Studies in the Development of USP Dissolution Test Method Number 2

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In 1970, the United States Pharmacopeial Convention (USPC) established in-vitro dissolution test standards for several simple compressed-tablet products.[1] The test procedure was a variation of the basket method developed by Pernarowski.[2] This method has since been revised by a change from the resin kettle to the current vessel and is now referred to as the United States Pharmacopeia (USP) Dissolution Test Method 1. In recent years, tests performed at the National Center for Drug Analysis (NCDA) with the basket method and the currently available apparatuses have shown good reproducibility and repeatability on many drug products, including digoxin tablets and digitoxin tablets.

On the other hand, severe problems were encountered by NCDA and several laboratories of the U. S. Food and Drug Administration (FDA) when the basket method was first applied to prednisone tablets. The problems encountered with this method and the development of the USP Dissolution Test Method 2 (paddle method) are the subject of this paper. It should be noted that the commercially available test equipment has undergone three major revisions from 1970 to 1982. These improvements are so significant that data obtained on earlier models may not properly be compared, in many instances, to those obtained on the newer equipment. It has been reported that the dissolution apparatuses currently produced by the four U. S. equipment manufacturers can meet the USP suitability test and geometric requirements.[3] In 1970 the USP required that prednisone tablets release 60% of the labeled amount in not more than 20 minutes when tested with the basket apparatus at 100 rpm. In 1971 NCDA conducted an analytical survey on products of all U. S. manufacturers to determine compliance with this new standard. This survey showed that 84 batches from 34 firms met the requirement and that 27 batches from 17 firms failed it.[4] Because this test procedure was new, those samples that appeared to fail the test requirement at NCDA were sent to the Dallas, Texas, FDA laboratory for confirmatory analyses. That laboratory found that only 14 of the 27 batches failed the requirement and in every instance obtained higher dissolution test results. A summary of the differences in mean dissolution values, in percentage of labeled amount, obtained by the two laboratories on the same samples is given in Figure 1. The data for four samples, the two that gave the best agreement between means and the two that gave the worst agreement, are given in Table 1. The disagreement between the laboratories in the worst cases was so severe that the ranges of the individual tablet dissolution values obtained do not even overlap. The primary difference between the laboratories was that the Dallas laboratory used a commercially available dissolution apparatus whereas NCDA used an apparatus constructed by FDA.

In 1974 a second survey of prednisone tablets was conducted at NCDA. In this survey it was found that 80 batches from 32 firms met the USP XVIII requirements when tested on the FDA-constructed apparatus and 15 batches from 10 firms failed to meet these requirements. When the failing batches were tested with a commercially available dissolution apparatus, only five of the 15 batches were found to fail the test requirements. In every instance the commercially available equipment gave higher results. A summary of the difference in mean dissolution values, in percentage of labeled amount, obtained on the two apparatuses is shown in Figure 2.[5] The data were consistent with those obtained in the previous study. A comparison of mean dissoluion values, in percentage of labeled amount, for the two best-agreeing and the two worst-agreeing samples is given in Table 2. The 15 samples that failed on the FDA-constructed apparatus, and which had been retested on a commercial apparatus at

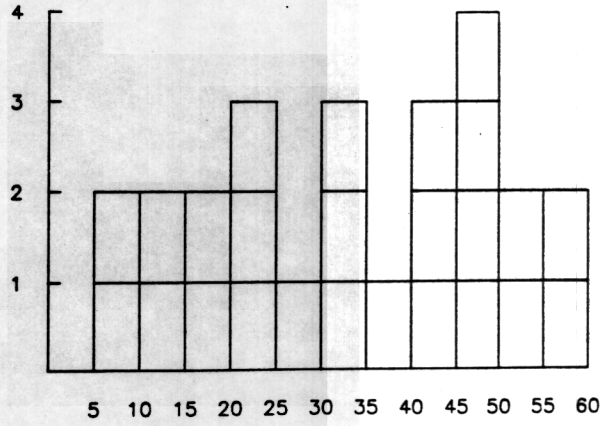

Fig. 1. Plot of the differences in average dissolution values for sets of six tablets in percentage of declared obtained by the USP XVIII Method by NCDA and the FDA Dallas Laboratory on the horizontal axis. The number of comparisons are shown on the vertical axis.

