AAPS PharmSciTech 2007; 8 (4) Article 82 (http://www.aapspharmscitech.org).

Gauge Repeatability and Reproducibility for Accessing Variability During Dissolution Testing: A Technical Note

Received: February 27, 2007; Final Revision Received: May 21, 2007; Accepted: May 26, 2007; Published: October 12, 2007

Zongming Gao,[1] Terry Moore,[1] Anjanette P. Smith,[1] William Doub,[1] Benjamin Westenberger,[1] and Lucinda Buhse[1]

[1]Food and Drug Administration, Center for Drug Evaluation and Research, Division of Pharmaceutical Analysis, St Louis, MO 63101

KEYWORDS: Dissolution test, gauge R&R, variability.

INTRODUCTION

Dissolution testing is widely used in the pharmaceutical industry for quality control and as an in vitro measure of drug availability. Although in vitro dissolution testing has seen continuous improvements for several decades, a better understanding of the underlying principles of dissolution testing has led to an appreciation of new problems with the technology.[1-5] The lack of repeatability and reproducibility are of particular concern to the pharmaceutical industry. Computer modeling and dye studies have shown nonuniformity of the flow patterns in the dissolution vessel,[6-9] but the quantitative contribution of the various sources of variability, such as apparatus, operators, and tablets, has not been addressed. Isolating sources of variation is important to improving the dissolution measurement system and the evaluation of dissolution results.

Gauge repeatability and reproducibility (R&R) studies have been widely used for assessing the precision of a measurement system and identifying its sources of variability, including the contributions from operator, instrument, and random effects.[10-13] The variation observed when 1 operator measures the same part is called repeatability or pure error. The variation observed when 1 operator duplicates the measurement of another operator on the same part is called reproducibility.

In this study, gauge R&R analysis was performed on the paddle dissolution test measurement system (US Pharmacopeia [USP] apparatus 2)[14] to examine variability from the apparatus, operator, and tablets. JMP (version 5.1) statistical software was used to analyze variability contributions. Based on the analysis of variability sources, a change in the mechanical calibration for the measurement system was made to reduce instrument variability. A subsequent statistical analysis showed that the new mechanical calibration process improved the performance of the dissolution measurement system.

Corresponding Author: Zongming Gao, Food and Drug Administration, Division of Pharmaceutical Analysis, 1114 Market Street, Room 1002, St Louis, MO 63101. Tel: (314) 539-3817; Fax: (314) 539-2113; E-mail: Zongming.Gao@fda.hhs.gov

MATERIALS AND METHODS

Design of Experiment for Gauge R&R Study

Since dissolution tests are destructive tests where the sample factor (tablet) is nested in the other 2 factors (operator and apparatus), a 3-factor crossed then nested model was used.[15] Solid dosage forms have inherent variability arising from the manufacturing process. This variability raises the issue that tablets from within the same batch may yield significantly different results. One way to address the high within-sample variation is to increase the number of measurements per sample set, using the following formula[12]:

$$n = \frac{t^2 \sigma_V^2}{E^2} \quad (1)$$

where t = 2 (for a confidence level of approximately 95%), σ^2_V is the estimate of variability, and E is the margin of error. Based on historical data for our internal calibration tablets, National Center for Drug Analysis (NCDA)#2 (10 mg prednisone), the estimate of within-sample variability is 6% (Moore T, Shangraw and Habib,[1] unpublished data, August 1999). The number of measurements required to have a margin of error of ±2% with a 95% confidence level is calculated at 36 tablets. Therefore, 6 replications (6 tablets each) for each operator were made on each apparatus to meet this requirement.

Data Analysis

JMP (version 5.1) statistical software (SAS Institute Inc, Cary, NC) was used to analyze variability contributions from the tablet, operator, and instrument.[16] The probability distribution of dissolution results at 30 minutes was obtained by the following equation[17]:

$$f(x; \mu, \sigma) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right) \quad (2)$$

where x is the measured value, μ is the mean of all measured values, and σ^2 is the variance of all measured values. Figure 1

