dx.doi.org/10.14227/DT320125P6

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies of the USPC or the USP Council of Experts

Characterization of Apex Vessel Geometries and Irregularities

Satish Perivilli[1] and Mark R. Liddell[1]

[1]United States Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD, USA.

Correspondence should be addressed to:
Margareth R.C. Marques, Senior Principal Scientist
US Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790
email: mrm@usp.org

This article was originally published as a stimuli article in issue 51(1) of the United States Pharmacopeia's (USP) *Pharmacopeial Forum* (PF). PF is a free bimonthly online journal in which USP publishes items for public review and comment. The commenting period for this stimuli article in PF is open until March 31, 2025. Please visit the following website to comment on the stimuli article: https://doi.org/10.31003/USPNF_S203304_10101_01. All other correspondence on this article should be addressed to Margareth R. C. Marques as noted above.

ABSTRACT

Apex vessels, previously referred to as PEAK vessels, are commonly used in dissolution experiments with Apparatus 2. They are mentioned in *The Dissolution Procedure: Development and Validation* <1092> for their utility in the possible elimination of coning associated with using standard vessels. A *Stimuli* article, *The Case for Apex Vessels*, discussing the benefits of including apex vessels in *USP–NF* general chapters was published in *PF* 47(6) (Nov–Dec 2021). The objective of the study discussed in the new Stimuli article below was to characterize apex vessels, available from different manufacturers, more comprehensively with the objective of understanding their geometries and associated variabilities. A coordinate measuring machine (CMM) was used to evaluate 37 selected characterization parameters associated with the apex vessel geometries and inherent geometric irregularities. Six vessels, each from seven manufacturers, were characterized. Measurement data was analyzed using skewness plots and statistical tools to understand the variability in all parameters considered. Upon analysis, the apex characterization parameters were found to exhibit intra- and inter-manufacturer variability, indicating variability in the geometries of apex vessels available commercially. Measurements of the geometric irregularities associated with the apexes also presented similar variability across all vessels considered. Results from this study indicate that end-users of apex vessels should be aware of the variabilities in commercially available vessels and should consider controlling the source of apex vessels used with dissolution testing.

INTRODUCTION

Apex vessels are noncompendial glass vessels typically used with *Dissolution* <711> Apparatus 2. There are currently several manufacturers of apex vessels. *The Dissolution Procedure: Development and Validation* <1092> mentions the utility of using apex vessels to possibly eliminate coning usually observed towards the lowest point of the vessel bottom (directly underneath the rotating paddle) with a disintegrating dosage form. A *Stimuli* article, *The Case for Apex Vessels*, discussing the benefits of including apex vessels in *USP–NF* general chapters was published in *PF* 47(6) (Nov–Dec 2021). The article proposed the apex height, the apex external angle, and the deviation of the apex from the vessel centerline as three possible parameter choices for providing specifications specific to apex vessels. While these can be useful, many other geometric parameters characterize the vessels and can thus be used for a similar purpose. Hence, it was of substantial interest to gain a comprehensive understanding of the ranges and variabilities in measurements of these (i.e., both proposed and additional) parameters and associated geometric irregularities. For this purpose, five sets of six vessels each were procured on loan (or as donations) from the different manufacturers who provided vessels for the *2021 Stimuli article*, namely Agilent, Distek, Erweka, Hanson, and Sotax. Additionally, two sets of apex vessels purchased previously from Quality Lab Accessories and Vankel were also included in the study.

A review of available literature indicates that apex (previously known as PEAK) vessels have been an area of substantial interest over the past several years. Studies that focused on the comparison of dissolution results obtained while using PEAK and standard vessels are readily available. For example, an early study by Beckett et al. (*1*) showed that the effect of deaeration on dissolution was not as marked as with standard vessels when PEAK vessels were used by comparing the dissolution behaviors of FDA Prednisone NCDA#2 10 mg, USP Prednisone Calibrator 50 mg, and USP Salicylic Acid Calibrator 300 mg tablets. Similar outcomes were also exemplified with changes to the paddle rotational speed for the first two formulations. Collins and Nair (*2*), in another study, compared the dissolution results of acetaminophen and naproxen sodium tablets at four different paddle rotation speeds with three different dissolution media under deaerated and nondeaerated conditions. For acetaminophen, at the lowest rpm investigated, it was shown that a substantially higher percentage (about 100%) of the drug was released while using PEAK vessels in about half the time (15 min) compared to about 55% in 30 min with standard vessels using Apparatus 2. Higher rpm results indicated faster rates of dissolution with PEAK vessels initially, even though the release profiles showed no difference with standard vessels towards later time points. Naproxen tablets, on the other hand, were shown to have relatively similar release rates throughout the runs, with both vessels at the lowest rpm. However, increasing rpm indicated faster dissolution rates initially with the PEAK vessels with the differences decreasing with time. Rotational speed and deaeration were found to influence dissolution results with both vessels.

Mirza et al. (*3*) compared the percentage of releases with both a "low solubility drug" and a "high solubility drug" while using standard, PEAK and flat-bottom vessels. It was shown that the PEAK vessels generated the highest percent release for both drugs. Furthermore, Baxter et al. (*4*) conducted flow visualization studies and ran computational fluid dynamics (CFD) simulations to understand the hydrodynamics associated with PEAK vessels. It was shown that a dosage form would be subjected to only high shear rates with PEAK vessels as opposed to low shear rates surrounded by higher shear rates with standard vessels. In a more recent article, Yoshida et al. (*5*) investigated the effects of using five different apex vessels with varying apex diameters and heights (and, in the case of the fifth vessel, with a 3-mm offset of the apex from the center axis) on the dissolution profiles of disintegrating tablets (USP Prednisone Tablet RS, lot No. R132B0 and amlodipine besylate tablets), sticking tablets (atorvastatin calcium hydrate tablets 10 mg), and large volume excipient formulations (levofloxacin fine granules 10%) and compared them with data using standard vessels. It should be noted that three of the vessels were custom-made for the study and are not available commercially. Dissolution profiles were evaluated for similarity using the FDA guidelines' similarity factor, f_2. It was shown that the dissolution behavior of the disintegrating and sticking tablets obtained with vessels with high apexes (with the paddle rotating at 50 rpm) was similar to that of using compendial vessels at 75 rpm. The apex centering was shown to have no effect on the dissolution of prednisone tablets and levofloxacin formulation at varying paddle rotation speeds from 30 to 100 rpm. All formulations, in general, were shown to dissolve faster at 50 rpm with the apex vessels in comparison to standard vessels. The effect on the "mount" at the bottom of the apex vessels was found to vary with formulation.

Even with the availability of dissolution results that show *improved* performance with apex vessels, such as from some studies mentioned above, there is still a lack of comprehensive understanding of the vessels themselves. Some of the key missing pieces of information include knowledge of geometric variabilities in commercially available apex vessels, the influence of any inherent variabilities on the resultant hydrodynamics and/or associated dissolution results, a standardized procedure for mechanical calibration and/or a performance verification test (PVT), etc. Some of these concerns have been highlighted in expert reviews/perspectives published previously. For example, Gray et al. (*6*), in their expert review, while acknowledging some of the aforementioned work and the impact on dissolution data of changing vessel geometries (such as with apex vessels), suggested caution in balancing the overall objectives of the test itself (for example, its discriminating capability) with changes to dissolution rate and variance. In another perspective article, Grady et al. (*7*) pointed out the limitations of using PEAK vessels: their noncompendial status and nonexistence of a "mechanical calibration procedure". Additionally, Baxter et al. (*4*) also indicated that the high shear rates observed around the dosage form might affect the discriminating ability of the apparatus. Concerns about sufficient discriminative ability with the usage of apex vessels were also raised by Yoshida et al. (*5*).

