

Perturbation Study of Dissolution Apparatus Variables—A Design of Experiment Approach

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Abstract

The specifications and acceptable ranges for nine critical dissolution apparatus variables were examined during a perturbation study of USP dissolution Apparatus 2 using USP Prednisone Reference Standard (RS) Tablets. A Design of Experiment (1) approach was used to screen the nine variables to determine the contribution of each, alone and in combination, to mean percent dissolved and standard deviation results. We observed a wide range of dissolution results, including several values that fell outside of current acceptance limits, even though the variables were kept within currently acceptable ranges. When we analyzed mean percent dissolved results, we found three variables that were statistically significant: level of deaeration, vessel type, and rotation speed. When we examined standard deviation results, we found that five variables or combinations of variables were statistically significant: vessel type, level of deaeration, paddle height, paddle height–vessel type interaction, and paddle height–level of deaeration interaction. We also found that the other variables examined—temperature, shaft wobble, vessel centering, vessel tilt, and base plate levelness—were not statistically significant within the ranges explored in this study. Acceptance ranges for several assembly variables may need to be more stringent or more precisely defined in order to decrease inter- and intralaboratory variability (reproducibility and repeatability) in dissolution testing.

Introduction

For nonsolution, orally administered dosage forms, the USP Performance test can rely on either disintegration (General Chapter *Disintegration* <701>) or dissolution (General Chapter *Dissolution* <711>). The dissolution procedure is an important test both to establish bioequivalence and also for quality control. The procedure includes a complex sample preparation step in a dissolution apparatus. General Chapter <711> specifies acceptance ranges for the dissolution vessel and variables of operation (2). During its multilaboratory studies of new Lot P Prednisone Reference Standard Tablets (Prednisone RS Tablets) used in periodic performance testing (PVT), USP noted substantial interlaboratory variability in results. This has led USP to conduct a comprehensive set of studies to examine potential assembly deviations that contribute to this variability. This study is one of a series of reports of these investigations (3–6). Based on these studies, USP may change statements in <711> and allied documents to assist manufacturers in improving the USP Performance test when the dissolution procedure is chosen.

We designed this study to screen variables for Apparatus 2 (Paddle), with plans for a similar study of Apparatus 1 (basket) later on. Because this was a screening study, we did not examine exhaustively the effects of each variable but rather attempted to identify which variables were the most essential to control in order to achieve accurate and reproducible dissolution results. Previous research has focused on assembly variables such as dissolved gas, ves-

sel centering, vibration, vessel tilt, paddle height, rotation speed, base plate levelness, shaft wobble, temperature, vessel shape, belt tension, and shaft verticality (3, 7–12). Building on these earlier studies, we attempted a more systematic approach that included an assessment of combination effects from two or more concurrently perturbed variables. In this study, nine variables were evaluated using

Table 1. Variables Included in Design of Experiment Study.

Variable	Units	-1 Value	+1 Value
Temperature	°C	36.5	37.5
Shaft wobble	mm total runout	0.0	0.5
Rotation speed	rpm	48.0	52.0
Vessel centering	mm total runout	0.0	2.0
Vessel tilt	°	0.0	1.0
Paddle height	mm	23.0	25.0
Base plate levelness	°	0.0	1.0
Vessel types	N/A	Manufacturer's	Replacement
Level of deaeration	N/A	USP-deaerated	Non-deaerated

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a Design of Experiment approach: temperature, shaft wobble, rotation speed, vessel centering, vessel tilt, paddle height, base plate levelness, vessel type, and level of deaeration.

Methods

Vessel specifications and other aspects for mechanical calibration for a dissolution assembly and media are available to the dissolution chemist. General Chapter <711> provides guidance for most of these. PhRMA (7) and ASTM (13) also provide acceptable ranges for the procedure.

Perturbation Settings

The perturbation settings used in this study were chosen to be near but within the upper or lower bound of ranges provided in USP, PhRMA, and ASTM references (Table 1).

1. Temperature

The dissolution medium temperature was maintained at 36.5 °C or 37.5 °C and was measured using an external thermometer placed inside the vessel.