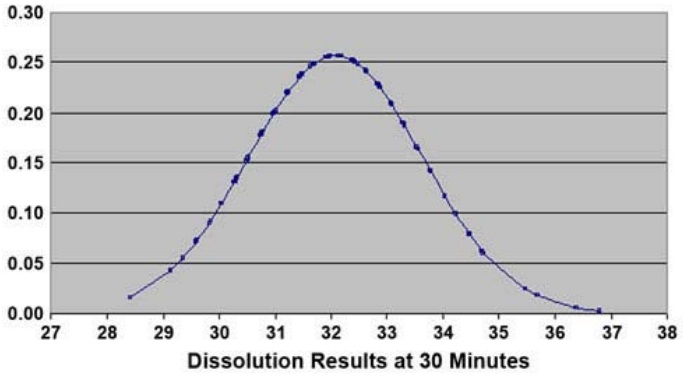

Figure 1. The probability distribution of dissolution results at 30 minutes.

shows that the dissolution data at 30 minutes are normally distributed. JMP software is able to do a 1-way analysis of variance (ANOVA) to test whether the means of the groups are equal.

Dissolution Instruments and Conditions

Two mechanically calibrated paddle dissolution apparatuses (USP apparatus 2) were used in this study. The initial mechanical calibration procedure used by the US Food and Drug Administration (FDA) Division of Pharmaceutical Analysis (DPA) is based on the Pharmaceutical Research and Manufacturers of America (PhRMA) recommendations from 1999.[18,19] Subsequent mechanical calibration procedures used a 2-point centering check to ensure vessel verticality.[20] Operators were well-trained chemists who routinely use the USP apparatus. Dissolution testing was performed using 10 mg prednisone tablets, known as NCDA#2 tablets, which are known to be sensitive to dissolution parameters.[1] Additional details are as follows:

- USP apparatus 2 (paddle), Distek dissolution apparatus Model 2100A (North Brunswick, NJ)
  - Apparatus A: serial no D12547291
  - Apparatus B: serial no D12547292
- 500 mL of DPA method degassed[21] deionized water at 37ºC, and a 50-rpm paddle speed
- Sample filtration through Distek 10-μm ultra-high-molecular-weight polyethylene filter tips
- Online Hewlett-Packard 8452A UV/vis (Palo Alto, CA) with a 0.5-cm cell at a 242-nm wavelength

Vessel Centering and Verticality

Following the DPA procedure for mechanical calibration,[19] only 1 centering tool was initially used to check the centering of dissolution vessels with respect to the shaft. However, initial gauge R&R results led to improved precision through use of 2 points to check vessel centering, which also ensured vessel verticality. This is shown diagrammatically in Figure 2.

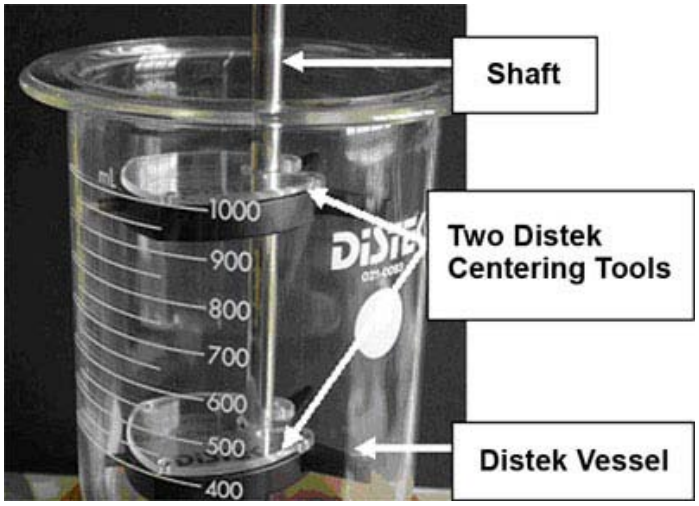

Figure 2. Setup of 2-point vessel centering/verticality check.

The procedure is as follows: 1 centering tool (Distek Center-CheK, Model 170, North Brunswick, NJ) is clamped on the shaft ~2 mm above the top of the paddle blade, and a second is clamped on the shaft 70 mm above the first, with the probes positioned in the same direction. This setup results in 1 centering tool being positioned near the 350-mL level and the second at about the 900-mL level. The shaft is slowly turned, and both probe readings are checked. If the vessel is not centered according to both probes, the vessel is adjusted by rotating, moving the vessel within the centering collar, or placing shims under 1 side of the lip of the vessel or vessel-centering collar. This process is repeated until both bottom and top positions are centered within a tolerance of 1 mm. This tolerance ensures that the vessel is no more than 1 degree from vertical and the vessel is centered on the shaft.