The current study on apex vessel characterization focused on the first piece of missing information, i.e., a complete characterization of apex vessels available commercially with the objective of identifying ranges and variabilities in values of key geometric parameters. The results of this characterization would assist towards anticipated CFD simulation project(s). The CFD projects (parametric studies) would help understand the impact of changing geometries (for example, various apex definitions) on the associated hydrodynamics—the second piece of missing information. Anticipated in-tandem dissolution experiments with various commercially available apex vessels will provide additional insights into understanding apex vessels. Results from the current and planned studies would aid in establishing specifications based on a robust scientific foundation for apex vessel geometries. For this current study, an approach similar to that previously used by Liddell et al. (*8*) for the characterization of standard vessels was followed. Liddell et al. mapped the coordinates of discrete points using a three-dimensional coordinate measuring machine (CMM) and measured several geometric dimensions and irregularities across vessels. Results were analyzed to highlight differences between vessels from not only different manufacturers but also among vessels from the same manufacturer. As with the measurements in Liddell et al., services of Brandywine Metrology Associates, Inc. (BMA; West Chester, Pennsylvania) were retained for performing the CMM measurements for this study too. The seven sets of vessels were shipped to BMA at convenient intervals for data collection. In this article, comparisons of results obtained from the current study were made with those available in the previous publication (*8*) wherever possible.

CHARACTERIZATION PARAMETERS

Several sizing dimensions and irregularities of interest were identified to help characterize apex vessels comprehensively. For this study, the characterization was broken down into three main elements: the vessel geometry (i.e., the geometry that does not include the apex), the apex geometry, and irregularities associated with both the vessel and apex geometries. Basic definitions associated with the geometry of the vessels and the apex—such as diameters, radii, heights, and, as applicable, width, thickness, and angles—are referred to as "sizing parameters" in this article. Other parameters that represent geometric characteristics, such as circularities and perpendicularities associated with both the vessel and apex geometries, are presented as geometric irregularities.

Analysis of the measurements is presented through skewness plots (i.e., plots of raw data categorized by manufacturer) and data tables that show averages of values and standard deviations within a manufacturer set. The tables also include ranges, averages, and standard deviations across all 42 vessels. Additionally, three specific approaches, i.e., evaluations for intra-manufacturer variability (ratio of standard deviation to average values within a manufacturer set of vessels), inter-manufacturer variability (ratio of standard deviation to average values within all 42 vessels), and range variation (change from minimum to maximum values expressed as a relative percentage of the minimum value), were used to quantify and compare differences in the characterization parameters. It should be noted that individual outliers affect the values of the range variation differently than either the intra- or inter-manufacturer variability values.

Sizing Parameters—Vessel Geometry

Cylinder Diameter

The diameter of the cylindrical part of each vessel was measured at five distinct elevations along its height (locations might have differed based on vessel height), as depicted in Figure 1a. At each of the five elevations (i.e., along horizontal planes at locations 1–5), the diameter was calculated as the average of 50 evenly distributed measurement points taken around the circumference of the vessel at that specific elevation. The cylinder diameter, corresponding to each vessel, was determined by averaging values from the 250 points that made up the five locations for that vessel. For the sake of brevity, only data for the cylinder diameter is presented in Figure 2a.

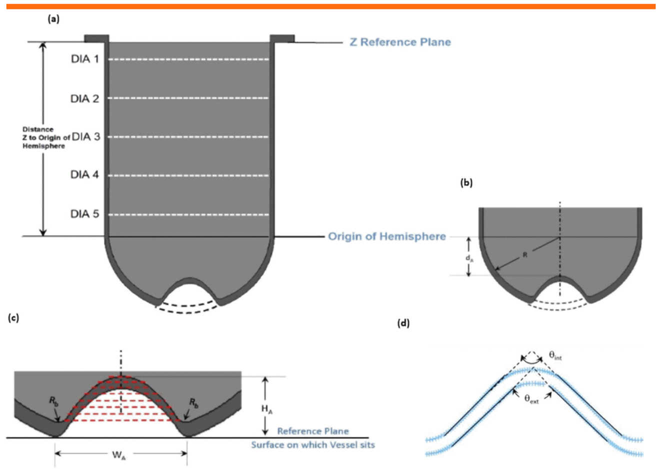


Figure 1. Schematic representations of (a) cylinder diameter locations and cylinder height, (b) hemisphere radius and distance of apex to hemisphere origin, (c) apex diameter locations, height, width, and blend radius and (d) apex internal and external surface angles.

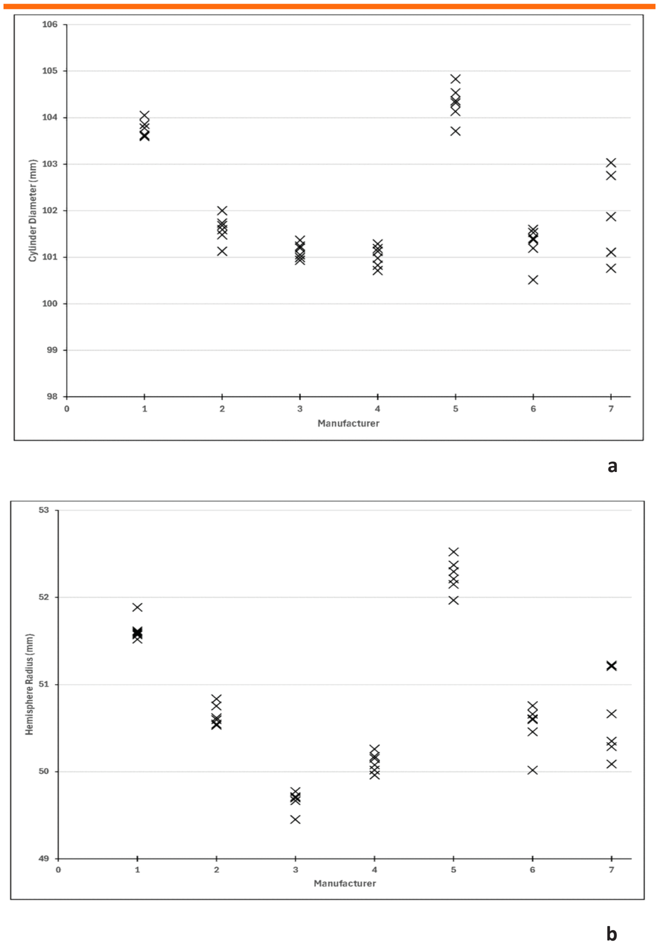


*Figure 2. Skewness plots for cylinder diameter (**a**) and hemisphere radius (**b**).*

Hemisphere Radius

The hemisphere radius, denoted by *R* in Figure 1b, was defined to be the average value evaluated from 100 evenly distributed points on the hemisphere's inner surface, i.e., from the top of the hemisphere to the apex transition region. Data for the hemisphere radius is shown in Figure 2b. While the hemisphere radius compares favorably with half of the cylinder diameter values for most manufacturers, data from certain manufacturers indicate slight differences. This observation is important as it indicates that the vessel diameter might not be characterized by a single value (i.e., either the cylinder or hemisphere diameter) for all vessels.

Compiled numerical values for the sizing parameters associated with the vessel geometries are presented in Table 1. Analysis of Table 1 for intra-manufacturer variability of the cylinder diameter shows that the standard deviation, within any manufacturer, was typically < 1% of the associated average value while comparing the data for inter-manufacturer variability (i.e., variability across manufacturers) shows that the standard deviation was about 1.3% of its associated average value. The variation from the minimum cylinder diameter value to its maximum across all 42 vessels considered in this study is limited to only about 4%. Moreover, an examination of the ranges indicates that all values fall well within the specifications of <711> (i.e., 98–106 mm). Thus, it can be reasonably concluded that the cylinder diameters with available apex vessels are well-controlled, and that the specifications provided in <711> are likely sufficient for this parameter. Table 1 also shows that, within each manufacturer, the hemisphere radius by itself is well controlled to be within the specifications of <711>, in that all values were within one-half of the specifications for the diameter of standard vessels, i.e., 98–106 mm.

