Evaluation of Glass Dissolution Vessel Dimensions and Irregularities

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Abstract

This paper reports on studies of the geometric dimensions and irregularities in the surface of standard 1-L glass dissolution vessels. Eleven sets of six dissolution vessels from 10 commercial sources were selected for study. A three-dimensional coordinate measuring machine (CMM) was used to obtain results. The geometric dimensions studied were height, inner diameter of the cylindrical portion of the vessel, and radius of the hemispheric region. The following irregularities of the flange and of the internal surface of dissolution vessels were quantified: (1) flatness of the vessel flange, (2) roundness of the hemisphere at the base of the vessel, required to ensure smooth, unperturbed media flow, (3) cylindricity, roundness, and perpendicularity of the cylinder (i.e., the degree to which the walls of the cylindrical portion of the vessel were equidistant from a common axis, did not deviate from circular form, and were perpendicular to the common axis—in other words, how well this portion of the apparatus matched the characteristics of an ideal cylinder), and (4) concentricity between the hemisphere and the cylinder (i.e., the degree to which the axis of the cylinder aligned with the axis of the hemisphere, see Table 1 and Figure 1). Vessels from different sources displayed differences both for geometric dimensions and for surface irregularity measurements. Differences in hemisphere radius can result in as much as an 18% change in the volume of dissolution media surrounding the paddle. Measurements of cylinder and hemisphere roundness revealed as much as a 10-fold difference among vessels from different sources. Although differences were most noticeable among dissolution vessels from different commercial sources, differences among dissolution vessels from the same source were also observed.

Introduction

Used in the private or public USP Performance test, dissolution testing plays an important role in both product development and quality assurance for nonsolution oral dosage forms. The dissolution procedure itself, as described in USP General Chapter *Dissolution* <711>, is sensitive and specific but requires special care in execution. Results of a recent USP collaborative study of new Lot P Prednisone Reference Standard Tablets indicate much higher reproducibility (interlaboratory variance) than repeatability (intralaboratory variance) (*1, 2*). To improve reproducibility, the USP Biopharmaceutics Expert Committee recommends careful IQ, OQ, and PQ (mechanical calibration), as well as a Performance Verification Test (PVT); the latter two typically are performed at six-month intervals. Several variables such as shaft rotation speed, shaft and vessel alignment, basket/paddle height, and bath levelness have been cited as factors that contribute to high variability of the dissolution procedure. Missing from this list are factors relating to vessel dimension and irregularities, which are the subject of this report.

Methods

Dissolution Vessels

Dissolution vessels are commercially available from sources in the United States, Japan, and Europe. Five sets of dissolution vessels (six vessels per set) were obtained from the following dissolution apparatus manufacturers: Distek, Erweka, Hanson, Jasco, and VanKel. Six sets were obtained from the following dissolution glassware suppliers: Kimax, Kontes, Quality Lab Accessories (QLA; two sets), Sun, and Takao. Although they were purchased from the same commercial source, replacement vessels provided by QLA come

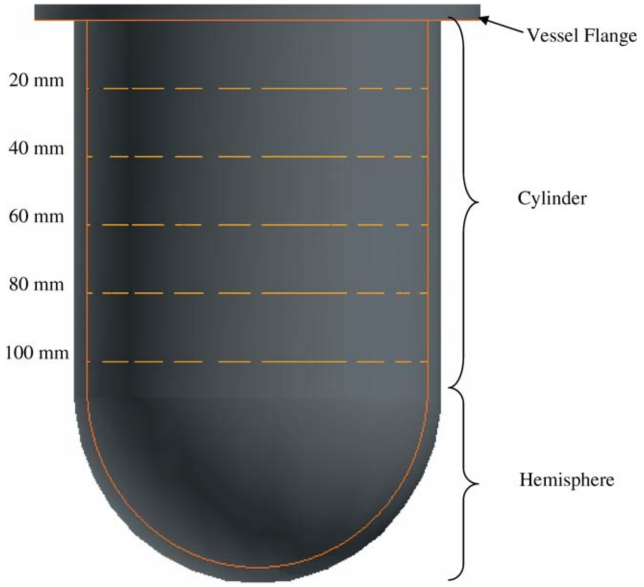

Figure 1. Schematic of glass dissolution vessel. Solid orange lines show the bottom of the vessel flange and the inner surface of the vessel. Dashed orange lines represent the location of horizontal planes at 20, 40, 60, 80, and 100 mm from the bottom surface of the flange.