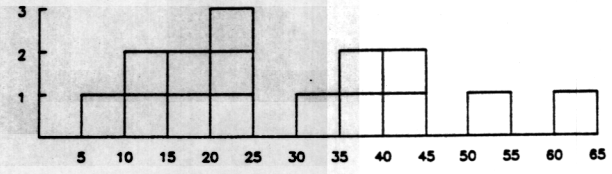

Fig. 2. Plot of the differences in average dissolution values for sets of six tablets in percentage of declared obtained by the USP XVIII Method at NCDA on commercially available and FDA constructed apparatuses on the horizontal axis. The number of comparisons are shown on the vertical axis.

Table 1

	NCDA (Range)	Dallas (Range)	Difference in Means
Best	50.1 (40.0 to 62.9)	55.1 (48.4 to 66.2)	5.0
	4.8 (1.6 to 8.2)	10.0 (4.1 to 23.4)	5.2
Worst	50.6 (31.2 to 77.9)	106.3 (96.2 to 114.2)	55.7%
	26.6 (14.1 to 40.1)	84.6 (76.9 to 94.9)	58.0%

Table 2

	FDA-Built Apparatus	Commercial Apparatus	Difference in Means
Best	49.3	57.2	7.9%
	39.0	51.3	12.3%
Worst	40.4	95.0	54.6%
	32.8	94.7	61.9%

Table 3

	NCDA (Commercial)	Philadelphia (Commercial)	Difference in Means
Best	76.6	76.7	0.1%
	95.0	95.9	0.9%
Worst	73.6	88.2	14.6%
	82.4	99.6	17.2%

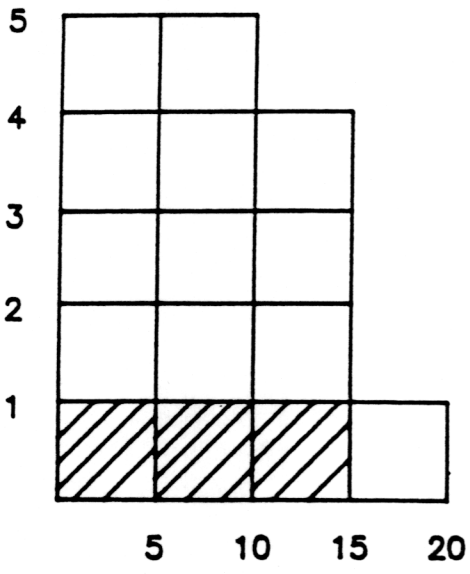

Fig. 3. Plot of the differences in average dissolution values for sets of six tablets in percentage of declared obtained by the USP XVIII Method by NCDA and the FDA Philadelphia Laboratory on the same model and brand of a commercially available apparatus on the horizontal axis. The number of comparisons are shown on the vertical axis. The shaded blocks indicated instances where the Philadelphia Laboratory obtained lower dissolution results.

NCDA, were sent to the Philadelphia FDA laboratory for confirmatory analyses with the same brand and model of commercial equipment. A comparison of mean dissolution values obtained by the NCDA and Philadelphia laboratories with the commercial equipment on the 15 samples is shown in Figure 3.[6] The reduction in the difference in mean dissolution values obtained is striking when compared to the data obtained in the earlier comparisons. The means for the two samples that gave the best agreement and the two samples that gave the worst agreement are presented in Table 3.

Our analysts felt that the major difference between the commercial and FDA-constructed apparatuses was the higher vibration level in the spindles of the commercial unit. It was thought that these vibrations were transmitted directly to the basket and that this caused the consistently higher dissolution results with the commercial unit. In order to lessen the effect of spindle vibration, investigations were begun on the Poole method,[7] which employs a three-neck, 1-liter flask with a stirring paddle. In this method there is no mechanical contact between the tablet and the stirring element. This method also had been investigated extensively by Wagner et al.[8] Five samples that had been tested by the Poole method at NCDA were sent to Professor Wagner for additional testing by that method. The

Table 4

	NCDA	Wagner	Difference in Means
Best	99.6	100.0	0.4%
	96.0	93.7	2.3%
Worst	104.0	100.0	4.0%
	85.9	81.8	4.1%