2. Shaft wobble

For zero-wobble experiments, the paddle shafts supplied by the manufacturer were used. For 0.5-mm wobble experiments, another set of shafts that had been previously bent by a machine shop were used. Wobble measurements were made using a wobble meter at a point approximately 1 cm above the paddle blade with the paddles raised above the top of the vessels. The entire head plate was then lowered to the appropriate height, maintaining the position of the shafts in the chuck.

3. Rotation speed

The speed was set to either 48.0 rpm or 52.0 rpm and confirmed using an external tachometer.

4. Vessel centering

Vessels were manually set to either 0 mm or 2 mm as measured using a centering device. The centering device was placed approximately 1 cm above the paddle blade, and the measurement was made inside the vessel with the paddle at 23 mm or 25 mm.

5. Vessel tilt

Shims were inserted on the base plate underneath the vessel flange at the same position for all vessels to achieve a 1.0° tilt as measured using a digital protractor on the top of the vessel. Shims were removed for 0°-tilt experiments.

6. Paddle height

The paddles were manually adjusted to 23 mm or 25 mm as measured by a depth gauge.

7. Base plate levelness

Shims were inserted under the leveling feet on one side of the dissolution tester to achieve a base plate levelness of

1.0° as measured using a digital level. These were removed for zero-degree base plate levelness experiments.

8. Vessel types

The appropriate vessel types, manufacturer's or replacement, were used for each experiment.

9. Deaeration

The appropriate medium, USP deaerated or non-deaerated, was used for each experiment. A dissolved-gas meter capable of measuring total dissolved gas pressure (TDGP) and oxygen concentration was used to record these measurements.

Dissolution

Apparatus 2 dissolution experiments were performed using USP Prednisone RS Tablets Lot P0E203, six tablets per run. After 30 min, samples were manually collected and filtered using a hydrophilic PVDF 0.45-µm syringe filter (Millex-HV, Millipore Corporation, Billerica, MA), discarding the first 5 mL. Prednisone concentrations were determined using UV analysis at 242.0 nm; percent dissolved values were calculated using the label claim of 10 mg. All experiments were conducted by the same analyst on the same dissolution assembly without provision of the manufacturer's name to preserve anonymity. All vessels and paddle shafts were serialized and kept in the same position for each experiment. All thermometers, timers, wobble meters, tachometers, levels, centering devices, depth gauges, and dissolved gas meters were within calibration. For USP-deaerated medium, Milli-Q water was heated to approximately 45 °C, vacuum filtered through a 0.45-µm membrane filter, then vacuum degassed for an additional five minutes. For non-deaerated medium, Milli-Q water was heated to approximately 41 °C and held at 41 °C for at least 30 min. The temperature was closely monitored to ensure a minimal equilibration time (less than 15 min) for the dissolution medium inside the vessels. Manufacturer's vessels refer to the vessels supplied by the manufacturer of the dissolution tester. Replacement vessels refer to vessels manufactured by another company and sold as replacement vessels for the specific dissolution tester in use. Two responses were recorded for each experiment, the mean percent dissolved for the six positions of the test and the standard deviation of each mean percent dissolved value.

Experimental Design

Full-factorial designs involve a substantial number of experiments (2⁹ or 512 experiments in this case) and thus are not ideal for a screening process. With an incomplete factorial design, some effects are aliased with other effects. We thus chose an incomplete factorial design in which all main effects of each variable and all two-factor interactions were not aliased with each other. They were, however, aliased with three-factor and higher-order interactions, so we assumed those higher-order interactions were negligible enough that our choice of variables for further study

Table 2. Experimental Design and Results.

