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Geometric Irregularities Common to the Dissolution Vessel

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Introduction

Dissolution testing is an attempt to create a perfectly controlled space, with a hydrodynamically consistent environment. Much has been done to obtain a consistent output. This can only be achieved when there is control of the input variables. Many discussions have occurred concerning the effects of centering, vibration, wobble, level, verticality, and other parameters. Some of these discussions have lead to tightened specifications over the history of dissolution testing. However, very little discussion has occurred on one set of input variables that impacts the final output. Those variables are contour imperfections that occur in dissolution vessels and the wide geometric tolerances.

Unknown to many who use glass vessels is that each one is an individual handcrafted product. This manufacturing process creates flaws and imperfections that produce unique flow dynamics for each vessel. The reality is that there are no perfect geometric shapes in the real world; they only exist in the mathematical definitions. Everything is an approximation of the ideal. The question is how far off can we be? While the individual dosage form will demonstrate the greatest variability, the desire is to understand and remove dissolution apparatus biases. Some vessel variability may have little impact on certain dosage forms, but it has been shown that some individual vessels will statistically yield higher or lower results.

This statement appeared in the 1978 *Guidelines for Dissolution Testing*, shortly after dissolution was added to the USP: "Ideally the upper portion of each vessel would be perfectly cylindrical, and its bottom would be a perfect hemisphere… They are made one at time by manually blowing a molten mass of glass into a mold. As a result, the vessels are not uniform with respect to weight, height, cylindrical shape, hemispherical curvature, and inner diameter…The inside surface of each should be inspected for abnormalities."(1). The recognized variability led to the creation of USP specifications for dissolution vessels. But these specifications only defined the inner diameter and the height. Studies have concluded that a major source of dissolution result variability appears to be the geometric parameters of the dissolution vessel and stirring mechanism (2)(3). Other studies have shown high variability within the vessel flow when using Apparatus 2. This can result in extreme variation in flow dynamics along the hemispherical surface (4).

By the mid 1980's specifications were established, (5) but were later extended to include taller vessels. One assumption made in these specifications is that the cylinder and hemisphere of the vessel is perfectly uniform with only the height and width needing measurement. Since the glass vessels are individually made, the vessel will always fall short of perfection, both in the cylinder and the hemisphere. One proposal is the use of plastic vessels as an alternative to glass. While plastic allows manufacturing to tighter tolerances, strictly speaking, plastic vessels have slightly tapered cylinders due to the manufacturing process. They will not necessarily be equivalent to glass vessels. Another issue associated with plastic vessels is poor heat transfer. The consequence of this is that if one relies on a water bath to bring the medium to proper temperature, a great deal of efficiency is lost due to the time required for heating.

The Cylinder

In order to better understand the vessel shape, we need to better define the parts and shape of the dissolution vessel. The vessel is cylindrical, with a hemispherical bottom (6). Borrowing a term from architectural geometry, it would be called an inverted cupola. Starting with the upper cylindrical wall, we need to better define the cylinder. The cylinder was first extensively studied by Archimedes in his two-volume work on the sphere and cylinder. Archimedes' mathematical definition of the cylinder included all curved surfaces bounded by two parallel planes. This pure mathematical definition would include elliptic cylinders, oblique cylinders, and conic frustrums (tapered cylinders). However, in common usage the term "cylinder" generally refers to the particular case of a right constant-width circular solid.

Using the definition right constant-width circular solid, let us examine all the geometric flaws that make the cylinder fall short of this geometric definition. A cylinder is called a right cylinder if it is "straight" in the sense that its cross sections lay directly on top of each other; otherwise, the cylinder is called **oblique**. Current specifications assume that the oblique angle is 0. This may or may not be true. A cylinder is also assumed to have a constant radius from the seam to the top of the dissolution vessel. If this is not true and flaring occurs from the bottom to the top it is called a **conic frustrum**. Since upper flaring is more common due to manufacturing techniques, one could define a tapering number as (t) in which $t=(A-X)/X=(A/X)-1$. A is the upper major axis radius and X is the lower major axis radius. (Figure 1) Here we would have an ideal tapering number of 0. The current specifications assume the cylindrical flaring does not occur.