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Table 1. List of definitions for common terms used to describe geometric tolerance deviations (3).

Common Geometric Tolerancing Terms	Definition
Concentricity	Describes a condition in which two or more features (cylinders, cones, spheres, etc.) in any combination have a common axis.
Cylindricity	Describes a condition of a surface of revolution in which all points of a surface are equidistant from a common axis.
Datum	A point, line, plane, cylinder, axis, etc., from which the location or geometric relationship of other part features may be established or related.
Flatness	The condition of a surface having all elements in one plane.
Perpendicularity	The condition of a surface, axis, or line, which is 90 degrees from a datum plane or datum axis.
Roundness	Describes the condition on a surface of revolution (cylinder, cone, or sphere) where all points of the surface intersected by any plane (1) perpendicular to a common axis (cylinder, cone) or (2) passing through a common center (sphere) are equidistant from the center.

from different manufacturing sites and were therefore treated as originating from independent sources. All purchases were made as ordinary transactions with no mention of this study. Dissolution vessel sources have been numerically coded to mask the identity of the sources.

Measurements

Vessel measurements were divided into two categories: (1) geometric dimensions and (2) internal surface and flange irregularity measurements. Measures of geometric dimensions included vessel height, inner diameter (average of five measurements taken at five horizontal positions along the vertical axis of the cylinder; see Figure 1), and radius of the hemisphere**.** Study of a vessel's inner surface with a coordinate measuring machine (CMM; details given below) allowed quantification of irregularities in the shape of the vessel flange and inner surface. The CMM employs a touch probe to record the location of points taken from the inner surface and flange of the vessel. The points are then plotted in three-dimensional space, and relationships between each of the points are established using software provided by the CMM manufacturer. Several different methods can be applied to measure and evaluate surface irregularities. In this report, we chose terms commonly used by engineers to describe geometric tolerance deviations (Table 2), expressed as deviations (*3*). The value of a deviation is the difference between the maximum positive and maximum negative deviations, with a minimum value of zero. Using roundness as an example, the CMM measures several points along the inner circumference of the vessel and uses a best-fit algorithm to fit a perfect circle through the collected data points. The value of the geometric tolerance deviation for roundness is then the difference between the point lying farthest outside of the best-fit circle and the point lying the farthest inside the best-fit circle. If the part being measured were perfectly round, the

Table 2. Dissolution vessel dimensions (mean ± standard deviation [SD]) for 11 sets of 6 vessels from 10 different sources. Also shown are the current specifications given in USP <711>. The units of measure are mm. Highlighted values show the minimum (blue) and maximum (red) dimensions measured.

Source	Vessel Height *	Inner Diameter	Radius of Hemisphere
1	**151.8 ± 0.2**	100.06 ± 0.03	50.01 ± 0.03
2	158.7 ± 1.8	101.40 ± 0.57	50.64 ± 0.45
3	158.0 ± 0.5	101.05 ± 0.21	50.45 ± 0.13
4	153.5 ± 0.8	104.12 ± 0.16	52.04 ± 0.06
5	159.7 ± 0.4	**99.96 ± 0.02**	**49.99 ± 0.02**
6	158.5 ± 0.9	101.40 ± 0.83	50.81 ± 0.36
7	158.5 ± 0.4	101.70 ± 0.25	51.10 ± 0.24
8	**161.9 ± 0.6**	104.44 ± 0.22	**52.33 ± 0.32**
9	160.8 ± 1.0	101.22 ± 0.41	50.69 ± 0.28
10	158.8 ± 0.5	**104.53 ± 0.17**	52.21 ± 0.22
11	160.6 ± 1.3	102.46 ± 0.50	51.28 ± 0.57
USP <711>	160–210	98–106	NS[†]

**Vessel height measured from bottom of flange to inside bottom of vessel.*
[†]Not specified in current USP.

best-fit circle would overlay all of the data points, and the roundness deviation would be zero.