Run	Temp	Shaft Wobble	Rotation Speed	Vessel Centering	Vessel Tilt	Paddle Height	Base Plate Levelness	Vessels	Deaeration	Percent Dissolved	
										Mean	SD
A ¹	37.0°	-	50.0	-	-	+	-	-	-	43.3	1.2
B ¹	37.0°	-	50.0	-	-	+	-	-	-	44.1	1.7
C ¹	37.0°	-	50.0	-	-	+	-	-	-	43.3	1.0
1	+	-	+	-	-	-	-	-	-	46.3	1.5
2	-	+	-	-	+	-	+	+	+	58.0	7.6
3	-	+	+	+	-	+	-	+	+	87.6	0.7
4	+	+	-	-	+	-	-	-	+	49.8	1.1
5	+	-	-	-	-	-	+	+	-	48.1	8.7
6	-	-	-	-	-	-	-	-	-	42.7	1.9
7	-	+	+	-	-	-	-	-	-	46.4	2.3
8	-	-	+	-	+	+	-	-	-	45.9	0.9
9	-	+	+	+	-	-	+	+	+	74.8	6.6
10	-	+	+	+	+	-	-	+	-	62.5	6.9
11	+	-	-	-	-	-	-	+	+	70.6	9.8
12	+	+	+	+	+	-	+	-	-	46.5	2.2
13	+	-	+	+	+	+	+	-	-	48.1	1.6
14	-	-	+	-	-	-	-	+	-	49.2	6.2
15	-	-	-	+	+	-	+	+	-	48.7	8.5
16	-	-	+	+	-	+	+	-	-	44.1	1.8
17	+	+	-	-	-	+	-	+	+	56.4	7.8
18	+	-	+	-	+	-	+	+	+	55.7	11.2
19	-	-	+	+	+	-	-	-	+	58.5	2.1
20	-	-	+	-	+	-	+	-	-	43.7	1.4
21	-	+	-	+	-	+	+	+	-	42.6	1.5
22	+	+	+	-	-	-	+	-	+	72.4	0.7
23	+	-	-	+	-	+	-	+	-	43.7	1.0
24	-	-	-	-	+	+	+	+	-	41.5	1.3
25	-	+	-	-	-	+	+	-	+	68.4	5.4
26	-	-	+	-	-	+	+	-	+	55.5	1.8
27	-	+	-	-	+	+	-	-	-	42.6	1.5
28	+	+	+	+	-	-	-	+	-	48.8	2.8
29	+	+	-	-	-	+	+	-	-	43.2	1.1
30	+	+	+	+	-	+	+	-	+	50.0	2.0
31	-	-	-	+	+	+	+	-	+	48.8	1.9
32	+	-	-	+	-	+	-	-	+	51.0	2.5
33	+	+	+	-	-	+	+	+	-	45.2	1.4
34	+	+	-	+	+	-	-	+	+	56.3	11.5
35	-	-	-	+	-	+	+	+	+	55.4	2.5
36	+	+	-	+	+	+	+	+	-	44.7	2.0
37	+	+	+	-	+	+	+	-	+	56.9	2.8
38	-	-	-	-	+	+	-	+	+	70.4	8.7
39	+	-	-	+	+	-	-	-	-	42.1	1.2

Table 2. Experimental Design and Results. (continued)

Run	Temp	Shaft Wobble	Rotation Speed	Vessel Centering	Vessel Tilt	Paddle Height	Base Plate Levelness	Vessels	Deaeration	Percent Dissolved	
										Mean	SD
40	+	+	+	+	+	+	-	-	-	45.7	1.1
41	-	+	-	+	-	-	-	-	+	54.7	2.9
42	-	-	+	+	+	+	+	+	+	66.4	14.8
43	+	-	+	+	+	+	-	+	+	74.6	4.6
44	+	-	-	+	-	-	+	-	+	44.4	0.5
45	+	+	-	-	+	-	-	+	-	44.5	2.9
46	-	+	+	-	+	-	-	+	+	75.6	8.9

[†]These data are obtained under baseline, nonperturbed conditions.

was correct. A Design of Experiment statistical software package (Design-Expert Version 7.0.2, Stat-Ease, Inc., Minneapolis, MN) was employed to design a set of experiments that satisfied this condition for aliasing and then to analyze the data. The design with the smallest number of experiments that satisfied our aliasing requirement was a minimum run resolution V design with the minimum number of experiments with two levels (denoted -1 and +1) of each of our nine factors (Table 1). (Resolution V describes the level of aliasing; e.g., that the two-factor interactions are aliased with three-factor interactions.) Two responses were recorded: mean percent dissolved and standard deviation of each run of six tablets. The total number of experiments was 46, and the order of experiments was randomized. Each factor was run an equal number of times, 23, at its -1 and +1 levels. Experiments were not replicated in this design, which made it imperative for scientists to accurately and precisely set each factor for each experiment. Data

Table 3. Effects List for Mean Percent Dissolved Results.