Results and Discussion

Gauge R&R Study

In dissolution testing, when a properly degassed medium is used, the variability arises primarily from 3 factors: apparatus, operator, and sample tablet. It is important to make

Table 1. Summary Dissolution Results (% Dissolved at 30 Minutes for 2 Operators Using 1-Point Centering)*

	Apparatus A	Apparatus B
Number of data points	72	72
Average (%)	32.3	31.9
SD	1.62	1.47
% CV	5.02	4.60
Range (%)	28.4-36.8	29.1-35.7
Width of range	8.38	6.55

*CV indicates coefficient of variation.

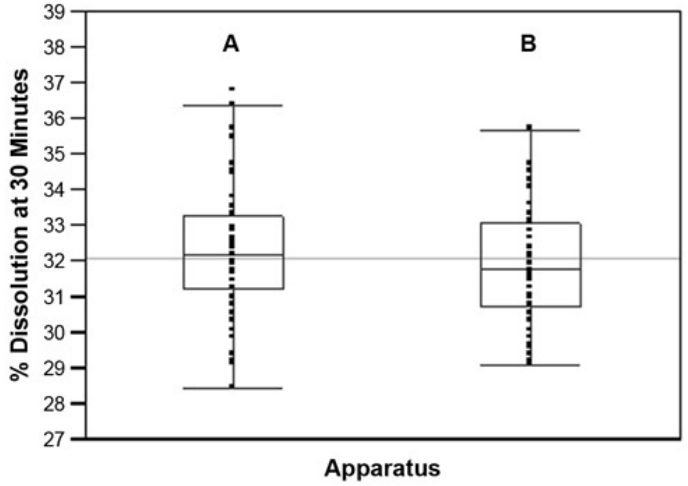

Figure 3. Box-and-whisker plot for comparison of percent dissolved at 30 minutes for 2 apparatuses.

sure that the variation due to the measurement system is small relative to the variation in the tablets. Use of gauge R&R enabled assignment of relative contributions to the total variability from operators, instruments, and tablets based on significant differences in mean or variance.

Table 1 shows the summary dissolution data for each apparatus (combined data for both operators). ANOVA was also used to compare the grand means for the 2 apparatuses; the resulting box-and-whisker plots are shown in Figure 3.

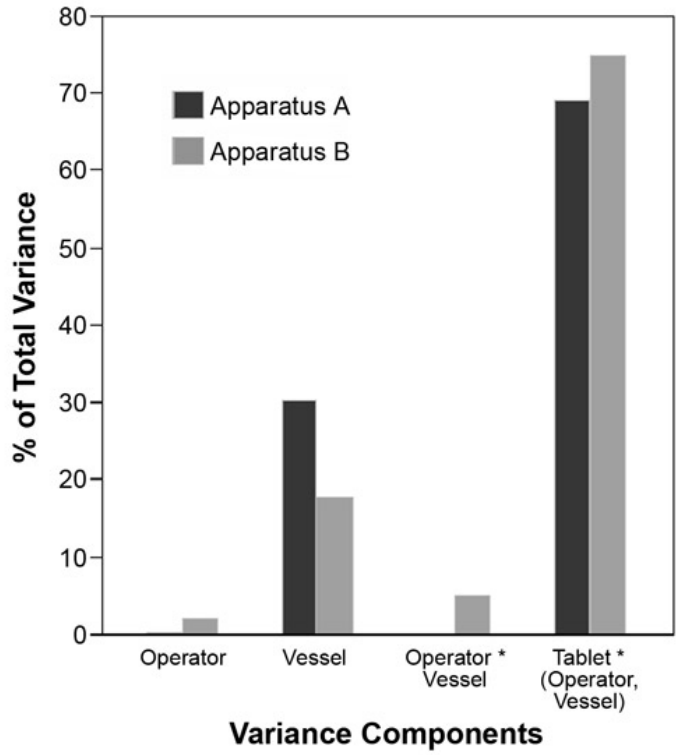

Figure 4. Variance components of apparatus A and apparatus B.