Vessel Height

The vessel height, H_V, (i.e., the distance between the top of the vessel and the surface on which the vessel sits) can be calculated as:

$$H_V = d_{Z,hs} + d_A + H_A$$

where $d_{Z,hs}$, d_A, and H_A are, respectively, the distance *Z* to the origin of the hemisphere, the distance of the apex to the origin of the hemisphere, and the apex height, as shown in Figure 1a, Figure 1b, and Figure 1c. The distance *Z* to the origin of the hemisphere was determined as the distance between two points — one at the top of the vessel and another point determined to be the center of a theoretical sphere created by the data points taken on the hemisphere.

Data for the vessel height, H_V, across all 42 vessels considered in this study indicates a range of values from approximately 156.106 to 197.944 mm. It should be noted that these values are smaller in comparison to the standard vessel heights specified in <711> due to the apex "cuts" during manufacturing of the apex vessels. The height of the *missing* portion of the vessels, when compared to standard vessels, was limited to as much as 6.8 mm across all 42 vessels considered in the study.

Sizing Parameters—Apex Geometry

Distance of Apex to Hemisphere, Apex Diameters, and Top of Apex Radius

The distance of the apex to the origin of the hemisphere, d_A in Figure 1b, was evaluated to be the distance between two points — one at the top of the apex and another at the theoretical center point of the sphere previously described with the measurements of $d_{Z,hs}$. Measurement values for the distance of the apex to the hemisphere origin are depicted in Figure 3a. These values are indications of the difference between the hemisphere

Table 1. Selected Statistics of Sizing Parameters for Vessel Geometries

Characterization Parameter	Individual Manufacturer (Mfr) Data, Average ± SD							All Vessels	
	Mfr. 1	Mfr. 2	Mfr. 3	Mfr. 4	Mfr. 5	Mfr. 6	Mfr. 7	Range	Average ± SD
Cylinder diameter (mm)	103.750 ± 0.181	101.603 ± 0.290	101.130 ± 0.165	101.020 ± 0.220	104.315 ± 0.379	101.269 ± 0.395	101.772 ± 0.945	100.515–104.831	102.123 ± 1.321
Hemisphere radius, *R* (mm)	51.630 ± 0.130	50.646 ± 0.122	49.668 ± 0.112	50.106 ± 0.110	52.253 ± 0.191	50.516 ± 0.264	50.635 ± 0.485	49.451–52.522	50.779 ± 0.857

radius, presented previously in Figure 1b, and the apex height for each vessel (data of which follow) and thus are a function of both parameters.

Diameters at the apex were evaluated at different elevations, using an approach similar to that used with the cylinder diameter. However, due to the apex curvature, nine locations (instead of five, as with the vessel cylinder) were used to obtain a more detailed description of the apexes. An illustration of the diameter locations or elevations used to characterize the apexes is shown in Figure 1c. Starting with 20 evenly distributed data points at the bottommost location (location 1 for apexes), the number of data points was decreased by one for each subsequent location due to the decreasing diameter of apexes going from bottom to top. The diameter at each location was evaluated as an average value from the associated data points along the circle corresponding to that specific location.

It should be noted that the locations of measurement varied from one manufacturer to another, due to differences in apex heights between manufacturers. However, for consistency, each apex diameter location was separated by 1 mm, and the distance within which all the nine locations fell was retained to be 8 mm across all manufacturer vessels. There was no discrepancy in locations within a single manufacturer's set of vessels. The distribution of apex diameter values at location 1 is shown in Figure 3b.

The top of the apex radius was evaluated from 30 data points and is defined as the radius of curvature at the top of the apex inside the vessel. The center of the apex radius at the top, for this evaluation, was based on the center axis of the apex at the smallest diameter measured at the top of the apex. It was thus assumed that there is only minimal deviation between the actual center at the top of the apex compared to the center obtained from the lowest diameter elevation directly adjacent to the topmost measurements.

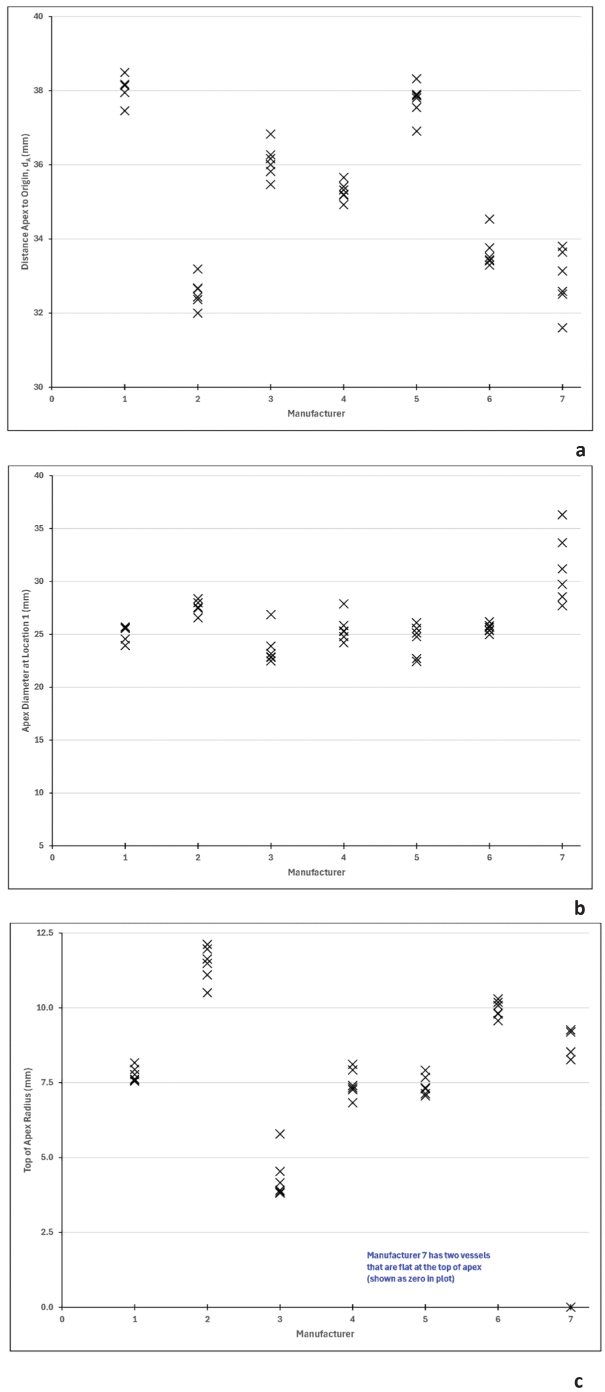


*Figure 3. Skewness plots for apex distance to hemisphere origin (**a**), apex diameters at location 1 (**b**), and top of the apex radius (**c**).*

Data for the top of the apex radius is presented in Figure 3c. As can be seen from the figure, the radius at the top of the apex varied considerably from one manufacturer to another. Additionally, within the manufacturer 7 data, two vessels were observed to have flat surfaces at the top (instead of the usual curved surfaces). These vessels were depicted as having a radius of 0 in the data set. This observation of flat surfaces at the apex top was not associated with vessels from any of the other manufacturers.

Table 2 presents statistical data for the sizing parameters associated with the apex geometries. The intra-manufacturer variability associated with the distance of apex to the hemisphere origin, d_A, varied from 0.70% to 2.49% for each manufacturer considered. When all 42 vessels were considered together, the inter-manufacturer variability was within about 6.11% of the average value. Evaluation of the range in values across all vessels indicated a variation of about 22% when compared to the minimum value measured.