Term	Effect*	% Contribution
Temperature	-4.5	1.1
Shaft wobble	0.9	0.7
Rotation speed	12.1	9.4
Vessel centering	-0.7	0.4
Vessel tilt	1.6	0.0
Paddle height	-2.4	0.5
Base plate levelness	-2.2	1.2
Vessel type	12.8	10.4
Level of deaeration	31.0	52.3
All 2-factor interactions (n = 36)	N/A	24.2
Total	N/A	100.0

*The effect size is the difference between the estimated average at the +1 setting minus that at the -1 setting (see Table 1) as a percent of the average at the -1 setting.

analysis used a base 10 log transformation for both mean percent dissolved and standard deviation. Half-normal probability plots and the Shapiro-Wilk normality test were used to guide selection of the significant factors for both mean percent dissolved and standard deviation analyses. To illustrate the important variables, we present Pareto charts that show significance levels with (Bonferroni) and without adjustment for multiple testing. Because this was intended as a screening study, we did not adjust for multiple testing. Resulting *p* values for all unselected factors were greater than 0.10, and *p* values for significant factors were all less than 0.05. An analysis of variance (partial sum of squares-type III) was performed for both mean and standard deviation of percent dissolved to quantify the contribution of each factor.

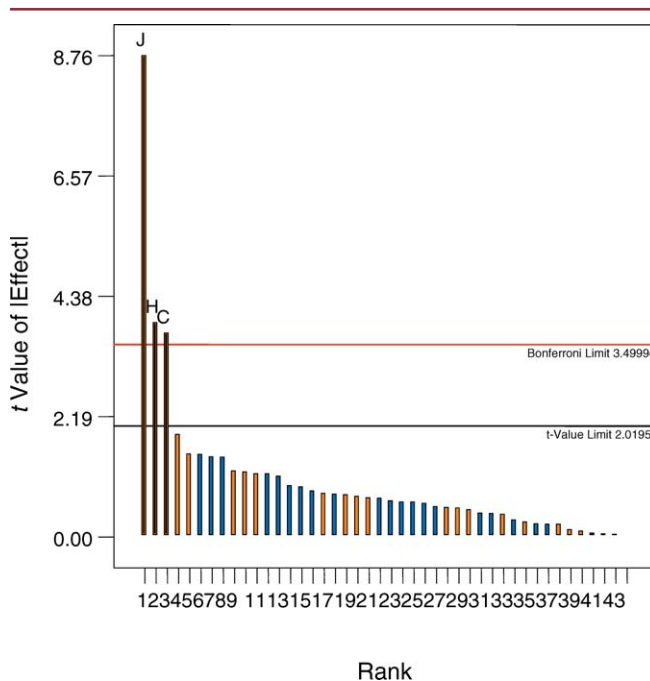


Figure 1. Pareto Chart for the analysis of mean percent dissolved showing the three significant variables: Level of Deaeration (J), Vessel Type (H), and Rotation Speed (C).

Results

Experimental results demonstrate that combined perturbations affect both the mean percent dissolved values and the standard deviation values (Table 2). The baseline data obtained under nonperturbed conditions are listed at the top of the table. The 46 experiments performed under perturbed conditions, as indicated by a + or – for each variable, are listed next. Mean percent dissolved values ranged from 41.5% to 87.6%, and standard deviation results ranged from 0.5 to 14.8. Several experiments included values that fell outside of currently acceptable ranges (14).