CMM measurements were performed by Brandywine Metrology Associates, Inc. (West Chester, PA), using a Brown & Sharpe Global A Image (Brown & Sharpe, North Kingstown, RI). Figure 1 is a schematic of the dissolution vessels investigated in the current study. Solid and dashed lines indicate the location of measurements taken by the CMM. Thirty-six evenly spaced data points were collected from the bottom surface of the vessel flange. Points collected from the flange were used to calculate the flatness of the flange and to create a data plane from which other measurements were referenced. Thirty-six data points were collected along the inner circumference of each of five horizontal planes located at 20, 40, 60, 80, and 100 mm along the vertical axis of the dissolution vessel. Approximately 100 evenly spaced data points were collected within the hemispheric portion of the dissolution vessel. The CMM data were used to quantify the following dimensions and geometric tolerance deviations of the inner surface and flange of the dissolution vessels: flatness of the vessel flange; height of the vessel (measured from the bottom of the flange to the inside bottom of the vessel); radius and roundness of the hemisphere; inner diameter, cylindricity, circularity, and perpendicularity of the cylinder; and the concentricity between the hemisphere and the cylinder.

Statistical Analysis

In analyzing the data collected from the current study, we hoped to answer two questions: (1) are dissolution vessels from different sources interchangeable in dissolution assemblies from different manufacturers, when feasible, and (2) are individual vessels from the same source relatively consistent both for dimensions and geometric tolerance deviations? Both questions were addressed using hierarchical clustering. With this technique, the analysis starts with each vessel as its own cluster of size one and continues step by step until there is a single cluster containing all vessels. At each step, the two clusters that are closest together are merged to form a single new cluster. Distance between clusters is determined as the average distance between all possible vessel pairs, and each pair consists of one vessel from each of the two previous clusters. Distance between vessels was the square root of the sum of squared deviations. We determined clusters based on all variables, then based on subsets corresponding deviations related to the flange, cylinder, hemisphere, perpendicularity, and concentricity. We report only the results using all variables. For variables measured at multiple distances from the cylinder top, the data were reduced to a mean and logarithm of a standard deviation. Two pairs of variables were very highly correlated (Spearman correlations of about 0.9); for these two pairs, only one of each was included in the analyses.

To test for differences among the mean value of dimensions and geometric tolerance deviations for sets of vessels from different sources, we used one-way analysis-of-variance (ANOVA).

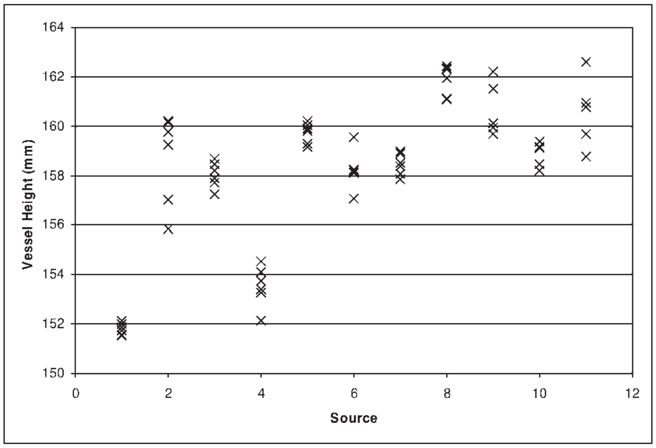

Figure 2. Vessel height of individual vessels. Vessel height is defined as the distance from the bottom of the flange to the inside bottom of the dissolution vessel.

