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Effect of the Irregular Inner Shape of a Glass Vessel on Prednisone Dissolution Results

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Abstract

The effect of the irregular inner shape of a glass vessel on drug dissolution results was investigated. The inner shapes of commercially available glass vessels obtained from three different manufacturers were examined for unevenness of the inner surface of the vessel and for distortion of the inner shape as a whole using a three-dimensional coordinate measuring machine. A precision vessel (Takao, Japan) was manufactured by a new glass processing technology and displayed an almost ideal inner shape consisting of a cylinder and hemisphere. In contrast, two conventional vessels, vessel A (manufacturer A, Japan) and vessel B (manufacturer B, USA), exhibited distortion, and unevenness in various places. The vessel bottoms in particular deviated from the ideal hemispherical shape, and curvature among vessels differed widely. The inside of the cylinder of these two manufacturers' vessels also deviated from the ideal circular shape. The dissolution results of USP Prednisone Calibrator tablets were compared for the precision vessel and vessel A. Variability in test results was markedly lower when the precision vessel was used. For vessel A, however, test results varied widely between vessels used and between positions in the dissolution tester. In addition, the mean values of prednisone dissolution percentages obtained from six positions differed significantly ($p < 0.05$) among vessels. These results suggest that the shape of a glass vessel is critical to obtaining unvarying and reproducible dissolution test results.

Introduction

Dissolution testing has increased in value and significance over the last quarter century. It has been used extensively to guide formulation development and to monitor formulation development, formulation changes, and manufacturing of products for new drugs. It is also widely used as a quality control tool to monitor the batch-to-batch consistency of drug release from a product.

There are reports that dissolution testing involves a large number of variable factors and that obtaining reproducible results between apparatus, within laboratories, and between laboratories is difficult (1, 2). The fact that significant within- and between-apparatus variability can exist for certain formulations, even though these apparatus meet the USP calibration criteria, has been reported (3). Recent research results have confirmed that dissolution testing is a highly variable technique such that test results for the same lot of USP calibrator tablets deviated from the acceptable USP range at 15 of 28 laboratories performing dissolution testing (4).

In recent years, significant modifications and improvements have been made to the apparatus used in dissolution testing. Often overlooked is a critical technical issue that remains with regard to the glass vessel in the dissolution tester. A glass vessel is generally made from large–diameter glass tubing, and the bottom of the vessel is shaped by hand from the outside while the tubing is heated (5). Irregular interior surfaces result, and the curvature of the inner bottom varies from one vessel to the next, producing variation in dissolution test results (6, 7). The vessels formed using such glass tubing are widely used in dissolution testing.

A glass vessel with an almost ideal inner shape was recently developed using a new glass processing technology.

This paper describes the effects of the irregular inner shape of a glass vessel on drug dissolution results. The shape of the inside of two conventional vessels, vessel A (manufacturer A, Japan) and vessel B (manufacturer B, USA), was measured using a three-dimensional coordinate measuring machine. The results were compared with those for a recently developed glass vessel (precision vessel). In addition, dissolution of USP Prednisone Calibrator tablets was compared using vessel A and the precision vessel.

Experimental

Materials

USP Prednisone Calibrator tablets (10 mg, Lot O0C056) were obtained from USP (Rockville, MD, USA). Prednisone Reference Standard (Lot LIB251) was obtained from USP (Rockville, MD, USA). All other chemicals were reagent grade.

Glass vessels

Commercially available vessels that were manufactured by Takao Manufacturing Co., Ltd. (Kyoto, Japan) were used in this study as the precision vessel. The precision vessel had a product specification of 100.06 ± 0.08 mm for the inner diameter of the cylinder and 50.03 ± 0.08 mm for the radius of the hemisphere portion. Two conventional vessels—vessel A and vessel B—that are commercially available in Japan were purchased from manufacturer A (Japan) and manufacturer B (USA), respectively. The precision vessel and vessel A that were used in the dissolution test had the same