Mean Percent Dissolved Results

Of the nine variables and 36 two-factor variables (Table 3, Figure 1), three variables significantly affected mean percent dissolved: deaeration, vessel type, and rotation speed. A marginal effect due to temperature seems to be due to one observation (Run 3 in Table 2). When this data point is removed, temperature is not significantly affected by the specified perturbation (below the *t*-value limit) without affecting results for the other variables. All results are presented, therefore, with the data from run 3 omitted. The effects listed in Table 3 refer to the difference between the estimated average at the +1 setting minus that at the –1

setting (see Table 1) as a percent of the average at the –1 setting. For example, when the rotation speed changes from 48.0 rpm to 52.0 rpm, mean percent dissolved values increased by 12.1% (from 40.7% dissolved at 48.0 rpm to 45.6% dissolved at 52.0 rpm).

Standard Deviation Results

Of the nine variables and 36 two-factor variables (Table 4, Figure 2), five variables significantly affected standard deviation results. Single-factor variables were vessel type, level of deaeration, and paddle height, and two-factor variables were paddle height–vessel type interaction and paddle height–level of deaeration interaction. Run 3 in Table 2 gave a standard deviation value that was identified to be an outlier. As noted above, reported results did not include this run. Inclusion of run 3 did not affect the results significantly. The effects listed in Table 4 were calculated as for Table 3.

Discussion

From many collaborative studies performed to determine the acceptance ranges for USP Prednisone RS Tablets (5), we have observed a high level of interlaboratory variability. Although a certain degree of interlaboratory variability is expected, it is possible that the dissolution test needs to be more precisely specified and performed in order to reduce this variability. One of the goals of this study was to identify apparatus variables that require more stringent acceptance criteria to achieve this type of specificity. We found six variables or combinations of variables that contributed significantly (mean and/or standard deviation) to dissolution results and five variables that did not.

Table 4. Effects List for Standard Deviation Results.

Term	Effect*	% Contribution
Temperature	–21.2	2.1
Shaft wobble	17.5	0.0
Rotation speed	11.8	0.1
Vessel centering	18.7	0.0
Vessel tilt	13.1	1.1
Paddle height	–27.1	3.5
Base plate levelness	–4.7	0.2
Vessel type	182.1	37.7
Level of deaeration	78.9	11.8
Paddle height/vessel type	–41.1	9.8
Paddle height/level of deaeration	61.3	8.0
All other 2-factor interactions (n = 34)	N/A	25.7
Total	N/A	100.0

*The effect size is the difference between the estimated average at the +1 setting minus that at the –1 setting (see Table 1) as a percent of the average at the –1 setting.

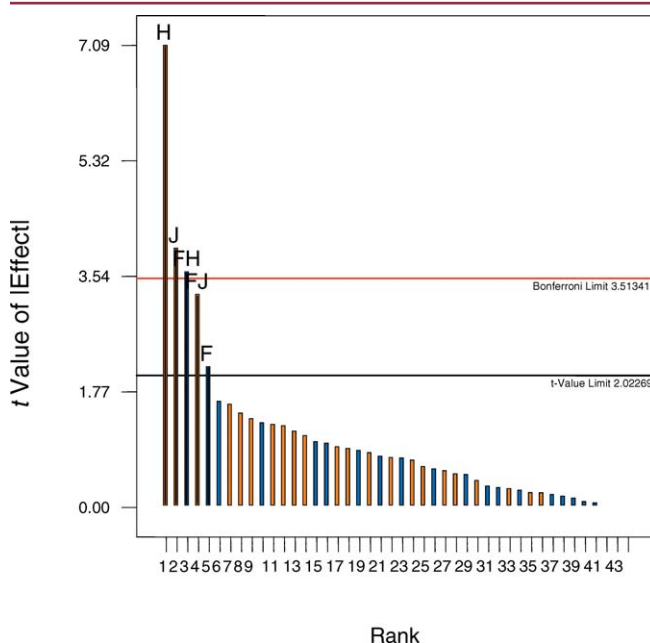


Figure 2. Pareto chart for standard deviation results showing the five significant variables: Vessel Type (H), Level of Deaeration (J), Paddle Height/Vessel Type (FH), Paddle Height/Level of Deaeration (FJ), and Paddle Height (F).