Finally, a right constant-width circular cylinder assumes that two congruent circles bound each end of the cylinder.

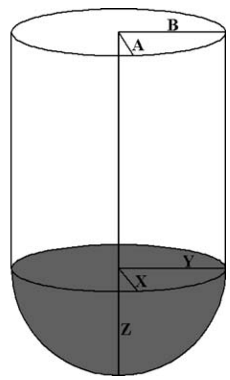

Figure 1. The 5 major axes defining the curvature of the dissolution vessel.

One of the hardest geometric shapes to manufacture mechanically is the circle. Many forces such as gravity, viscosity, and friction prevent the manufacturer from achieving a perfect circle. When a circle falls short of perfection, then it actually falls under the definition of an ellipse. **Eccentricity** is the measure of how far a circular shape is from being perfectly circular. You can think of a circle as an ellipse with an eccentricity of 0 (A=B). The equation for eccentricity is defined as follows, e=(SQT (A^2-B^2))/A. The cylinder becomes an elliptical cylinder due to eccentricity of the circular shape. This appears to be the most common flaw occurring in the cylinder of the vessel, creating an eccentricity to the cylindrical shape. The changing radius of the cylinder will alter the angular momentum of particles rotating in dissolution media, as well as the tangential flow patterns. Vessels may prove to give differing results depending on their dissimilarity.

The Seam

Moving down the vessels we reach the point in which the cylinder merges with the hemisphere of the vessel. Historically, the glass vessel was created by fusing two separate pieces of glass, the cylinder and hemisphere, producing the finished shape. This can create a **ridge** or crest where the two parts unite. The ridge may not be seen but can often be felt. Such a ridge could alter the axial flow pattern of the vessel. Some manufacturers have decided to manufacture their vessels from one continuous piece of glass, in which a tube is formed and then sealed. The newer methods tend to eliminate seam flaws. It is a good practice to inquire as to which method is currently used by your equipment manufacturer.

The Hemisphere

Below the seam is perhaps what is the most critical shape of the dissolution vessel, the hemisphere. A sphere is defined as a set of points in three-dimensional space that are a fixed distance from a given point. (7) A spheroid is a body or figure approaching to a sphere, but not perfectly spherical. The hemisphere is one half of a sphere, when divided by a plane passing through its center. The true shape that commonly occurs is the hemispheriod and not the hemisphere. True spheres are difficult to manufacture, therefore the vessel bottom is really only an approximation of spherical. There is an area directly below the rotating paddles often called the low velocity domain. A lengthening or shortening of the vertical radius in comparison to the horizontal radii has been empirically known to alter the coning of prednisone and other similar cone forming tablets in the low velocity domain. This altered coning will change the output of the test results.

Every hemisphere has three orthogonal radii. The first two consist of the horizontal or equatorial axes (X, Y) and the third axis is the vertical often known as the polar axis (Z). For a hemisphere to be perfect, X and Y radii would be congruent to Z, and to each other. **Prolation** is a lengthening of a spherical shape in the vertical axis. **Oblation** is the shortening of a spherical shape in the polar axis. If the oblation or **flattening** of a vessel hemisphere were given the value (f), then one could establish the flatness as a ratio of the reduction to the polar axis to the equatorial axis. Thus the equation f=(X-Z)/X=1-(Z/X) gives us a measure of the vessel flatness, with 0 being the ideal hemispherical shape. A perfectly flat vessel would have an f-number of 1. It has been observed that the hemisphere is very frequently flawed; prolation and oblation can frequently cause low velocity domain size shifts, altering **axial, tangential and radial** flow sub-paddle.

While prolate and oblate spheroids occur frequently, a final variation is also a possibility. This flaw is known as the ellipsoid. The prolate and oblate hemispheroids occur when X=Y and Z is larger or smaller. The **ellipsoid** is when X≠Y, regardless of Z. This would cause changes in distance perpendicularly from the axis (also known as moment arm) and flow patterns of the aggregates and particles. Conservation of angular momentum would increase the velocity with decreases in the moment arm.