Results

Geometric Dimension Results

Height: The mean geometric dimensions for sets of six vessels from each source are summarized in Table 2. Many of the mean vessel heights do not appear to meet the specifications (160–210 mm) provided in *USP* <711>. This is probably a result of the way in which we have defined vessel height. The height reported in Table 2 has been measured from the bottom of the flange to the inside bottom of the vessel. It is not clear from the instructions in <711> whether vessel height refers to the overall dimensions of the vessel or to the dimensions of the volume inside the vessel. If we add the vessel flange thickness and the vessel wall thickness (ranging from 6 to 12 mm of total thickness), the overall height of the dissolution vessels meet the specifications in <711>. Not only are there significant differences ($p < 0.001$) in the height of vessels from different sources, but there are also differences in height among vessels from the same source. Figure 2 shows a plot of the height measurements for individual vessels. The height of vessels from sources 2 and 11 differ by as much as 4 mm. According to <711>, the distance between the bottom of the paddle and the inside bottom of the dissolution vessel should be maintained at 25 ± 2 mm. Given the variability in the observed vessel heights, technicians should pay careful attention to ensure that paddle/basket height is verified each time a vessel is replaced or moved to a different location within the same dissolution test assembly.

Inner Diameter of Cylinder: All of the vessels investigated have inner diameters (ID) of 98–106 mm. The ID of vessels from different sources covers a wide range of values (99.9–104.5 mm). The observed differences are relatively wide when compared to the specifications given for paddle and basket dimensions (typically not more than ± 1.0 mm). Figure 3 shows the ID for individual vessels. In addi-

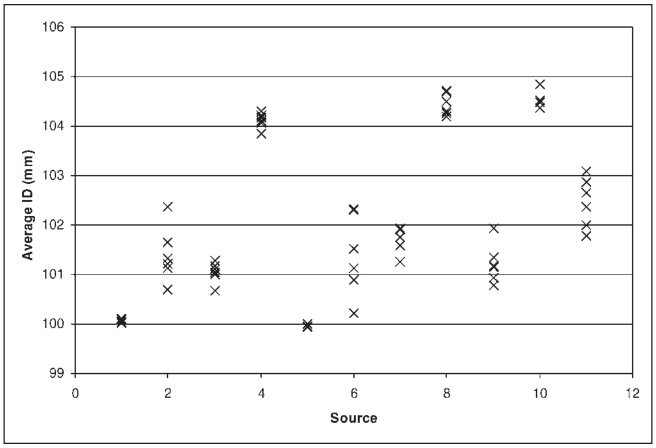

Figure 3. Inner diameter measurements for individual vessels. The measurements shown are the average of the 5 ID measurements taken at 20, 40, 60, 80, and 100 cm along the vertical axis of the cylinder.

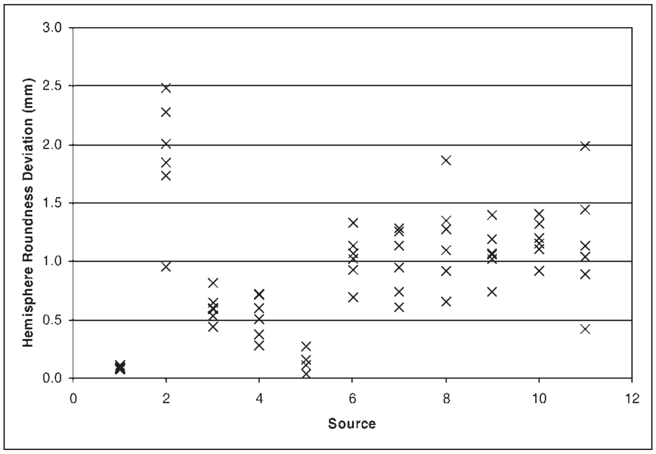

Figure 4. Hemisphere roundness deviations for individual vessels.

tion to differences among vessels from different sources, Figure 3 shows that the ID of vessels from the same source can vary by as much as 2.0 mm.