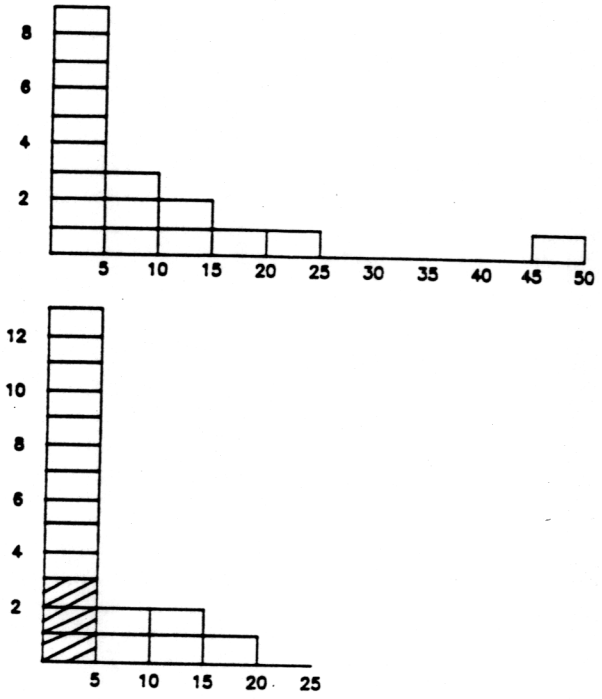

Fig. 4. Plots of the differences in average dissolution values for sets of six tablets in percentage of declared obtained on commercially available and FDA constructed apparatuses on the horizontal axes. The number of comparisons are shown on the vertical axes. The values on the upper plot were obtained by the USP XVIII basket method. The values on the lower plot were obtained using the paddle as described by Poole with the resin kettle described in USP XVIII. Sampling was conducted at 20 minutes in both cases. The shaded portion indicates samples where values obtained on the commercially available apparatus were lower than those obtained on the FDA constructed apparatus.

results obtained by the two laboratories were quite good.[9] The means for the two samples that gave the best agreement and the two samples that gave the worst agreement are given in Table 4.

Because the results with the Poole apparatus from the two laboratories were encouraging, studies were undertaken to determine if the Poole apparatus could be modified to make it more convenient, and thus more likely to be accepted as a routine quality-control method. The first modification was to substitute the 1-liter resin kettle, specified in USP XVIII for the basket method, for the three-neck flask. The reasons were twofold. First, the three-neck, 1-liter flasks were difficult to mount in the available apparatuses. Second, it was more difficult to insure that the paddle blade was level in the three-neck flask.

Six tablets from each of eighteen samples were tested by both the USP basket method and the paddle stirrer with the resin kettle. The differences in the mean dissolution values obtained with the commercial and FDA apparatuses by these two methods is presented in Figure 4.[10] That the differences between apparatuses could be reduced by the use of a paddle stirring element was clearly shown by these experiments. A round-bottom, 1-liter vessel that would fit the available dissolution test apparatuses and that more closely conformed to the vessel used in the Poole method was developed later.[11] It was felt that this vessel would allow the use of our available equipment and also direct collaboration with laboratories that used the Poole method. This latter goal was not achieved.

In 1976 a major effort was undertaken to reduce the variables of the test procedure. The paddle stirrer with the round-bottom kettle was selected for this work because this method had been shown to be less susceptible to differences between the test apparatuses. The first results of this effort were published as an article on how to perform the test.[12] This article focused on the mechanics of performing the procedure and did not present the underlying rationale. The research efforts which provided the basis for that article were published later.[13,14,15] In the Fourth Supplement to USP XIX and to NF XIV the paddle method was adopted for dissolution testing of prednisone tablets. The method was later modified to include the currently official fixed-blade paddle in the Fifth Supplement to USP XIX and to NF XIV.