The decrease in apex diameter going from location 1 to location 9 within a vessel is evident from Table 2. Because of the retention of the locations within a manufacturer, an intra-manufacturer variability analysis would be similar to that of any other parameter. An analysis of ranges of intra-manufacturer variability at each location indicated that the lowest and highest values (of 1.64% and 18.41%, respectively) were associated with the bottommost and topmost locations. It should, however, be noted that there was no relationship between the location and maxima or

Table 2. Selected Statistics of Sizing Parameters for Apex Geometries

Characterization Parameter	Individual Manufacturer (Mfr) Data, Average ± SD							All Vessels	
	Mfr. 1	Mfr. 2	Mfr. 3	Mfr. 4	Mfr. 5	Mfr. 6	Mfr. 7	Range	Average ± SD
Distance of apex to hemisphere origin, d_A (mm)	38.063 ± 0.344	32.549 ± 0.397	36.091 ± 0.458	35.280 ± 0.247	37.722 ± 0.472	33.655 ± 0.455	32.879 ± 0.819	31.605–38.489	35.177 ± 2.148
Apex diameter at location 1 (mm)	25.148 ± 0.736	27.571 ± 0.607	23.675 ± 1.629	25.539 ± 1.270	24.440 ± 1.523	25.555 ± 0.419	31.180 ± 3.272	22.427–36.295	26.158 ± 2.796
Apex diameter at location 2 (mm)	22.694 ± 0.685	25.536 ± 0.562	20.686 ± 1.490	23.199 ± 1.111	22.364 ± 1.456	23.527 ± 0.430	27.939 ± 2.494	19.599–32.217	23.706 ± 2.542
Apex diameter at location 3 (mm)	20.646 ± 0.737	23.595 ± 0.548	17.894 ± 1.331	21.099 ± 1.009	20.598 ± 1.433	21.643 ± 0.416	25.007 ± 1.861	16.964–28.453	21.497 ± 2.395
Apex diameter at location 4 (mm)	18.717 ± 0.779	21.711 ± 0.561	15.283 ± 1.084	19.152 ± 0.952	18.910 ± 1.398	19.882 ± 0.407	21.916 ± 1.045	14.272–23.800	19.367 ± 2.257
Apex diameter at location 5 (mm)	16.835 ± 0.804	19.849 ± 0.587	13.033 ± 0.909	17.278 ± 0.936	17.184 ± 1.335	18.192 ± 0.384	19.848 ± 1.211	11.885–22.006	17.460 ± 2.331
Apex diameter at location 6 (mm)	14.957 ± 0.783	17.975 ± 0.610	11.261 ± 0.812	15.395 ± 0.951	15.336 ± 1.240	16.493 ± 0.347	17.528 ± 1.181	10.242–19.260	15.564 ± 2.236
Apex diameter at location 7 (mm)	13.020 ± 0.710	16.014 ± 0.615	9.722 ± 0.732	13.412 ± 0.991	13.282 ± 1.106	14.672 ± 0.304	15.292 ± 1.299	8.915–16.787	13.630 ± 2.090
Apex diameter at location 8 (mm)	10.960 ± 0.634	13.808 ± 0.598	8.084 ± 0.654	11.211 ± 1.071	10.907 ± 0.942	12.515 ± 0.262	13.465 ± 1.462	7.465–15.030	11.564 ± 1.992
Apex diameter at location 9 (mm)	8.610 ± 0.637	11.052 ± 0.590	6.039 ± 0.550	8.552 ± 1.302	7.997 ± 0.734	9.649 ± 0.207	10.326 ± 1.901	5.587–12.586	8.889 ± 1.803
Top of apex radius (mm)	7.773 ± 0.240	11.467 ± 0.593	4.343 ± 0.756	7.479 ± 0.465	7.401 ± 0.328	9.957 ± 0.277	8.813 ± 0.491	3.816–12.117	8.144 ± 2.201
Apex height, H_A (mm)	13.298 ± 0.639	15.430 ± 0.509	13.250 ± 0.155	14.335 ± 0.380	15.023 ± 0.431	15.269 ± 0.250	13.640 ± 0.781	12.293–15.802	14.321 ± 0.989
Apex width, W_A (mm)	32.853 ± 0.721	39.417 ± 0.499	31.887 ± 1.049	35.138 ± 0.070	33.867 ± 1.022	35.890 ± 1.297	42.489 ± 3.886	30.125–47.222	35.934 ± 3.869
Apex thickness (mm)	2.133 ± 0.273	2.763 ± 0.344	2.006 ± 0.301	2.374 ± 0.186	3.230 ± 0.228	2.825 ± 0.103	1.820 ± 0.355	1.420–3.486	2.450 ± 0.537
Apex internal angle, θ_{int} (°)	88.138 ± 2.266	90.972 ± 4.385	93.466 ± 5.647	87.509 ± 1.338	91.935 ± 1.224	92.822 ± 0.743	99.001 ± 6.831	83.422–107.671	91.978 ± 5.089
Apex external angle, θ_{ext} (°)	90.041 ± 1.261	92.776 ± 1.466	84.842 ± 6.248	93.912 ± 1.912	90.079 ± 1.000	88.305 ± 1.322	99.767 ± 6.715	75.087–108.058	91.389 ± 5.582
Blend radius, R_b (mm)	5.616 ± 0.933	6.246 ± 0.357	5.952 ± 0.552	4.411 ± 0.136	5.527 ± 0.290	4.897 ± 0.740	6.320 ± 1.028	4.012–7.672	5.567 ± 0.895

minima of the variabilities, i.e., the intra-manufacturer variabilities did not change in any particular order with the location.

An inter-manufacturer variability analysis was also performed because the locations were at similar relative positions across all manufacturers. The variabilities increased from 10.69% to 20.29% from location 1 to location 9, progressively, in that order. This indicates that measurements are closer to each other towards the bottom of the apex (i.e., location 1) than towards the top (i.e., location 9). This increasing variability is also shown in how the location maxima varied with the associated minima. The maxima were found to be from 61.8% to 125% of the corresponding minima for locations 1 through 9. Whether this is because of the geometry of the apex (and the associated variability in the manufacturing process) or the decreasing resolution in measurement points (with the number of measurement points decreasing by 1 with each changing location) is a point of consideration. Regardless, and especially because the number of measurement points at each location was dictated by the available geometry (i.e., region), it can be concluded that apex geometries are not well controlled from one manufacturer to another or even within a single manufacturer's set of vessels.

Apex Height, Width, Thickness, and Blend Radii

Representations for the height and width of the apex and blend radius are shown in Figure 1c. The apex height, H_A, was evaluated as the perpendicular distance from a point at the top of the apex to the horizontal surface along which the vessels rest. The horizontal distance between the two points on which the vessels sat was defined to be the apex width, W_A. The apex thickness was evaluated as a least squares fit gap based on 100 data points each on the cross-sections of the internal and external surfaces of the apex through a selected axis. The blend radius, R_b, was also evaluated as a least squares fit value based on 30 points around the blend collected on the internal surface of the hemisphere of the vessel.

Data corresponding to the apex height, width, and thickness are presented in Figure 4a, Figure 4b, and Figure 4c, while that associated with the blend radii of