Radius of Hemisphere: The radius of the hemisphere varied among vessels from the same source and among sets of vessels from different sources (Table 2). Based on the minimum and maximum hemisphere radii observed, we calculate that the volume of liquid beneath the paddle can differ by about 7% (from 33 to 35 mL). Perhaps more important is the possible variation in the volume contained in the hemispheric region of different dissolution vessels, which can vary by as much as 18% (from 260 to 307 mL). In the case of Apparatus 2, variability in the radius of the hemispheric region of dissolution vessels also affects the clearance between the tip of the paddle blade and the vessel wall.

Geometric Tolerance Deviation Results

Individual Geometric Tolerance Deviations: Results for all six geometric tolerance deviation measurements appear in Table 3. Their relative magnitudes and the variability of the mean values are discussed in the following paragraph. We found differences among all mean geometric tolerance deviations for vessels from different sources, some of which are statistically significant ($p < 0.05$). There was also a difference of as much as tenfold in the variance of the cylinder and hemisphere roundness and cylindricity deviations among sets of vessels from different sources.

Table 3. Average geometric tolerance deviations (mean ± SD) for eleven sets of 6 vessels from 10 sources (in mm). Highlighted values show the minimum (blue) and maximum (red) for each of the geometric tolerance deviations. The cylinder roundness and cylinder–hemisphere concentricity reported here are an average of five measurements taken at 20, 40, 60, 80, and 100 mm along the vertical axis of the cylinder.

Source	Flange Flatness	Cylinder Roundness	Cylindricity of Cylinder	Cylinder Perpendicularity	Hemisphere Roundness	Cylinder/ Hemisphere Concentricity
1	**0.08 ± 0.04**	**0.02 ± 0.01**	**0.06 ± 0.01**	**0.07 ± 0.06**	**0.10 ± 0.02**	**0.55 ± 0.08**
2	0.25 ± 0.08	**0.52 ± 0.30**	**0.74 ± 0.38**	0.27 ± 0.12	**1.89 ± 0.53**	**1.31 ± 0.54**
3	0.14 ± 0.07	0.25 ± 0.06	0.38 ± 0.06	0.17 ± 0.10	0.60 ± 0.13	0.80 ± 0.18
4	0.21 ± 0.11	0.27 ± 0.09	0.36 ± 0.11	0.13 ± 0.07	0.53 ± 0.18	0.72 ± 0.22
5	0.12 ± 0.04	0.07 ± 0.04	0.17 ± 0.08	0.10 ± 0.05	0.11 ± 0.09	0.57 ± 0.08
6	0.13 ± 0.05	0.32 ± 0.12	0.50 ± 0.22	0.22 ± 0.12	1.03 ± 0.21	0.86 ± 0.34
7	0.16 ± 0.05	0.33 ± 0.04	0.64 ± 0.20	0.26 ± 0.08	1.00 ± 0.28	0.94 ± 0.26
8	**0.27 ± 0.08**	0.22 ± 0.03	0.39 ± 0.08	**0.36 ± 0.08**	1.20 ± 0.42	1.20 ± 0.25
9	0.24 ± 0.10	0.24 ± 0.09	0.41 ± 0.11	0.31 ± 0.17	1.08 ± 0.21	0.85 ± 0.31
10	0.18 ± 0.04	0.34 ± 0.08	0.58 ± 0.12	0.17 ± 0.07	1.18 ± 0.17	0.87 ± 0.26
11	0.19 ± 0.15	0.19 ± 0.08	0.44 ± 0.20	0.21 ± 0.04	1.15 ± 0.53	0.96 ± 0.43
p	0.004	<0.001	<0.001	<0.001	<0.001	0.024