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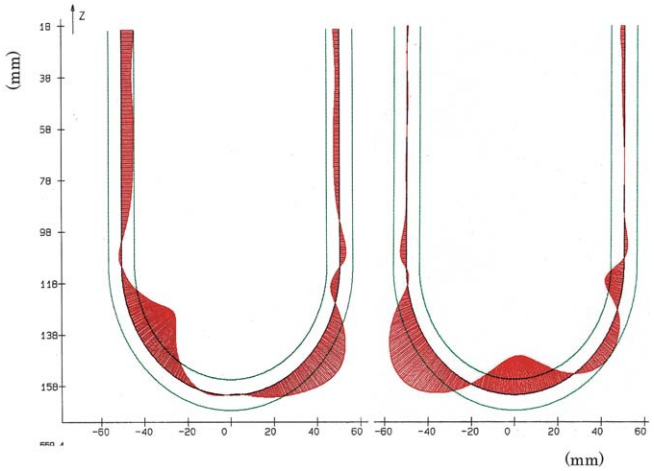

Figure 1. Inner Shape of Vessel A. The center of the three lines indicates the ideal shape of the cylinder and hemisphere. The two lines drawn on both sides represent ± 0.3 mm from the center line.

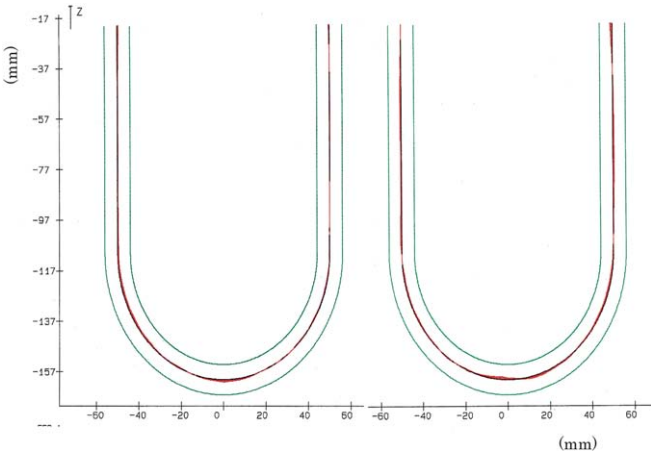

Figure 2. Inner Shape of the Precision Vessel. The center of the three lines indicates the ideal shape of the cylinder and hemisphere. The two lines drawn on both sides represent ±0.3 mm from the center line.

physical dimensions as the precision vessel in terms of the inner diameter of the cylindrical portion, the depth from the flange top to the inner bottom, and the flange diameter.

Evaluation of Irregularities of the Vessel Inner Shape

Deviation from the ideal inner shape of a vessel was measured using a three-dimensional coordinate measuring machine (Brown & Sharpe Wetzlar, GMBH). Vessels subjected to measurement totaled 26, 10, and 4 vessels for the precision vessel, vessel A, and vessel B, respectively. Four deviations were measured to evaluate the extent of deviation from the ideal inner shape: deviation from circularity for the inner cylinder, deviation from cylindricity for the entire cylindrical shape, deviation from sphericity for the bottom shape, and deviation from concentricity for the center of the sphere.

Dissolution Testing

Dissolution tests were conducted using a semi-automated dissolution tester (Japan) consisting of a bath with six vessels; the tester met physical and mechanical specifications as required by the USP and JP. The dissolution tests were all entrusted to external laboratories. Four precision vessels and four vessel A's were involved in this test. All vessels used in the test were fresh and had not been used for previous testing.

The eight vessels were individually numbered. Six of the total eight vessels were first installed in the apparatus so that the precision vessel and vessel A were placed at six positions side by side. The vessels were then moved one position in a clockwise direction for each test. This procedure was continued until a vessel had been tested in all six positions. Shaft centering was always confirmed using a tool after a vessel was moved to the next position. The dissolution test was conducted in accordance with the procedures described in the sheet for USP Prednisone Calibrator tablets. Briefly, the tests were conducted by the paddle method at 37 °C using 500 ml of deaerated water at 50 rpm. The dissolution media was kept at 45 °C and deaerated while stirred for 2 h before use (8). The amount of prednisone dissolved at 30 min, for each spindle, expressed as percent of the labeled amount, was measured in a spectrophotometer at 242 nm for comparison with a standard prednisone solution of known concentration. The position of a tablet settling at the bottom after it was dropped into the vessel was visually inspected in each vessel. Statistical analysis was performed using two-way ANOVA, and the differences were assumed to be significant at $p < 0.05$. The precision vessel and vessel A in which sphericity deviation was close to the mean values illustrated in Figure 4 were used in this test.