This analysis indicates that there is no significant difference between these 2 USP apparatuses for dissolution testing of NCDA#2 tablets (95% confidence level). The variance component analysis is shown in Figure 4. The result indicates that the tablet, confounded with the operator and the vessel, is the main contribution to the variance. The vessel contributes up to 30% of the total variance, and the variability component from the vessels for apparatus A is larger than that for apparatus B. Operators and interactions between operator and vessel contribute minimally to variability.

Modification of Mechanical Calibration Process

Because the initial analysis showed that, for apparatus A, 30% of the variability arises from the vessels, dissolution results from each vessel were statistically analyzed. Results are shown as a box-and-whisker plot in Figure 5 (1-point centering). The average percent dissolution results from vessels 1 and 3 are higher than those from vessels 5 and 6, and a Student *t* test at a 95% confidence level shows that there are significant differences between many of the vessels (Table 2). The differences shown are thought to reflect vessel imperfections or improper vessel setup. To find potential causes of this variability, each vessel as well as all other relevant parts of the apparatus were rechecked, and the DPA mechanical calibration process was reviewed.

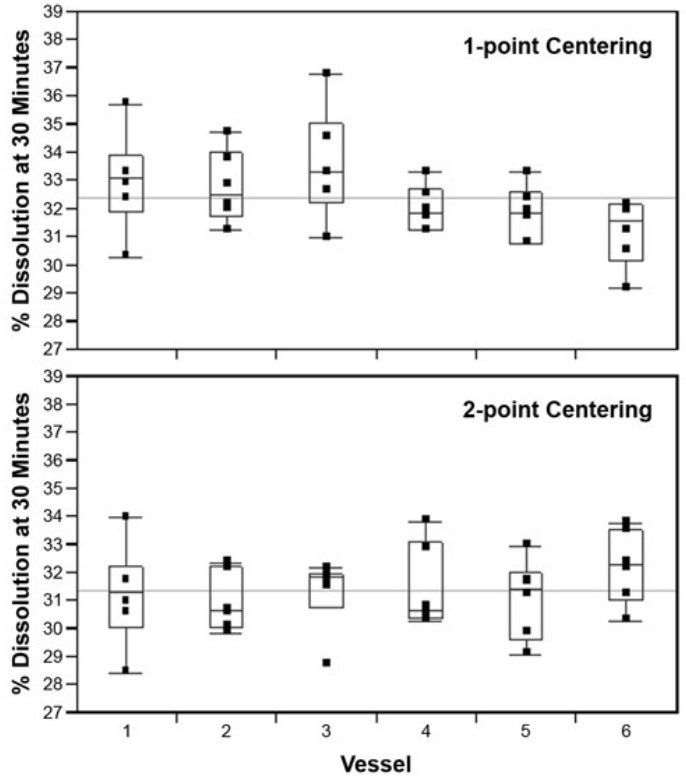

Figure 5. Box-and-whisker plot for comparison of dissolution from individual vessels of apparatus A after mechanical calibration using 1-point and 2-point centering.

Table 2. Comparison of Dissolution Results at 30 Minutes for Each Pair of Vessels in Apparatus A Using Student *t* Test at 95% Confidence Level After Mechanical Calibration With 1-Point Centering of Vessels*

Vessel Number	1	2	3	4	5	6
1	—	X	X	X	√	√
2	X	—	X	X	X	X
3	X	X	—	√	√	√
4	X	X	√	—	X	X
5	√	X	√	X	—	X
6	√	X	√	X	X	—

*√ indicates significant difference; X, no significant difference.

Based on the vessel check, it was found that the rims of some glass vessels were not of uniform thickness (Table 3). In the DPA mechanical calibration process, after the vessel plate is leveled, the vessel/shaft centering process uses 1 centering tool that is clamped on the shaft ~2 mm above the top of the paddle blade. Because of uneven glass rims, confirmation of a level vessel plate and 1-point centered vessel does not ensure that the vessel itself is vertical relative to the shaft. To address this concern, the plate-leveling procedure was eliminated, and 2 centering tools were used. Employing this process for checking vessel centering at 2 points guarantees that not only is the vessel centered around the shaft, but it is also vertical relative to the shaft, irrespective of any unevenness of vessel rim or warping of apparatus base plate.