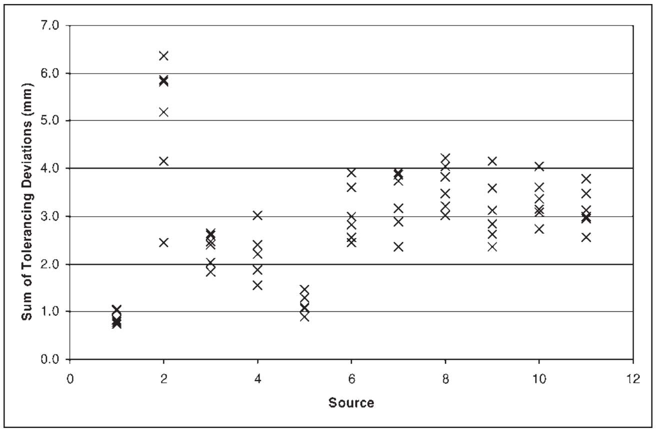

Figure 5. Sum of geometric tolerance deviations for individual vessels. The sum included deviations of the flange flatness, cylinder roundness, cylindricity and perpendicularity of the cylinder, roundness of the hemisphere, and cylinder–hemisphere concentricity.

The largest differences in geometric tolerance deviations were observed for the roundness deviations of both the cylinder and hemisphere. Vessels from source 2 showed roundness deviations as large as 2.5 mm. Figure 4 shows the results of roundness deviation measurements for the hemispheric portion of individual vessels. Because this portion of the vessel is typically formed by hand, a high degree of variability in the roundness of the hemispheric region of glass dissolution vessels is not surprising. Although a template may be used in an attempt to control the radius of the hemisphere, typically the outside dimensions of both the cylinder and hemisphere are controlled during the glass-blowing process; however, it is the inside dimensions of the dissolution vessels that are critical.

Sum of Geometric Tolerance Deviations: Figure 5 is a plot of the sum of geometric tolerance deviations for individual vessels. Although individual parameters may affect the performance of the dissolution test assembly in their own unique way, summing all geometric tolerance deviations can provide insight into the control that a dissolution vessel manufacturer has over its manufacturing process and may help to answer questions regarding the interchangeability of vessels from different sources. Vessels from source 2 show both a higher mean value and a considerably larger range of values compared to vessels from other sources. For the majority of vessel sources shown in Figure 5, the sum of geometric tolerance deviations is similar. Vessels from sources 1 and 5 show noticeably lower geometric tolerance deviations compared to vessels from all other sources, demonstrating that it is possible for manufacturers to consistently produce dissolution vessels with minimal geometric tolerance deviations.

Cluster Analysis of Dissolution Vessels

By summing all of the surface irregularities, we hoped to demonstrate how sets of vessels group together. However, this approach considered only the geometric tolerancing deviations and did not include the vessel dimensions. We conducted cluster analyses in order to group vessels based on all of the variables measured using the CMM (Figure 6). The dashed line is added to show the grouping at the time the number of clusters is five. By this stage in the clustering, all the vessels for a given source have grouped together in the same cluster, so the remaining clustering represents differences between sources. This is consistent with the measurements' being relatively uniform among vessels from the same source compared to those from other sources. Vessels from source 1, the top six vessels in Figure 6, are quite unique compared to vessels from the other sources. Working from right to left, after source 1, the next most different is source 5, followed by, in order, source 4, and then a combination of sources 8 and 10. The remaining six sources formed one large cluster.

Because of concern that vessel height, as the largest magnitude of measurement, might dominate the calculation of distance between vessel clusters, we repeated the cluster analysis excluding height from the analysis. The results are essentially the same. Working from right to left using the new analysis, we found that the most unique cluster is source 5; the next most different is source 1; this is followed by sources 4, 8, and 10 in one cluster. Again, the same six sources formed one large cluster.