Results and Discussion

Inner Shape of Glass Vessels

The USP, EP, and JP specify that the inner shape of vessels be cylindrical with a hemispherical bottom. Deviation from the ideal inner shape was, therefore, determined using a three-dimensional measuring machine. Figure 1 depicts measurements for two vessel A's. The center of the three lines illustrated in the figure indicates the ideal cylindrical and hemispherical shape of the vessel. The extent of deviation from the ideal shape is illustrated with the zone. The outer edge of the zone implies the actual inner shape of the vessel. Unevenness was present on the surface of the inside wall, and unevenness spanning more than 1.5 mm from trough to peak was observed at various places on the inner bottom in particular. In addition, the bottom shape differed considerably between the two vessels measured.

Cox et al. reported that the glass vessels had non-uniform inner bottom curvatures that varied from one vessel to the next, after they performed a visual inspection of plaster casts of the vessel bottoms (6). The finding agrees with the current three-dimensional measurement in that a deviation in shape was present inside the vessel and the shape differed widely among vessels.

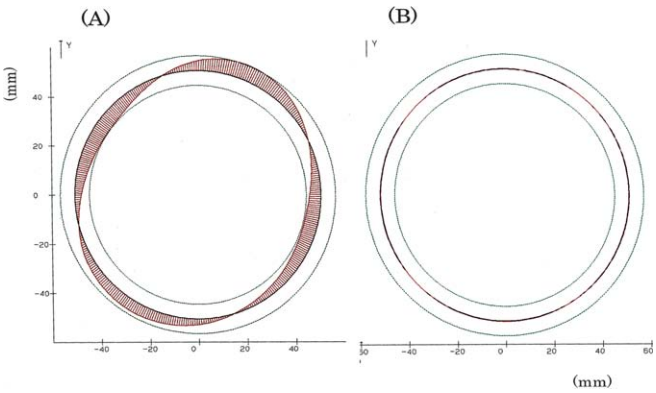

Figure 3. Inner Shape at Cylinder of Vessel A and the Precision Vessel. (A) vessel A, (B) the precision vessel. The center of the three lines indicates the ideal shape of the cylinder and hemisphere. The two lines drawn on both sides represent ±0.3 mm from the center line.

In the precision vessel, no apparent irregularities were observed in the cylinder or in the bottom (Fig. 2). This result reveals that the precision vessel possessed a nearly ideal cylindrical and hemispherical inner shape.

There is little information on the inner shape of a cylinder. Thus, cross-sectional observation of the inner cylindrical shape of vessel A and of the precision vessel was conducted at the midpoint of the length of each cylinder (Fig. 3). The figure represents an example in which the inner cylindrical shape of vessel A was closer to an ellipse than a circle. In this case, there was a difference of approximately 1.1 mm in the inner diameter of the cylinder within the vessel. The elliptical shape has been reported to be the most common flaw occurring in the cylinder of vessel (7). In contrast, the precision vessel exhibits a satisfactory circular shape without showing any apparent deviation.

Measurement of Geometric Errors

Sphericity, circularity, cylindricity, and concentricity deviation were measured as parameters to represent the extent of deviation from the ideal shape in terms of the two conventional vessels, vessels A and B, and of the precision vessel (Fig. 4). The numerical value of zero on the Y axis represents a perfect shape that is completely free from deviation. The deviation in shape increases with larger values. The values obtained from vessel A and vessel B were all much higher than those from the precision vessel, indicating that those two conventional vessels had greater unevenness and distortion in shape as a whole. No significant differences in values between vessels A and B were observed. In the two conventional vessels, the highest value was observed for the sphericity deviation together with quite a higher standard deviation. This is probably due to manual glass processing when forming the bottom, resulting in considerably larger differences in the bottom shape among vessels. In the precision vessel, sphericity deviation was 0.05, which is 16