Geometric Tolerances

Beyond the issue of geometric irregularities, which will exist despite the best control, the other issue is the variability that arises not from manufacturing but from tolerances in the existing design. Just considering the height of the vessel, one is allowed from 160 to 210 mm (cylindrical axis + hemispherical altitude). If this height only varied in the cylindrical axis, then the excess height only creates empty space. If, however, the height variability includes the hemispherical altitude as well as the cylindrical altitude, *Table of Definitions*

Cylindrical terminology	Definition
Oblique	Cylinder cross sections do not lay directly on top of each other
Frustrum	Flaring or tapered cylinder
Eccentricity	A measure of how far an ellipse differs from being a circle
Hemispherical terminology	**Definition**
Prolation	A lengthening of a spherical shape vertically
Oblation	A shortening of a spherical shape vertically
Flattening	A measure of how far a spheroid differs vertically from being a sphere
Ellipsoid	A solid of revolution created by rotated an ellipse around one of its axes
Flow terminology	**Definition**
Axial flow	Movement parallel to the main axis
Tangential flow	Movement in the direction of circular agitation
Radial flow	Movement parallel to the cylindrical radius
Flaw terminology	**Definition**
Ridge	Long narrow raised area
Spur	A small bump
Fan	A large raised area
Draw	A small indentation
Depression	A large indented area
Plain	A flattened curved surface

then prolation or oblation occurs, altering the flow dynamics. Considering the inner diameter width, variations in the current specifications (98-106mm) affect both the cylinder and hemisphere. Vessels may vary up to 8mm in diameter. Inconsistent diameters will result in differing angular momentum. Different manufacturer's vessels tend to be non-interchangeable due primarily to this parameter. Another aspect of inconsistent diameters is that the volume of the hemisphere will increase quickly with increasing width. This will result in more of the dissolving product being in the sub-paddle flow patterns, strongly tangential in flow patterns, rather than the super-paddles flow of the cylindrical section, which tend to be stronger in radial and axial flows. The volume of the sphere will increase 28%, more quickly than the volume of the cylinder increases. This will cause more of the volume to reside in the hemisphere in a wide vessel than would be there in a narrow vessel. Differing flow dynamics exist in the lower vessel than in the upper circulatory areas of the cylinder.

Flaws, Warps, and Scratches

In addition to wide geometric tolerances, other non-specified abnormalities could occur which should be observed. These are the contour variables, which create a less than perfect geometric curve. We have already seen the ridge, which could occur along the seam between the cylinder and the hemisphere. But within the hemisphere itself we could experience spurs, draws, fans, depressions, and a plain. Each of these is described with the point of view from the media side of the hemisphere.

The **spur** would be a small bump, while the **fan** would be a wider, more spread out spur. On the opposite end, a **draw** would be a small indentation, while a **depression** would be a larger, more spread out area. Finally, a **plain** would consist of a neutral flattening out of what should be a curved area. The issue of scratches should also be addressed. While plastic will give a better, more uniform shape in general than glass, it will scratch. Scratches should be watched to determine if they affect calibrators and established routine results.

Conclusion

While the dissolution vessel may have many of the flaws listed in this article, that same vessel is not addressed within the current regulatory specifications. Variability is a factor that must be minimized for the dissolution equipment of the 21st century to provide consistent output. While the science progresses toward more reliance on mechanical calibrations with a move away from chemical calibration, the impetus for improvement should be placed on the manufacturers. Mechanical calibration may not prove satisfactory until the additional vessel specifications of oblique, tapering, eccentricity, and flatness are better understood and controlled. The practical impact of any given flaw is largely unexplored. Because of the current state of vessel specification, it remains good practice to maintain a consistent location and orientation to vessels. Inspect all new vessels scrupulously before use, including inspection of the inner surface with the hand. While the assumption is that all vessels are equivalent, the reality is that all handmade vessels are unique and individual. Each contributes in its own way to the variability of the equipment.

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