Vessel Type

Vessel type studied in two sets of six had a significant impact on both mean percent dissolved and standard deviation results. Acceptance criteria for vessel dimensions are specified in <711>. However, recent research has shown that geometric irregularities are found in dissolution vessels and affect dissolution results using USP Prednisone RS Tablets (11, 15). The two sets of vessels used in this study were similar in their geometric properties as measured using a 3-dimensional coordinate measuring machine (16). The replacement vessels were set arbitrarily to the high (+1) value for the Design of Experiment study, not, however, because we believe them to be of inferior quality. This study shows that switching from one set of vessels to another, similar set of vessels leads to significant differences in both mean percent dissolved and standard deviation, suggesting that the current geometric acceptable ranges may not be appropriate.

Rotation Speed

We found that the current $\pm 4\%$ rotation speed range appears to be too wide because mean percent dissolved of prednisone RS is significantly affected by rotation speed in this range. Continuous rotation speed monitoring is desirable. Further studies are needed to establish new acceptance limits.

Paddle Height (Three Effects)

Paddle height, both individually and as a component of two-factor interactions, was significant in the standard deviation analysis. The combination effect of paddle height on the standard deviation was greater for replacement vessels and non-deaerated medium. Equivalently, the combination effect of deaeration was more important at the 25-mm height than at 23 mm, and the difference between replacement and manufacturer's vessels was more pronounced at 23 mm than 25 mm. Although these data may not be conclusive enough to warrant a tighter specification for paddle height, they do show that paddle height should be closely monitored (16). The height should be checked in conjunction with the vessel that will be used for the dissolution test using a gauge calibrated to be accurate. Heights should be periodically checked to ensure that no shafts have slipped out of their set positions.

Deaeration

Deaeration was the most significant variable for mean percent dissolved and the second most significant variable for standard deviation. The average oxygen concentration and total dissolved gas pressure (TDGP) for USP deaerated medium measured at the beginning of the experiment were 2.5 ± 0.5 mg/L and 350 ± 70 mm Hg, respectively. Values for non-deaerated medium were 6.8 ± 0.7 mg/L and 620 ± 20 mm Hg, respectively. Validating any deaeration procedure against the oxygen concentration and TDGP values obtained for USP deaerated medium is crucial in obtaining valid dissolution results for USP Prednisone RS Tablets (3).

Nonsignificant variables

Several variables—temperature, shaft wobble, vessel centering, vessel tilt, and base plate levelness—did not significantly affect either mean percent dissolved or standard deviation results. This does not imply that these variables are unimportant in dissolution testing. It only suggests that in the ranges examined in this study, dissolution results were not significantly affected by the specified perturbations.

Variability

The pooled tablet-to-tablet standard deviation value for the 23 experiments using the manufacturer's vessels was 2.1. This is consistent with data from experiments under normal (nonperturbed) conditions that have shown relatively low variability using USP Prednisone RS Tablets (6). These findings may also help explain previous data that show low intralaboratory variability but high interlaboratory variability of prednisone dissolution results (5). Under most of the conditions studied, we obtained good precision, even when perturbations were present. Dissolution practitioners should not assume that apparently precise results alone correlate with true and accurate dissolution apparatus performance. Perturbations may be present in the system and may affect the mean value, which is generally increased by perturbations, but not the precision between the 6–8 positions of the test.

Conclusions

By employing a Design of Experiment approach as a screening tool, we identified several variables that have a significant effect on mean percent dissolved and standard deviation results. Wide variation of results, including several that fell outside acceptance limits, were observed when variables were set to their upper and lower limits of currently acceptable ranges. Variables found to be significant—level of deaeration, vessel type (quality), rotation speed, and paddle height—may require more stringent acceptance criteria. Certain vessel attributes appear to be inadequately specified at this time and likely contribute to the high interlaboratory variability of prednisone dissolution results. Combination effects are present and make it more difficult to set appropriate mechanical calibration ranges. The ultimate goal is to determine acceptance criteria that will ensure acceptable accuracy and precision without unnecessarily tightening limits. USP will be conducting further experiments to identify these limits.

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