Comparison of 1-Point and 2-Point Centering Methods

Figure 6 shows the comparison of variability for vessels before and after 2-point centering for apparatus A. After the more precise 2-point centering, statistical analysis shows that over 90% of the variance is due to the tablets, suggesting that vessel setup has been improved. Some minimal operator * vessel contribution is seen, which is perhaps an indication of slight procedural differences between operators when using this new mechanical calibration process. A Student *t* test at a 95% confidence level shows no differences between any 2 vessels after this more exacting mechanical calibration

Table 3. Rim Thickness and Inside Dimensions of the Distek Vessels (Average of 4 Measurements With SD for Apparatus A)

Vessel Number	Thickness of the Rim (mm)	Inside Diameter (mm)	Inside Height (mm)
1	4.90 ± 0.41	100.7 ± 0.2	161.5 ± 0.4
2	4.36 ± 0.27	101.2 ± 0.2	162.3 ± 0.4
3	4.34 ± 0.51	100.7 ± 0.1	163.0 ± 0.4
4	4.18 ± 0.21	101.1 ± 0.4	163.1 ± 0.3
5	4.09 ± 0.19	101.1 ± 0.2	161.3 ± 0.3
6	4.28 ± 0.26	100.5 ± 0.3	162.3 ± 0.3

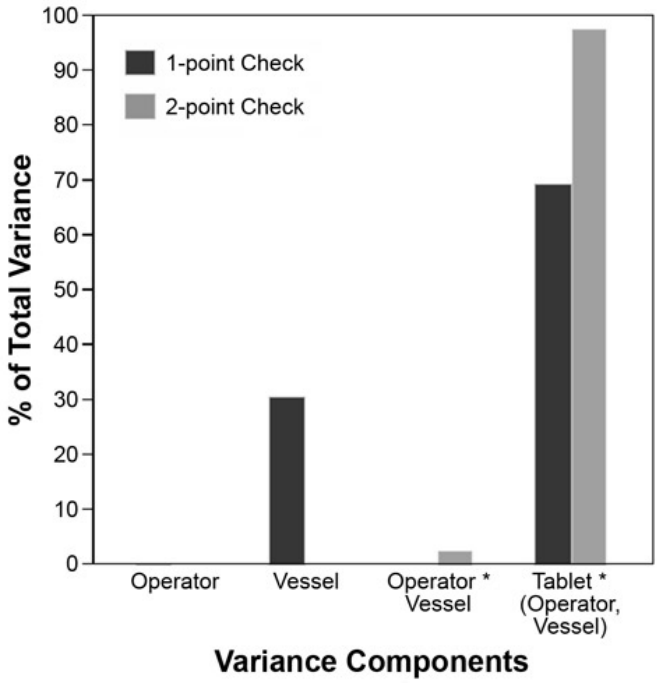

Figure 6. Comparison of variance components between 1-point centering and 2-point centering for apparatus A.

of the apparatus. The box-and-whisker plot in Figure 5 (2-point centering) shows a more consistent clustering of the percent dissolution for all vessels. Table 4 shows the dissolution results for 1 operator using apparatus A before and after 2-point centering. Both the range and the SD are decreased once the verticality of the vessels is ensured.

CONCLUSIONS

In this study, the gauge R&R method was used to analyze sources of variability for the paddle apparatus (USP apparatus 2). An initial evaluation of gauge R&R dissolution testing results using the amount dissolved at 30 minutes for a 10-mg prednisone tablet showed no instrument or operator

Table 4. Comparison of the Effect of 1-Point and 2-Point Centering on Dissolution Results (% Dissolved at 30 Minutes, for 1 Operator)

	Apparatus A One-Point Centering	Apparatus A 2-Point Centering
Number of data points	36	36
Average (%)	32.4	31.4
SD	1.51	1.38
% CV	4.66	4.40
Range (%)	29.1-36.8	28.4-34.0
Width of range	7.65	5.56

*CV indicates coefficient of variation.

contributions to variability but did highlight some vessel differences within an instrument. Based on this finding, a new mechanical calibration step was developed to improve the performance of the measurement system.

Gauge R&R analysis is useful for determining the sources of variability in a measurement system. In addition, the extensive characterization and variability knowledge obtained during gauge R&R testing of a product can be used to develop the mean and SD information necessary to set up an internal standard for dissolution testing.