In 1978 all manufacturers of tableted prednisone products in the U. S. were asked to submit samples to NCDA to determine their compliance with this new dissolution standard. The purpose of this "voluntary certification program" was to ensure the production of prednisone tablets that met the requirements set by the USP with a minimum of regulatory enforcement activity. To help assure that the dissolution test results were as reproducible and accurate as possible, two procedures were initiated. First, a sample of prednisone tablets was selected for use as a "performance standard." From previous studies it was known that these tablets were uniform in drug content but that small

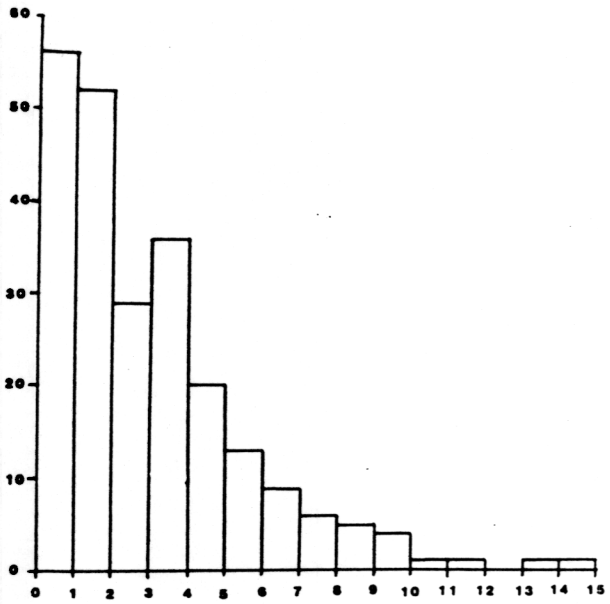

Fig. 5. Plot of the differences in average dissolution values for sets of six tablets in percentage of declared obtained by two different analysts using two different dissolution apparatuses on the horizontal axis. The results of analyses are presented here for all samples received from the initiation of the "voluntary certification program" April 1978 to December 1978. There were 234 comparisons over this time interval.

deviations from the optimum apparatus alignment resulted in large increases in the observed dissolution rate. The sample was designated as NCDA Performance Standard #1. It was used to test each dissolution apparatus, daily at first, and later weekly. Second, the dissolution test was performed on each sample by two different analysts using two different six-spindle dissolution apparatuses. The difference in mean dissolution test results, in percentage of labeled amount, obtained by the two analysts is shown in Figure 5. It should be noted that for 190 of the 234 samples tested in the first eight months of the program, the difference in mean dissolution values was less than five percent of the labeled amount. The means for the two samples that gave the best agreement and the two samples that gave the worst agreement are given in Table 5. It had been noted in earlier studies that air dissolved in the media frequently collected on the surface of the tablet and disintegrated particles. To investigate the degree of the effects of dissolved gases on the dissolution rate, the test was performed in deaerated and nondeaerated media for sets of six tablets from 50 of the 234 samples.

Table 6

		Analyst 1	Analyst 2
		Mean value	Mean value
Least:	Deaerated	78.3	78.2
	Nondeaerated	78.4	77.9
	Difference	0.1	0.3
Most:	Deaerated	34.9	36.9
	Nondeaerated	78.2	73.6
	Difference	43.3	36.7

The means, in percentage of declared, for the sample least influenced by excess gas in the medium and for the sample most influenced are given in Table 6. These results[16] show that some formulations are sensitive to aeration levels and others are not. Additional studies on the effect of deaeration have been published by Cox et al.[17]

The commercially available dissolution vessels used in these studies were manually formed by a glass blower. Later studies show that these vessels are not uniform and that these nonuniformities give differences in the dissolution results in some cases.[18]

In the certification study, the use of a "performance standard" or "calibrator" to help assure reproducibility between different apparatuses was important. In our studies, samples of commercially available tablets that were particularly sensitive to small changes in the hydrodynamic flow in the vessels were selected to be used as "performance standards." Although these tablets are useful, they are not a panacea, and the limitations in their use and the USP suitability test have been studied and published.[19]

The ultimate test of the utility of any analytical procedure is its reproducibility in other laboratories. As discussed earlier, it was difficult to get reproducible results among laboratories when USP Method 1 was used with the commercial and specially constructed dissolution apparatuses available in the early 1970's. The introduction of the paddle as the stirring device lessened the among-apparatus differences encountered

Table 5

	Analyst 1	Analyst 2	Difference in
	Mean value	Mean value	Mean value
Best	73.8	73.8	0
	51.2	51.1	0.1
Worst	74.2	87.7	13.6
	40.5	54.6	14.1

Table 7. Results Obtained on a Prednisone Collaborative Study Conducted at 11 FDA Laboratories[1]