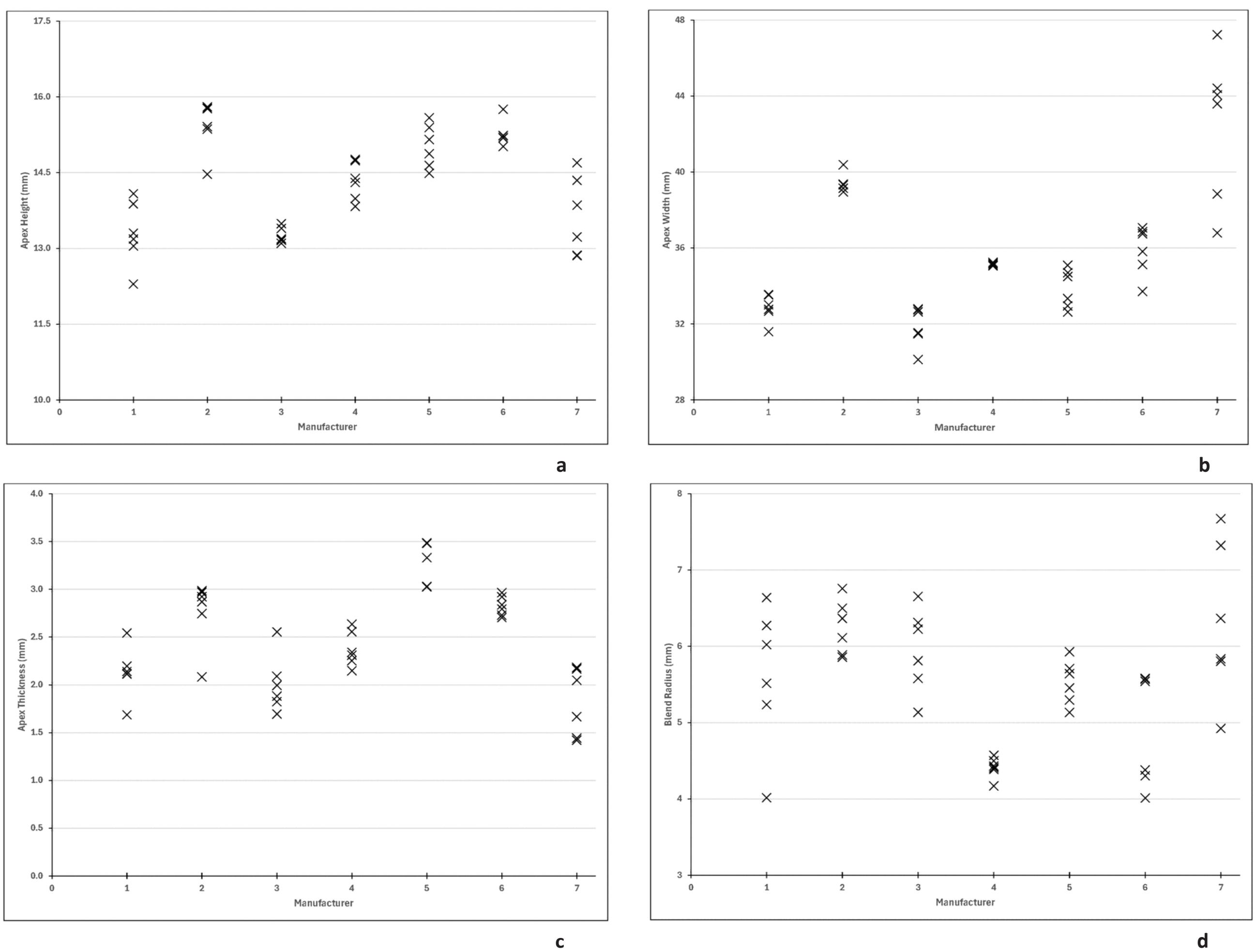


*Figure 4. Skewness plots for apex height (**a**), apex width (**b**), apex thickness (**c**), and blend radius (**d**).*

the apexes to the adjoining hemispherical parts of the vessels is shown in Figure 4d. Possibly due to the difficulty of standardizing the manufacturing process associated with the apex, considerable intra- and inter-manufacturer variabilities were observed in these values (most notably with the blend radius data).

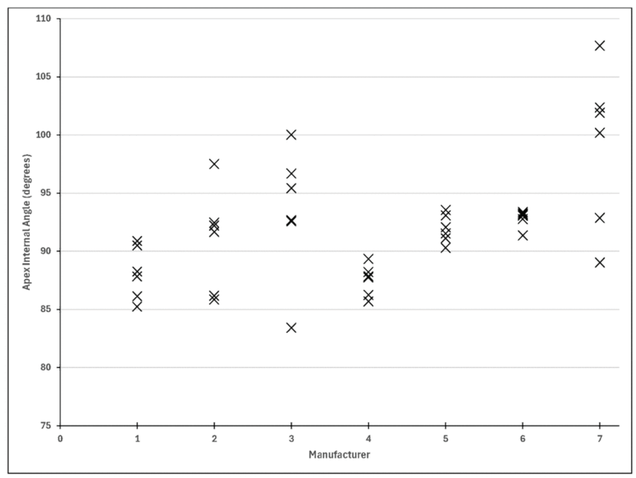
The apex height is one of the parameters whose specifications were proposed in the 2021 *Stimuli* article as a means of characterizing the apex vessels. The article proposed 15 ± 2.5 mm as possible specifications for this measurement. Analysis of the measurements taken for this study indicates that the values range from 12.293 to 15.802 mm, as shown in Table 2. Thus, the proposed specifications in the 2021 *Stimuli* article do not encompass data from all of the vessels evaluated and, therefore, may need to be modified. Additionally, the intra-manufacturer variability associated with the apex height ranged from 1.17% to 5.72%, while the inter-manufacturer variability was 6.91%. The variation from the minimum value observed across all vessels was 29%.

The intra-manufacturer variabilities associated with apex width and apex thickness were observed to be from 0.199% to 9.15% and from 3.66% to 19.5%, respectively. The corresponding inter-manufacturer variabilities were found to be 10.77% and 21.91%. The ranges also show considerable variability in measurements of these values across manufacturers. This might imply that in some dissolution equipment, specifically where the vertical position of the paddle-shaft assembly is fixed, any variability in apex height will also be reflected as variability of distance between the bottom of the paddle and the top of the apex. The impact that the variability in this distance may have on dissolution requires further investigation.

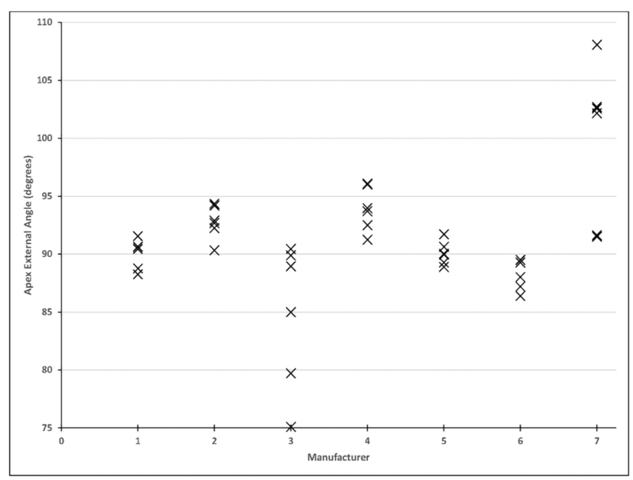
Apex Internal and External Surface Angles

To determine the internal and external surface angles shown in Figure 1d, 60 data points that best fit a straight line along the curvature of the apex on one side of a central axis of the apex were used. The central axis was derived from the 144 data points corresponding to the nine apex diameter locations described above. The angle between the axis and the best-fit lines created from the 60 data points was measured. Doubling the measured angle resulted in the total apex angle. This approach was adopted for both the apex internal surface angles and the external surface angles. Skewness plots associated with the apex internal and external angles are shown in Figure 5a and Figure 5b. As with the other parameters associated with the apex, data for both internal and external angles showed high intra- and inter-manufacturer variabilities.

The 2021 *Stimuli* article provides a specification for the apex external angle as 90 ± 3°. The range of measured values obtained from this study indicates that the external surface angles vary from about 75° to about 108° (a variation of 44% from the minimum), as shown in Table 2. Thus, there is a need to either revise the specifications proposed in the article to encompass vessels from all manufacturers or to modify the manufacturing process to obtain more consistent internal and external angles for the vessel apex. Additionally, the intra-manufacturer variabilities associated with the apex external surface angle were found to be from 1.11% to 7.36%. The inter-manufacturer variability was evaluated to be 6.11% across all manufacturers.



a



b

*Figure 5. Skewness plots for apex internal (**a**) and external (**b**) surface angles.*

In general, the apex internal surface angle could be assumed to be equal to the external surface angle if the two surfaces making up the apex thickness were parallel to each other. However, this was not found to be the case with apex vessels considered in this study. Analysis of

Figure 5a and Figure 5b show that while the values for external and internal surface angles compared favorably with each other for each vessel, the angles were rarely equal. Thus, it might be important to consider analyzing the apex internal surface angle separately in order to provide an apex angle specification for the vessels.

Geometric Irregularities

Cylinder Circularity And Cylindricity

The values of cylinder circularity and cylindricity are indicative of a separation distance, respectively, between two circles or two cylinders within which all measurements fell. Cylinder circularities at each of the five locations, along the cylinder height, were evaluated from the associated 50 data points. Similarly, the cylindricity of the cylindrical parts of the vessels was determined from all the associated 250 points. Analysis of the cylinder circularities at locations 1–5 showed that, in general, within a manufacturer set, all vessels tended to have similar circularities. However, some manufacturers' data indicated higher circularities when compared to others. The maxima for the cylinder circularities and cylindricity, as shown in Table 3, were 0.812 and 0.952 mm, respectively, across all manufacturer vessels. In ideal situations, where there are no imperfections in geometry, the values for these and most of the other following geometric irregularities should be equal to 0. More practically, values close to 0 indicate small deviations from the ideal setup and are considered acceptable as being a consequence of manufacturing processes.