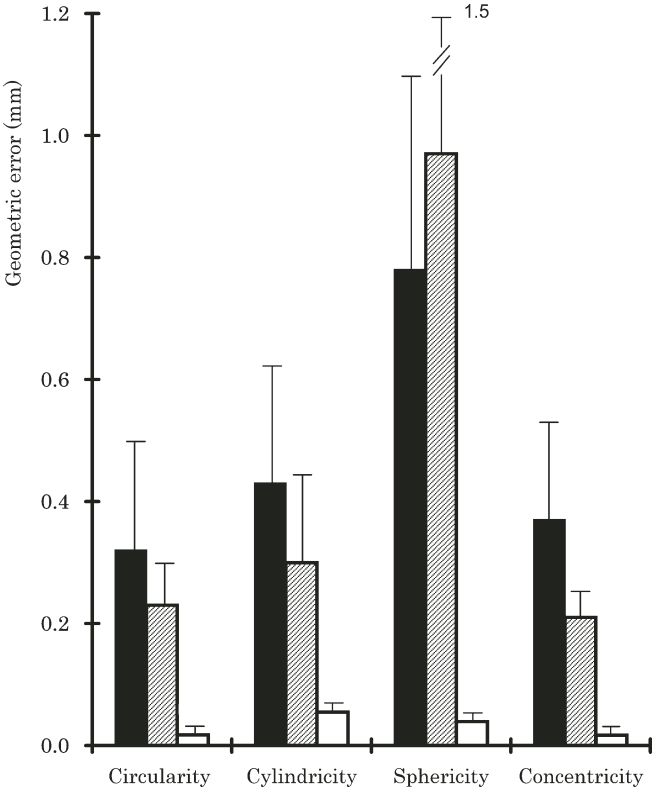

Figure 4. Comparison of Circularity, Cylindricity, Sphericity and Concentricity Deviation among Vessel A, Vessel B, and the Precision Vessel. ■, vessel A; ▨, vessel B; □, the precision vessel. Each vertical bar represents the mean and standard deviation.

times and 20 times lower than that for vessel A and vessel B, respectively. The standard deviation was also quite low. In addition, the other three values of circularity, cylindricity, and concentricity deviation for the precision vessel were also far smaller than those for the two conventional vessels; they were all close to zero. The deviation of the inner cylindrical shape in vessel A, as shown in Fig. 3, is reflected in higher circularity.

Effect of Inner Shape of Glass Vessels on Prednisone Dissolution

The dissolution test was conducted to determine the influence of the inner shape of the vessel on drug dissolution. Figure 5 shows the results of dissolution of prednisone tablets obtained using four vessel A's and four precision vessels. The dissolution values obtained from vessel A ranged from 32.0% to 60.0% and widely varied among vessels. Four of 24 results fell outside acceptable USP ranges. However, the dissolution values obtained from the precision vessel ranged from 29.9% to 39.1%, and variability was quite low. All 24 results were within acceptable USP ranges.

Figure 6 shows the mean values of prednisone dissolution percentages obtained after each vessel had been placed in all six positions on the apparatus. Vessel A had mean values that fluctuated widely, demonstrating a significant difference ($p < 0.05$) between the two vessels, numbers C2 and