	X (σ)[2]	Range[3]	CU (σ)[4]
NCDA #2[5]	38.9 (4.2)	33.9-46.3	–
A	98.9 (2.7)	94.4-101.9	98.7 (1.7)
B	76.3 (5.5)	70.8-86.9	95.1 (1.5)
C	76.5 (2.9)	69.1-80.5	105.1 (2.3)
D	66.1 (2.6)	61.9-68.8	–

1. The test procedures employed were those specified in Reference 12 using method VII given in Table 8. The detailed protocol can be obtained from authors cited in Reference 20.
2. Average of dissolution results in percentage of declared obtained on two sets of six tablets by each laboratory or a total of 132 tablets. The standard deviation is given in parentheses.
3. The ranges of the averages in percentage of declared obtained on each set of six tablets by the 11 laboratories. A total of 22 sets of data were obtained.
4. The average, in percentage of declared, obtained for the content uniformity with the standard deviation in parentheses. All data obtained at NCDA.
5. NCDA #2 is an internal "performance standard" or "calibrator" tablet sample. Samples A, B and C are samples of commercial products. Sample D is the USP disintegrating calibrator.

with the early equipment and, after further refinements, similar results could be obtained when analysts tested the same sample on different apparatuses. This agreement between analysts was further improved by the introduction of training aids and "performance standards."

In 1980 a collaborative study was conducted among 11 FDA laboratories. A summary of some of those results is shown in Table 7. The entire study wil be presented in a future publication.[20] The results obtained on tablets of NCDA #2 shown in Table 7 are those of a test sample or "performance standard." Only one of the 11 laboratories exceeded our acceptance requirements, and the results from that laboratory are included because the deviation was not excessive. Sample A consisted of tablets that essentially gave 100% release in 15 minutes, and it was included in the test protocol to measure the analytical error associated with the testing procedures. It should be noted that the overall mean for Sample A was very close to the mean of the results for content uniformity obtained by a different standard analytical procedure. The results obtained from the other samples show that the dissolution test procedure can be performed reproducibly among laboratories provided that standardized protocols are used, adequate training aids are available, and an adequate "performance standard" is used.

Summary

The dissolution test procedures that have been employed in our laboratory for prednisone tablets from 1971 to the present are summarized in Table 8. Our efforts were focused on prednisone tablets because they were the major problem at the time. We have since performed the dissolution test on thousands of batches of various simple compressed tablets by USP Methods 1 and 2, and have obtained reasonably reproducible test results. From 1971 to 1982 the commercially available dissolution test equipment has undergone major improvements in the reduction of vibration levels and in alignment. These improvements in every instance have lessened the problems of performing the dissolution test procedure reproducibly. The collaborative study has shown that USP Method 2 has been improved to the point where it can be considered a routine analytical test.

We have not yet observed a sample of simple compressed tablets whose standard physical and chemical properties were shown to be uniform by our testing and

Table 8. Summary of Dissolution Test Methods Used at NCDA for Prednisone Tablets

I. Basket method, resin kettle. About *1971*. USP XVIII.
II. Paddle Method *A*. Movable side mounted blade in three-neck, 1-liter flask. About *1974*. Reported by John Poole.[7] Chuck adaptors.
III. Paddle Method *B*. Movable side-mounted blade with resin kettle. About *1974*. Chuck adaptors.
IV. Paddle Method *C*. Movable side-mounted blade in an *exterior-molded* glass round-bottom kettle. About *1976*. Reported by Kirchhoefer.[10]
V. Paddle Method *D*. Fixed center-mounted blade in an *exterior-molded* glass round-bottom kettle. About *1977*. USP XIX, Fourth Supplement.
VI. Paddle Method *E*. Fixed center-mounted blade in a tube-based glass round-bottom kettle. About *1979*.
VII. Paddle Method *F1*. Fixed center-mounted blade in a molded plastic round-bottom kettle. About *1979*.
VIII. Paddle Method *F2*. As above with improved glass vessel with well defined geometry. *1982*.

whose dissolution rates were erratic. When tablet-to-tablet dissolution rates were found to be variable and drug content, etc., were uniform, the differences have in every instance been traced to variations in the performance of the test procedure.

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