Hemisphere Circularity

Similar to the cylinder circularity, the hemisphere circularity of a vessel is defined as the difference between the maximum and minimum values evaluated from the corresponding 100 data points previously used for the evaluation of the hemisphere radius. The hemisphere circularity values for all vessels are shown in Figure 6a. It can be observed that the hemispherical circularity values are comparatively higher than the cylinder cylindricity or circularity values. As shown in Table 3, in comparison across all 42 vessels, while the average value was 0.719 mm, the highest value was 1.535 mm. The average values for hemispherical circularity within a manufacturer's set of

Table 3. Selected Statistics of Geometric Irregularities in Apex Vessels

Characterization Parameter	Individual Manufacturer (Mfr) Data, Average ± SD							All Vessels	
	Mfr. 1	Mfr. 2	Mfr. 3	Mfr. 4	Mfr. 5	Mfr. 6	Mfr. 7	Range	Average ± SD
Cylinder circularity at location 1 (mm)	0.121 ± 0.060	0.276 ± 0.105	0.160 ± 0.111	0.153 ± 0.033	0.101 ± 0.039	0.134 ± 0.058	0.446 ± 0.072	0.056–0.569	0.199 ± 0.134
Cylinder circularity at location 2 (mm)	0.118 ± 0.064	0.298 ± 0.119	0.162 ± 0.112	0.152 ± 0.022	0.097 ± 0.043	0.138 ± 0.057	0.480 ± 0.085	0.045–0.600	0.206 ± 0.148
Cylinder circularity at location 3 (mm)	0.118 ± 0.058	0.309 ± 0.133	0.166 ± 0.105	0.160 ± 0.015	0.102 ± 0.044	0.139 ± 0.057	0.498 ± 0.112	0.050–0.624	0.213 ± 0.155
Cylinder circularity at location 4 (mm)	0.134 ± 0.055	0.321 ± 0.151	0.165 ± 0.096	0.182 ± 0.025	0.143 ± 0.094	0.144 ± 0.056	0.534 ± 0.139	0.051–0.684	0.232 ± 0.166
Cylinder circularity at location 5 (mm)	0.128 ± 0.052	0.331 ± 0.161	0.155 ± 0.084	0.221 ± 0.023	0.098 ± 0.081	0.149 ± 0.052	0.602 ± 0.170	0.031–0.812	0.241 ± 0.191
Cylinder cylindricity (mm)	0.313 ± 0.070	0.466 ± 0.192	0.253 ± 0.087	0.322 ± 0.064	0.312 ± 0.152	0.251 ± 0.046	0.732 ± 0.131	0.137–0.952	0.378 ± 0.194
Cylinder perpendicularity (mm)	0.053 ± 0.041	0.173 ± 0.136	0.134 ± 0.047	0.274 ± 0.082	0.152 ± 0.031	0.151 ± 0.084	0.489 ± 0.276	0.008–0.912	0.204 ± 0.177
Hemisphere circularity (mm)	0.548 ± 0.082	0.707 ± 0.045	0.970 ± 0.129	0.462 ± 0.086	1.042 ± 0.281	0.449 ± 0.074	0.852 ± 0.141	0.355–1.535	0.719 ± 0.262
Axis-cylinder and -hemisphere perpendicularity (mm)	0.107 ± 0.043	0.253 ± 0.165	0.199 ± 0.081	0.334 ± 0.057	0.332 ± 0.099	0.287 ± 0.099	0.442 ± 0.120	0.052–0.580	0.279 ± 0.138
Apex circularity (mm)	0.013 ± 0.007	0.032 ± 0.028	0.072 ± 0.036	0.007 ± 0.005	0.062 ± 0.069	0.052 ± 0.030	0.052 ± 0.038	0.001–0.202	0.041 ± 0.041
Apex perpendicularity (mm)	0.165 ± 0.093	0.176 ± 0.171	0.399 ± 0.132	0.158 ± 0.105	0.153 ± 0.056	0.176 ± 0.077	0.213 ± 0.116	0.051–0.597	0.206 ± 0.132
Axis-cylinder, -hemisphere, and -apex perpendicularity (mm)	0.708 ± 0.477	0.603 ± 0.221	0.411 ± 0.147	0.466 ± 0.042	0.477 ± 0.073	0.377 ± 0.169	0.606 ± 0.290	0.197–1.321	0.521 ± 0.252

vessels varied from 0.449 to 1.04 mm. In comparison, the average values for hemisphere roundness for standard vessels, as presented by Liddell et al. (*8*), varied from 0.10 to 1.9 mm.

Cylinder Perpendicularity

The cylinder perpendicularity, defined as the distance between two parallel planes that are perpendicular to the horizontal surfaces on which the vessel rests, was evaluated using five data points for each vessel. The five data points consisted of a representative point from each of the five diameter locations along the cylinder height. The cylinder perpendicularity is thus an indication of how the vertical surface of the cylinder lines up with the horizontal surface and is not connected to the axis perpendicularity defined below. Figure 6b presents the skewness plot for the cylinder perpendicularity. Data ranged from low to medium to high values (with changing variabilities) across manufacturers. Evaluation of the average and associated range indicates that while the average (of 0.204 mm) is lower in comparison, the maximum value extended to as much as 0.912 mm, as shown in Table 3. The average values for cylinder perpendicularity within a manufacturer's set of vessels varied from 0.053 to 0.49 mm. In comparison, the average values for cylinder perpendicularity for standard vessels, as presented by Liddell et al. (*8*), varied from 0.07 to 0.36 mm.

Axis-Cylinder and -Hemisphere Perpendicularity

Six data points were used to evaluate the axis-cylinder and -hemisphere perpendicularity. This perpendicularity, which covers only the perpendicularity between the cylinder and hemisphere for a vessel (i.e., not the apex), is defined as the diameter of an imaginary cylinder that is perpendicular to the horizontal surface on which the vessel rests, within which the data from the six points fell. A non-zero value for this geometric characteristic would indicate that the axes for the cylinder and hemisphere are not coincident. The skewness plots for axis-cylinder and -hemisphere perpendicularity are shown in Figure 6c. Analysis of the axis-cylinder and -hemisphere perpendicularity indicates that the offsets between the axes of the cylindrical and hemispherical parts of the vessel also varied both within a manufacturer set of vessels and from manufacturer to manufacturer. Across all manufacturers, the lowest, highest, and average values were 0.052, 0.580, and 0.279 mm, respectively (as presented in Table 3), which possibly indicates that the distribution of values across vessels is centered around the average value. This implies that the cylinder and hemisphere axes are offset, at least to some degree, in apex vessels. The average values for axis-cylinder and -hemisphere perpendicularity within a manufacturer's set of vessels varied from 0.107 to 0.442 mm. In comparison, the average values of cylinder–hemisphere concentricity for standard vessels, as presented by Liddell et al. (*8*), varied from 0.55 to 1.3 mm.