ACKNOWLEDGMENT

Opinions expressed in this report are those of the authors and do not necessarily reflect the views or policies of the FDA.

REFERENCES

1. Moore TW, Shangraw RF, Habib Y. Dissolution calibrator tablets: a recommendation for new calibrator tablets to replace both current USP calibrator tablets. *Pharmacacop Forum.* 1996;22:2423–2428.

2. Layloff T. Studies in the development of USP dissolution test method number 2. *Pharmacacop Forum.* 1983;9:3752–3757.

3. Cox DC, Furman WB, Thornton LK, Moore TW, Jefferson EH. Systematic error associated with apparatus 2 of the USP dissolution test III: limitations of calibrators and the USP suitability test. *J Pharm Sci.* 1983;72:910–913.

4. Cox DC, Furman WB. Collaborative study of the USP dissolution test for prednisone tablets with apparatus 2. *J Pharm Sci.* 1984;73:670–676.

5. Hamilton JF, Moore TW, Kerner CM. Reproducibility of dissolution test results. *Pharmacacop Forum.* 1995;21:1383–1386.

6. Qureshi SA, Shabnam J. Applications of a new device (spindle) for improved characterization of drug release (dissolution) of pharmaceutical products. *Eur J Pharm Sci.* 2003;19:291–297.

7. Kukura J, Baxter JL, Muzzio FJ. Shear distribution and variability in the USP apparatus 2 under turbulent conditions. *Int J Pharm.* 2004;279:9–17.

8. Healy AM, McCarthy LG, Gallagher KM, Corrigan OI. Sensitivity of dissolution rate to location in the paddle dissolution apparatus. *J Pharm Pharmacol.* 2002;54:441–444.

9. McCarthy LG, Kosiol C, Healy AM, Bradley G, Sexton JC, Corrigan OI. Simulating the Hydrodynamic Conditions in the United States Pharmacopeia Paddle Dissolution Apparatus. *AAPS PharmSciTech [serial online].* 2003;4:article 22.

10. Bergeret F, Maubert S, Sourd P. Improving and applying destructive gauge capability. *Qual Eng.* 2002;14:59–66.

11. Early TA, Neagu R. *Random and Fixed Factor ANOVA Models: Gauge R&R Studies. GE Research & Development Center, Technical Report.* Piscataway, NJ: General Electric Company; 1999.

12. Phillips AR, Jeffries R, Schneider J, Frankoski SP. Using repeatability and reproducibility studies to evaluate a destructive test method. *Qual Eng.* 1997;10:283–290.

13. Mast J, Trip A. Gauge R&R studies for destructive measurements. *J Qual Technol.* 2005;37:40–49.

14. The United States Pharmacopeia. *USP 29: General Chapter, Physical Tests and Determinations, <711> Dissolution.* Rockville, MD: United States Pharmacopeial Convention; 1995.

15. Gao Z, Moore TW, Smith AP, Doub WH, Westenberger BJ. Studies of variability in dissolution testing with USP apparatus 2. *J Pharm Sci.* 2007;96:1794–1801.

16. *Statistics and Graphics Guide, JMP 5.1.* Cary, NC: SAS; 1989.

17. Rosner B. *Fundamentals of Biostatistics.* Belmont, CA: Wadsworth Publishing Company; 1995.

18. Subcommittee on Dissolution Calibration. Dissolution calibration: recommendation for reduced chemical testing and enhanced mechanical calibration. *Pharmacacop Forum.* 2000;26:1149–1166.

19. Gao Z, Moore TW, Doub WH, Westenberger BJ, Buhse LF. Effects of deaeration methods on dissolution testing in aqueous media: a study using a total dissolved gas pressure meter. *J Pharm Sci.* 2006;95:1606–1613.

20. Mechanical Qualification of Dissolution Apparatus 1 and 2. US Food and Drug Administration, Center for Drug Evaluation and Research Web site. Available at: http://www.fda.gov/cder/offices/OTR/default.htm. Accessed February 8, 2007.

21. Moore TW. Dissolution testing: a fast, efficient procedure for degassing dissolution medium. *Dissolution Technol.* 1996;3:3–5.