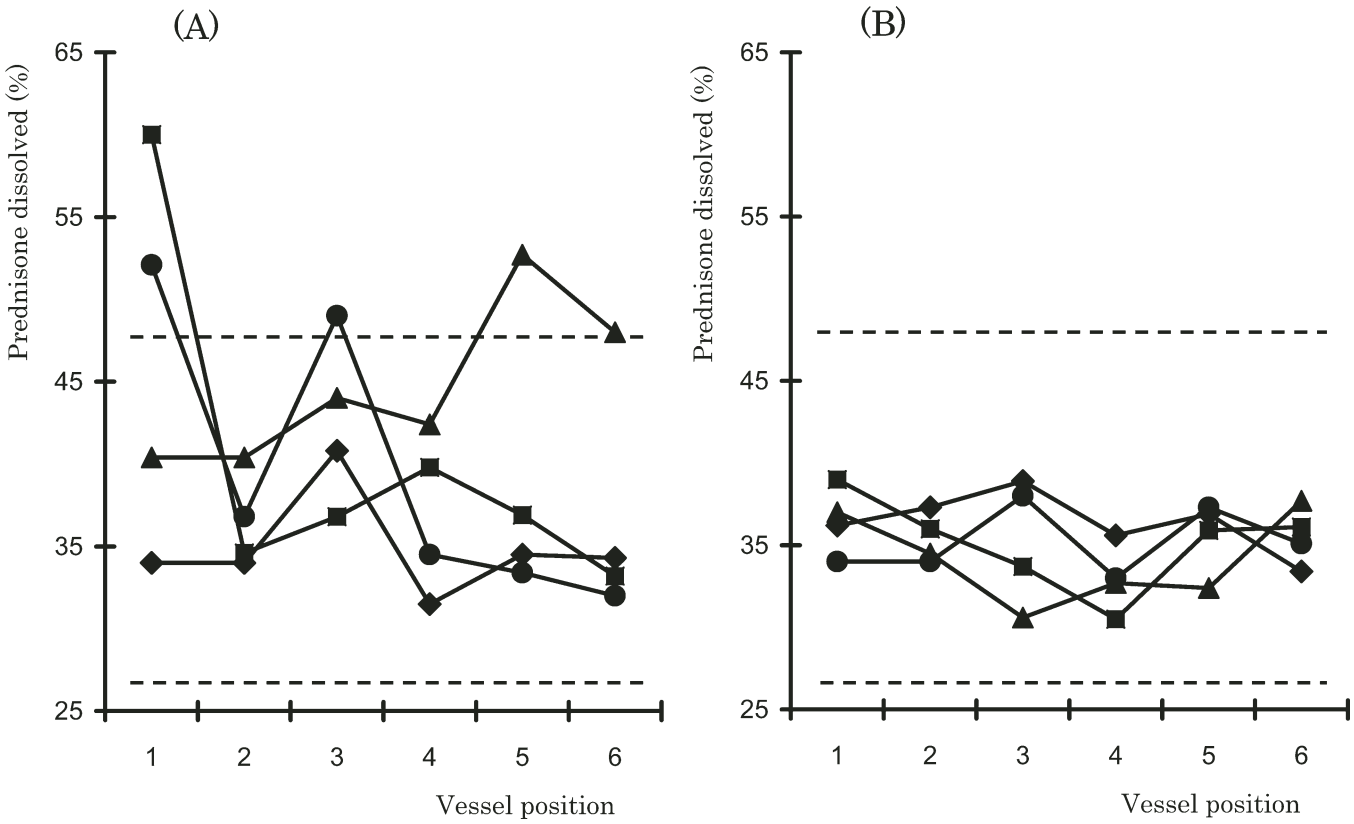

Figure 5. Dissolution Results for Prednisone Tablet Obtained from Vessel A and the Precision Vessel. (A) vessel A, (B) the precision vessel. Dotted lines represent the acceptable ranges (27–48%) for prednisone tablets (Lot O0C056) specified by USP.