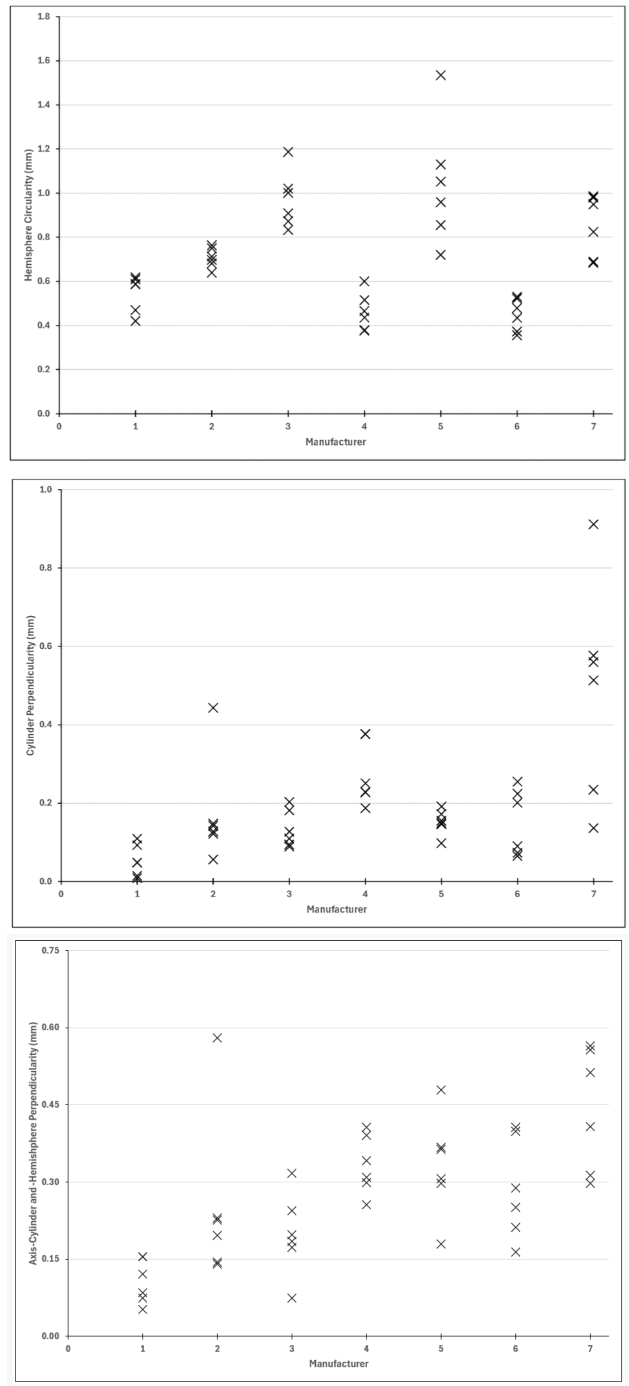


*Figure 6. Skewness plots for hemisphere circularity (**a**), cylinder perpendicularity (**b**), and axis-cylinder and -hemisphere perpendicularity (**c**).*
Note: Fig. 6c was printed incorrectly in PF 51(1) and corrected in a subsequently published Compendial Notice (https://www.uspnf.com/notices/stim-article-figure-correction-20250117).

Apex Circularity

The 144 points previously used for determining the apex diameters (i.e., concentric circles) at various locations along the apex height were used to evaluate the apex circularity as the difference in the maximum and minimum radii obtained from those points. This meant that the 144 points associated with an apex would fall within two concentric circles separated by the circularity for that apex. Also, the circularity consequently is a value that captures the greatest difference in points along the apex height and could be representative of differences in diameter values at two different axial locations within the same apex.

Skewness plots for the apex circularity are shown in Figure 7a. In general, except for certain manufacturers, data showed that the variability was observable within a manufacturer set of vessels. The values of apex circularities were, however, lower in comparison to the previously discussed cylinder and hemisphere circularities. Within a manufacturer set, as shown in Table 3, the average values were found to be typically low (and close to 0), which is possibly an indication of the fact that all points associated with the definition of this irregularity fell within two circles that are very close to each other. Across all 42 vessels, the highest apex circularity value was limited to 0.202 mm, while the average value was only 0.041 mm.

Apex Perpendicularity

As with the cylinder perpendicularity, the apex perpendicularity was evaluated from nine points, i.e., one each from the corresponding apex diameter evaluations along the apex height, as previously described. Skewness plots of the apex perpendicularity, shown in Figure 7b, indicated high intra-manufacturer variabilities. From Table 3, it can be seen that the apex perpendicularity values are typically non-zero and are more controlled with certain manufacturers than with others (as evidenced by the standard deviation values).

Axis-Cylinder, -Hemisphere, and -Apex Perpendicularity

The axis-cylinder, -hemisphere, and -apex perpendicularity is defined as the diameter of an imaginary cylinder perpendicular to the horizontal surface on which the associated vessel rests. For the evaluation of this characteristic, 15 data points were considered and thus, all points would fall within the imaginary cylinder with a diameter equal to the value of the axis-cylinder, -hemisphere, and -apex perpendicularity for that vessel. This perpendicularity covers all three geometric features of a vessel — the cylinder, the hemisphere, and the apex. Differences from the axis-cylinder and -hemisphere perpendicularity, described previously, would indicate offsets (i.e., off-centered positions) of the apex with the other parts of the vessel (i.e., cylinder and hemisphere). The axis-cylinder, -hemisphere, and -apex perpendicularity values were high, with a substantial amount of data points showing values between 0.5 and 1.5 mm regardless of the manufacturer, as shown in Figure 7c.

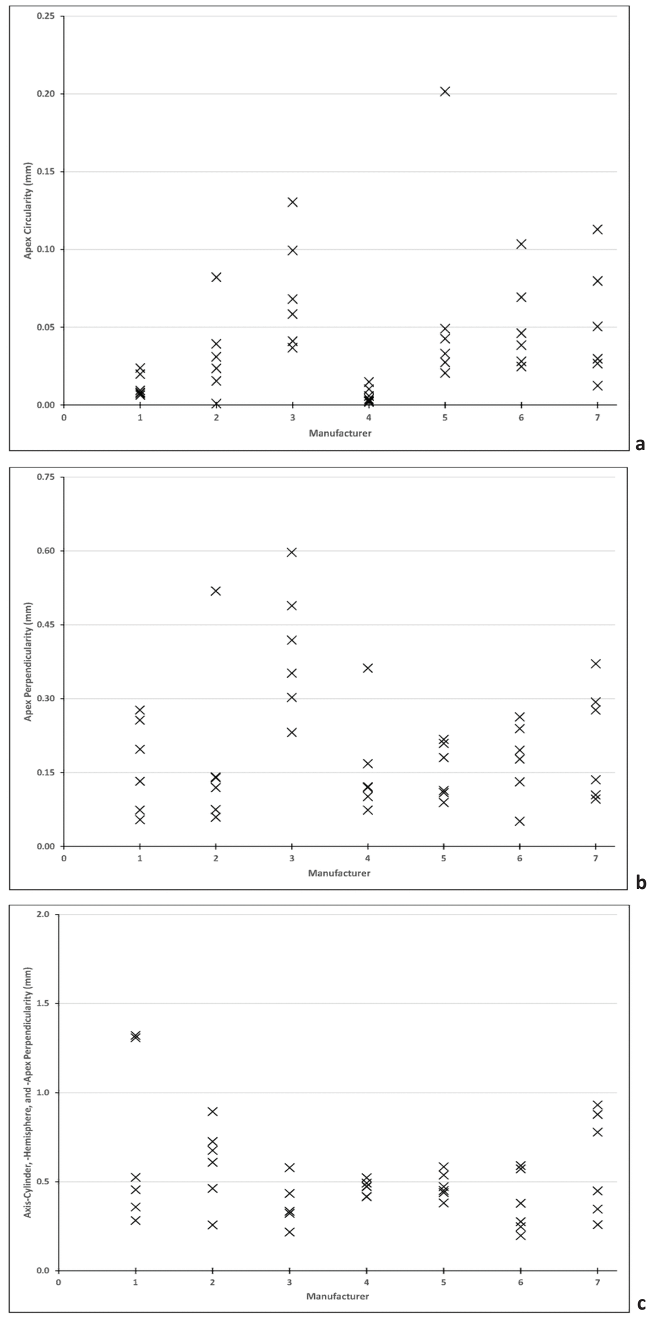


*Figure 7. Skewness plots for apex circularity (**a**), apex perpendicularity (**b**), and axis-cylinder, -hemisphere, and -apex perpendicularity (**c**).*

The axis-cylinder, -hemisphere, and -apex perpendicularity aligns with the proposed specification of apex centering (i.e., the deviation of apex from the vessel centerline) in the 2021 *Stimuli* article. The proposed specification value for the irregularity is to be ≤ 2 mm. Analysis of Table 3 indicates that the average values for any manufacturer and the range (and average values) across all manufacturers lie within the proposed specification. Given that the axis-cylinder and hemispherical perpendicularities are also non-zero, differences between the cylinder and hemisphere centering should additionally be considered when determining a specification for the apex centering. Furthermore, any additional offset in the impeller location (from the apparatus setup), depending on its direction, would also need to be considered in defining any specification for this axis-cylinder, -hemisphere, and -apex perpendicularity. For standard dissolution apparatuses, the impeller offset is defined to be ≤ 2 mm, i.e., the same value (see <711>). Thus, if it is desired to limit the total offset of the apex and impeller to a maximum of 2 mm, care should be taken to set specifications for impeller offsets with apex vessels. Additionally, the effect of impeller and apex offsets on hydrodynamics in apex vessels should be considered from both individual and combinational perspectives.

