in variation among the methods. However, using the Cochran C test (9) to compare homogeneity of variance at each time provided slightly different values. At 8, 12, 18, and 30 min, the calculated C values were 0.2998, 0.3797, 0.4090, and 0.3786, respectively, while the tabular $C(5,4)_{0.99}$ was 0.6329. Therefore, both of these methods indicate that the compiled variation from the three sources is not significantly different in any of the five methods studied and that the variation between tablets caused by each method is quite similar.

Figure 2 illustrates the release of drug from sodium butabarbital capsules using the five dissolution methods previously described. Table III shows the results of a two-way classification of an analysis of variance at 8, 10, 30, 80, 100, and 120 min. At 8 and 10 min, the calculated F values of 1.23 and 0.997, respectively, are less than $F(4,16)_{0.99}$ of 4.77, indicating that there is no significant difference among the methods at these two times. However, the percent drug released at 30, 80, and 100 min seems to show a greater divergence among the dissolution methods. This visual observation is confirmed by an analysis of variance. At these three times, the calculated F value exceeds the tabular F in all cases. At 120 min the lines start to converge, and further calcula-

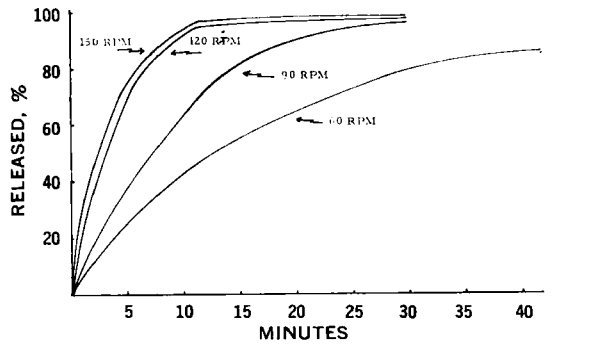

Figure 3—*Comparison of the dissolution rates of pentobarbituric acid tablets as a function of propeller speed using the regular magnetic basket dissolution apparatus.*

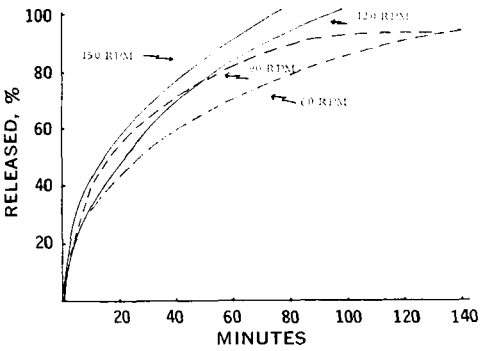

Figure 4—*Comparison of the dissolution rates of sodium butabarbital capsules as a function of propeller speed using the regular magnetic basket dissolution apparatus.*

tion reveals that the differences among the methods are no longer significant.

The average percent of drug released for each of the five dissolution methods at the three times found to be significant in the analysis of variance evaluation were compared using the Newman–Keuls sequential range test (8) to determine which dissolution methods were significantly different from the USP method while none of the other methods in any combination showed a difference in drug dissolution. With 80 min elapsed in the dissolution, the smaller mesh basket, the regular basket, and the Levy beaker methods were all significantly different from the USP method, but none of the other methods in any combination showed a difference in drug release. At 100 min, the results were similar to those seen at 80 min, with only the smaller mesh basket showing a significant difference from the USP method in the amount of drug released. Therefore, significant differences in drug dissolved from capsules from the same commercial lot number can be calculated for the five different dissolution methods studied. However, analysis of the entire dissolution profile is necessary to select the time at which these differences are significant.

The variation between the capsules due to the inherent variation in the manufacturing procedure, the assay procedure, or the dissolution methods should also be considered. In Table III the calculated F values for repeated dissolution of capsules at all of the times analyzed are definitely less than the tabular F value of 4.77. The homogeneity of variance may also be compared by using the standard deviations at each time interval from Table IV and applying the Cochran C test (9). Since at 8, 10, 30, 80, 100, and 120 min the calculated C values were 0.411, 0.341, 0.292, 0.403, 0.399, and 0.432, respectively, while the tabular value of $C(5,4)_{0.99}$ was 0.6329, all the variance between capsules was considered to be homogeneous. Since, as previously mentioned, the manufacturing, sampling, and assay variations are common to all methods, the lack of any significant difference in variation in either test indicates that the deviations due to the dissolution methods are of the same order.

Another factor that may affect the release of drug from a dosage form in each dissolution method is propeller speed. Figure 3 illustrates the differences in the dissolution profiles for the pentobarbituric acid tablets in the regular basket of the magnetic basket dissolution apparatus as a function of propeller revolutions per minute. The results agree with those of Levy (6) and Levy *et al.* (10) in that an increase in propeller speed provides an increase in drug release up to a maximum. An analysis of variance comparing the percent of drug released at 8 min *versus* revolutions per minute shows a significantly different dissolution, with the calculated F value equal to 26.74 and the tabular $F(3,16)_{0.99}$ equal to 5.29. The dissolution curves compared singly against each other using the Newman–Keuls sequential range test (8) show that the amount of drug released at 60 rpm is significantly different from that released at 120 and 150 rpm but not at 90 rpm. Furthermore, no difference can be seen between the average amount of drug released at 90, 120, and 150 rpm.

Figure 4 shows the dissolution of the sodium butabarbital capsules in the regular basket of the magnetic basket dissolution apparatus as a function of propeller speed. Upon increasing the revolutions per minute from 60 to 90 to 120 to 150, little difference in the release rate is seen. An analysis of variance at 8 min gives a calculated F value of 1.43 which, when compared to the tabular $F(3,16)_{0.99}$ of 5.29, shows no difference in the average amount of drug released at that time. If a comparison is made at 40 min where visual inspection shows a divergence of the dissolution profiles, the calculated analysis of variance increases to 3.37, which is still less than that necessary to show a significant difference in drug released at the different speeds.

In summary, the profiles produced by the five different dissolution methods for those tablets were significantly different at various selected times throughout the entire dissolution. The tablets produced a more significant difference between more of the methods at more times during the dissolution than did the capsules. The differences in variation produced by the different dissolution methods upon repeated dissolution of either tablets or capsules seemed to be of the same order.

The selection of an *in vitro* method to follow tablet and capsule dissolution should be dependent on the *in vivo* correlation desired or the quality control standard to be maintained because, although significant differences can be seen among the dissolution methods, each produces the same relative accuracy.

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