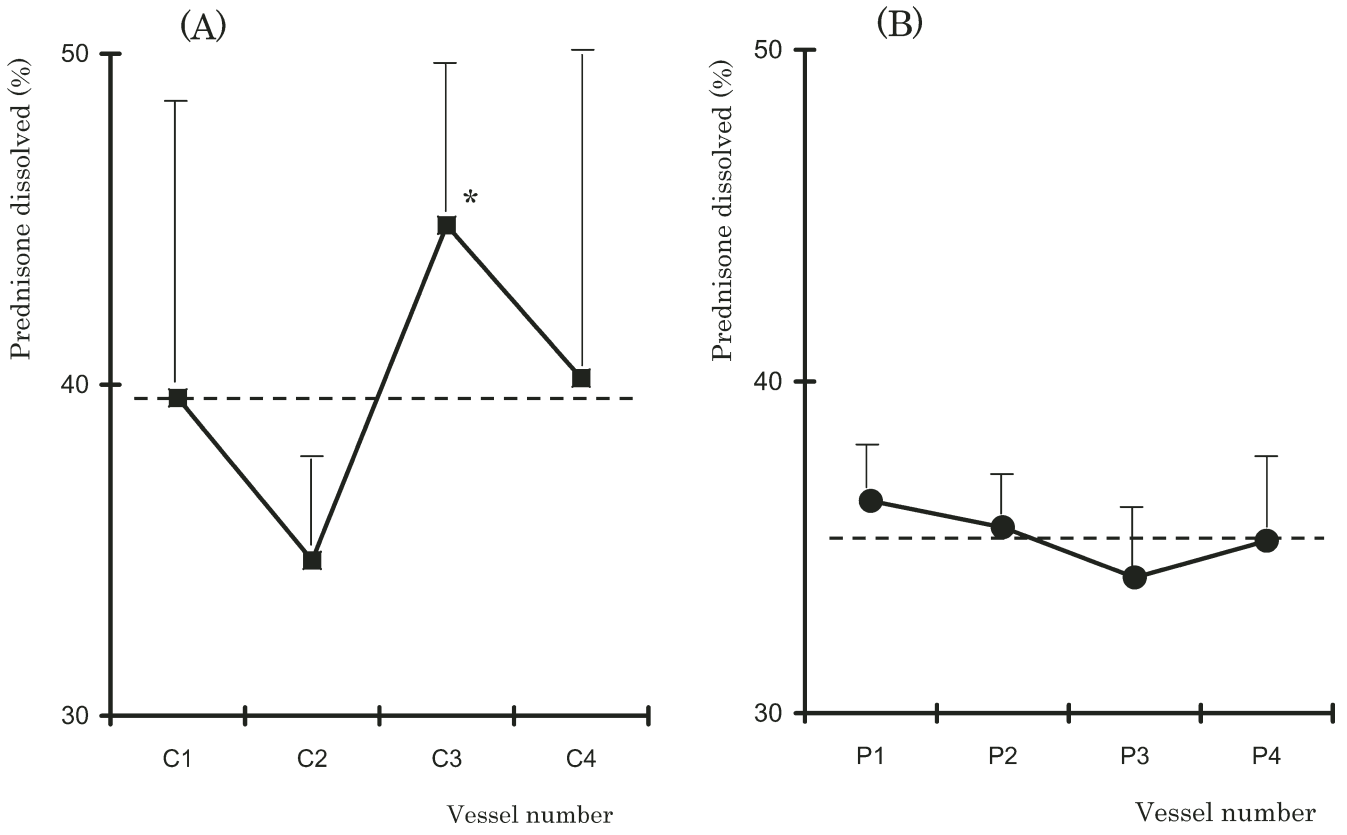

*Figure 6. Mean Dissolution Data for Prednisone Tablets Obtained from Six Vessel Positions. (A) vessel A, (B) the precision vessel. * $p<0.05$ vs. C2. Dotted line represents the mean value of 24 results. Each point represents the mean ± SD (vertical bar) of six determinations. ■, vessel A; ●, the precision vessel.*

C3. This indicates that the dissolution data varied depending on the vessel used and the position set when vessel A was used. In contrast, results for the precision vessel were always reproducible and less variable, regardless of the vessel and the position. This can be explained by the fact that an irregular inner shape such as that of vessel A disturbed and altered the flow dynamics, and the conical shape formed by tablet particles might be disrupted, resulting in such large data variation (6, 9, 10).

Table 1 shows the mean values of prednisone dissolution percentages for all 24 vessels and the standard deviation (SD). The mean value obtained from vessel A was significantly higher ($p < 0.05$) than that from the precision vessel. The SD obtained from vessel A was 3.2 times greater than that from the precision vessel, which is probably due to the change in flow dynamics in vessel A, as mentioned above. The relative standard deviation (RSD) in vessel A was 19.1%, while it was 6.8% in the precision vessel. The RSD in excess of 10% at timepoints once 10 min has passed following dissolution demonstrates that dissolution testing with vessel A was highly variable (11).