CONCLUSION

As a first step aimed toward understanding commercially available apex vessels, a geometry characterization study was completed. Seven sets of six apex vessels, each from different manufacturers, were characterized using a CMM. A total of 37 characterization parameters (associated with either the vessel geometry, the apex geometry, or geometric irregularities) that aid in the complete definition of the apex vessel geometries were identified. Measurement data was obtained individually for each vessel, and data from all vessels were compiled to obtain an understanding of both intra- and inter-manufacturer distributions using skewness plots. Additional information about the intra- and inter-manufacturer variabilities associated with these parameters was extracted by analyzing the associated averages, standard deviations, and ranges.

All sizing parameters pertaining to the vessel geometries considered in this study, i.e., without including the apexes, fall within the specifications set in <711> and exhibited low intra- and inter-manufacturer variability. Thus, the corresponding specifications for standard vessels can be applied to apex vessels as far as the vessel parameters are considered. However, data shows that certain parameters, for example hemisphere radius, fall within much narrower ranges. Hence, there is a possibility of providing tighter specifications for apex vessels if such a need arises.

On the other hand, all apex characterization parameters considered in this study were found to vary considerably both within a manufacturer set of vessels and between manufacturers. These variations were found with the diameters at various locations, height, width, thickness, and (internal and external) angles — thus indicating a wide variety of apex geometries available commercially. Measurements of geometric irregularities also presented similar variations across all apex vessels considered. Therefore, it is crucial for end-users of apex vessels to understand that these vessels can vary in geometry (across multiple parameters) even within a single manufacturer's set and to be aware of their potential impact on dissolution results. Consequently, it is advisable to control the source of apex vessels used in testing or at least use vessels with parameters that fall within a certain acceptable tolerance.

The measurements from this study were additionally compared against the three specifications proposed for apex vessels in the 2021 *Stimuli* article. Measurements for the apex height and the apex external angle indicated that there are values for each of these parameters outside the proposed specifications. On the other hand, measurements of axis-cylinder, -hemisphere, and -apex perpendicularity were within the proposed specification for apex centering. However, additional considerations, such as its association with the axis-cylinder and -hemisphere perpendicularity and any possible impeller offsets during operation of the apparatus, need to be evaluated before setting a specification for the apex centering.

Following the conclusion of this study, it is understood that there are variabilities associated with the defining parameters of apex vessel geometries and that there is a possible need to modify certain proposed specifications provided in the 2021 *Stimuli* article. Results from the proposed CFD and dissolution studies will provide more insights into a complete understanding of the apex vessels. Upon completion of these studies, a more comprehensive understanding of the specifications required to standardize the apex vessels can be achieved. We expect that a combination of direct and/or indirect measurements may be required to assess the geometric parameters detailed herein for use of the apex vessels in dissolution labs, as the expectation is not to conduct a detailed characterization by using CMM as discussed here.

GLOSSARY

d_A: Distance of apex to the origin of hemisphere (mm).

$d_{Z,hs}$: Distance Z to the origin of hemisphere (mm).

H_A: Apex height (mm).

H_V: Vessel height (mm).

R: Hemisphere radius (mm).

R_b: Blend radius between apex and adjoining vessel surfaces (mm).

W_A: Apex width (mm).

Z: Axial coordinate along vessel/apex heights (mm); $Z = 0$ at vessel top.

θ_{ext}: Apex external surface angle (degrees).

θ_{int}: Apex internal surface angle (degrees).

ACKNOWLEDGEMENTS

The authors thank Dr. James Mann and Dr. Gavin Reynolds of AstraZeneca for discussions on their 2021 *Stimuli* article, *The Case for Apex Vessels*, which took place prior to the study presented in this current article. The authors would also like to acknowledge the contributions of Naiffer Romero of USP in initiating and facilitating the conversations with AstraZeneca that led to this study. Specific thanks are also due to Dr. Mann for his support in the procurement of vessels used in this study from various vendors and to the vendors themselves for providing us with their vessels.

The authors would additionally like to acknowledge the significant contributions of Karl Barth, BMA, Inc., in carrying out the CMM data collection efforts, providing initial summaries of results and contributing to a more comprehensive understanding of the definitions and variations in some of the geometric parameters discussed in this article.

CONFLICT OF INTEREST STATEMENT

The authors are employees of the US Pharmacopeial Convention. USP offers documentary and physical reference standards for sale as part of its activities.

USP IDENTIFICATION OF BRANDED INSTRUMENTS OR EQUIPMENT DISCLAIMER

Certain commercial equipment, instruments, vendors, or materials may be identified in this article to specify adequately the experimental procedure. Such identification does not imply approval, endorsement, or certification by USP of a particular brand or product, nor does it imply that the equipment, instrument, vendor, or material is necessarily the best available for the purpose or that any other brand or product was judged to be unsatisfactory or inadequate.

REFERENCES

1. Beckett, A. H.; Quach, T. T.; Kurs, G. S. Improved hydrodynamics for USP apparatus 2. *Dissolut. Technol*. **1996**, *3* (2), 7–18. DOI: 10.14227/DT030296P7.
2. Collins, C. C.; Nair, R. R. Comparative evaluation of mixing dynamics in USP apparatus 2 using standard USP vessels and PEAK vessels. *Dissolut. Technol*. **1998**, *5* (2), 17–21. DOI: 10.14227/DT050298P17.
3. Mirza, T.; Joshi, Y.; Liu, Q.; Vivilecchia, R. Evaluation of dissolution hydrodynamics in the USP, PEAK and flat-bottom vessels using different solubility drugs. *Dissolut. Technol*. **2005**, *12* (1), 11–16. DOI: 10.14227/DT120105P11.
4. Baxter, J. L.; Kukura, J.; Muzzio, F. J. Shear-induced variability in the United States Pharmacopeia apparatus 2: modifications to the existing system. *AAPS J*. **2005**, *7*. DOI: 10.1208/aapsj070483.
5. Yoshida, H.; Morita, T.; Abe, Y.; et al. Effects of apex size on dissolution profiles in the USP II paddle apparatus. *AAPS PharmSciTech*. **2023**, *25* (1), 9. DOI: 10.1208/s12249-023-02722-5.
6. Gray, V.; Kelly, G.; Xia, M.; Butler, C.; Thomas, S.; Mayock, S. The science of USP 1 and 2 dissolution: present challenges and future relevance. *Pharm. Res*. **2009**, *26* (6), 1289–1302. DOI: 10.1007/s11095-008-9822-x.
7. Grady, H.; Elder, D.; Webster, G. K.; et al. Industry's view on using quality control, biorelevant, and clinically relevant dissolution tests for pharmaceutical development, registration, and commercialization. *J. Pharm. Sci*. **2018**, *107*, 34–41. DOI: 10.1016/j.xphs.2017.10.019.
8. Liddell, M. R.; Deng, G.; Hauck, W. W.; Brown, W. E.; Wahab, S. Z.; Manning, R. G. Evaluation of glass dissolution vessel dimensions and irregularities. *Dissolut. Technol*. **2007**, *14* (1), 28–33. DOI: 10.14227/DT140107P28.