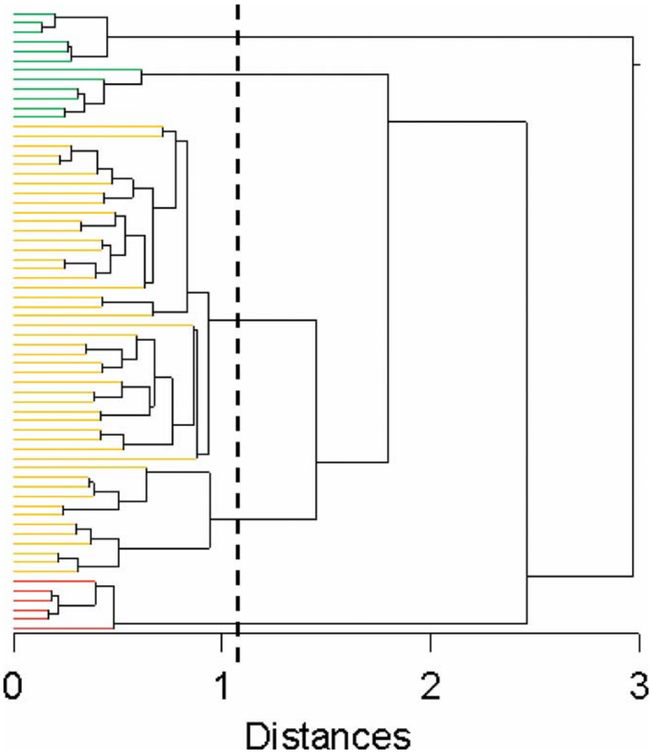

Figure 6. Cluster Analysis of Vessels. Cluster analysis was conducted in order to group vessels based on both the dimensions and geometric tolerance deviations of each vessel. The dashed line shows the grouping at the time the number of clusters is five. The distance between clusters represents the average distance between all possible vessel pairs, with a pair consisting of one vessel from each of the two clusters.

Discussion

The shape of the inner surface of glass dissolution vessels has been shown to have an impact on the results of dissolution experiments with disintegrating USP Prednisone Reference Standard Tablets (*4*, *5*). For dissolution vessels having a nominal capacity of 1 L, the specifications found in USP General Chapter *Dissolution* <711> include those for the inner diameter (98–106 mm) and the height (160–210 mm) of the dissolution vessel (*6*). Scott has described numerous additional ways in which the inner surface of glass dissolution vessels may be flawed (*7*). Tanaka et al. have shown that minimizing the irregularities in the inner surface of glass dissolution vessels leads to lower variability in dissolution tests with USP Lot O Prednisone Reference Standard Tablets (*5*). Recent dissolution variance studies conducted by USP suggest that the dissolution vessel and apparatus source can be a major cause of variability in dissolution results (*8*, *9*).

In the current study, we have quantified the geometric dimensions and irregularities of the flange and inner surface of commonly used glass dissolutuion vessels. Although most of the dissolution vessels characterized in these experiments meet the current specifications found in *USP* <711>, there were significant differences in both the geometric dimensions and tolerance deviations for sets of vessels obtained from different commercial sources. Differences in the dimensions result in measurable differences in both the paddle tip–vessel wall clearance and in the volume of dissolution media surrounding the paddle. It has been shown that heterogeneous shear rates exist in the hemispheric region of the dissolution vessel (*10*, *11*). Given the differences in both the paddle-vessel wall clearance and in the volume of dissolution media surrounding the paddle, hydrodynamics in the hemispheric region of the vessel could be influenced by variability of the dimensions of this critical region of the dissolution vessel. In addition to differences in the geometric dimensions, we also found notable differences in both the magnitude and variability of geometric tolerance deviations among vessels from different sources and, in some cases, among vessels from the same source. Although a certificate of analysis (COA) is available for glass dissolution vessels from several sources, the COA provided by many vendors may simply confirm that glass dissolution vessels meet current USP requirements for height and inner diameter.

Further studies are being conducted to understand the influence(s) that the differences among dissolution vessel dimensions and geometric tolerance deviations may have on both the hydrodynamics within the vessel and on the amount of drug dissolved during dissolution tests with USP Prednisone Reference Standard Tablets. The results of such studies may lead to more rigorous standards and more specific guidance for dissolution apparatus users and manufacturers regarding the consistency of vessel dimensions and control of geometric tolerance deviations for dissolution vessels.

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