This dissolution test was performed under the same experimental conditions using the precision vessel and vessel A, which have the same physical dimensions for the inner diameter of the cylinder and the vessel depth. There were no appreciable differences among vessels in the position where tablets settled after they were dropped into the vessels. However, the resulting data varied widely when vessel A was used, and the mean value of prednisone dissolution percentages was significantly higher ($p < 0.05$) than that for the precision vessel. In contrast, results for the precision vessel were reproducible and less variable. This reveals that the difference in variation of prednisone dissolution results for the precision vessel and vessel A was obviously correlated with the difference in the irregularity of the inner vessel shape.

Particular attention should also be given to the inner cylindrical shape, in addition to sphericity deviation of the bottom. Deviation from the ideal circular shape and cylindricity may generate an off-centering of paddles from the vessel center axis, resulting in asymmetrical liquid flow that will account for erroneous data. The combination of the irregular inner shape of the vessel itself and the resulting paddle misalignment is probably responsible for greater variability seen at different vessel positions (12). Further investigation is needed to clarify the relationship between the variability of dissolution results and quantitative determination of the vessel inner shape such as cylindricity or circularity deviation at the cylinder and sphericity deviation at the bottom.

Results demonstrated that the vessel inner shape was a critical factor resulting in variability of dissolution results. Results also revealed that the precision vessel used in this study possessed a nearly ideal inner geometry with respect to both the cylinder and bottom.

Table 1. Mean Dissolution Data for Prednisone Tablets Obtained from Vessel A and the Precision Vessel

	Vessel A	Precision vessel
Mean dissolution value[a]	39.8	35.3
Standard deviation	7.6	2.4

[a]n=24, Percent of label claim dissolved at 30 min.

References

1. Achanta, A, S., Gray, V.A., Cecil, T.L., Grady, L.T., "Evaluation of the performance of prednisone and salicylic acid USP dissolution calibrators", Drug Dev. Ind. Pharm., 21, 1171-1182, 1995.
2. Kaniwa, N., "Typical variability in dissolution testing and its qualification", Pharm. Tech. Japan, 18, 105-111, 2002.
3. Skoug, J.W., "Calibration of dissolution rate apparatuses: A User's Perspective", *Dissolution Technologies*, 1(2, Fall), 3-5, 1994.
4. Qureshi, S.A., McGilveray, I.J., "Typical variability in drug dissolution testing: study with USP and FDA calibrator tablets and a marketed drug (glibenclamide) product", Eur. J. Pharm. Sci. 7, 249-258, 1999.
5. Gray, V.A., "Identifying source of error and variability in dissolution calibration and sample testing", American Pharmaceutical Review, Summer, 8, 2002.
6. Cox, D.C., Wells, C.E., Furman, W.B., Savage, T.S., King, A.C., "Systematic error associated with apparatus 2 of the USP dissolution test II: Effects of deviations in vessel curvature from that of a sphere", J. Pharm. Sci., 71, 395-399, 1982.
7. Scott, P., "Geometric Irregularities Common to the Dissolution Vessel", *Dissolution Technologies,* 12, (1, February), 18-21, 2005.
8. Kaniwa, N., Katori, N., Aoyagi, N., Ishigame, N., Seta, Y., Shinba, T., Fujiwara, K., Nakai, T., Oda, Y., Kojima, S., "Collaborative study on the development of a standard for evaluation of vibration levels for dissolution apparatus", Int. J. Pharm., 175, 119-129, 1998.
9. Aoyagi, N., Katori, N., Izutsu, K., Kojima, S., The 123rd Annual Meeting of Pharmaceutical Society of Japan, Nagasaki, March 27, 2003.
10. Yano, H., Yada, M., Ohya, M., Shigyo, M., Hamaura, T., Koike, A., Takahashi, H., Kusai, A., The 124th Annual Meeting of Pharmaceutical Society of Japan, Osaka, March 30, 2004.
11. Pharmacopeial Forum, 27, 3432-3439, 2001.
12. Qureshi, S.A., Shabnam, J., "Cause of high variability in drug dissolution testing and its impact on setting tolerances", Eur. J. Pharm. Sci., 12, 271-276, 2001.