Implementation Guidance for American Society for Testing and Materials (ASTM) E 2503-07 "Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus"

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Abstract: This guidance is intended to serve as a companion document for ASTM Standard E 2503-07, "Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus", by providing practical information useful for the implementation of mechanical calibration. Particular focus is placed on use of the available tools to make the required measurements.

Keywords: Dissolution, Calibration, Mechanical calibration, Calibrator tablets, ASTM standard, Instrument qualification.

INTRODUCTION

The use of mechanical calibration for dissolution apparatus 1 and 2 without the need for USP calibrator tablets has been described in an January 2010 FDA Guidance Document [1]. The document states that an "appropriately rigorous mechanical calibration method properly executed will satisfy the cGMP requirement for dissolution apparatus calibration under § 211.160(b) [4]".

The FDA Guidance Document does not provide detail on how to perform an appropriately rigorous method of mechanical calibration. Additional detail, including acceptable tolerances, can be found in ASTM E 2503-07, "Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus" [2] and in CDER's "Mechanical Qualification of Dissolution Apparatus 1 and 2" [3]. However, even these documents are not specific enough to allow the user to independently execute sufficiently rigorous mechanical calibration.

Therefore, this Implementation Guidance was developed for those areas of ASTM Standard E 2503-07 (herein referred to as "the ASTM procedure") where the requirements differ from what has historically been done or where it was believed that additional information will be valuable to the practitioner of mechanical calibration.

APPARATUS SET-UP (SECTION 4.3)

Typically, critical dimensions for each part of the apparatus are provided by the supplier and accepted by the user based on a Certificate of Analysis. However, there may be occasions when the user needs to verify these critical dimensions. If so, the following information may be useful for making these measurements:

Verification of vessel dimensions can be conducted using calibrated calipers or micrometers. It is the internal dimensions that must be measured. In addition, the inner surface of the vessel should be smooth and regular. While quantitative measurements can be made using mechanical profiling tools such as a coordinate measuring machine, these are not practical for most users and a tactile evaluation of the inner surface is sufficient. The tactile evaluation as well as visual observations of defects should be used to assess the suitability of vessels prior to routine use.

Similarly, basket, shaft and paddle dimensions can be measured using calibrated calipers or micrometers.

These measurements and observations ensure the components are appropriate for use. Operators should routinely monitor for defects that may occur with continued use such as cracks in vessels, loss of integrity of the basket mesh or corrosion of metal parts.

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Depending on the adjustments necessary to meet the mechanical calibration criteria, denoting the position and orientation of each vessel may provide a proper, timely, and effective equipment set-up.

MECHANICAL CALIBRATION (SECTION 4.5)

Provided below are examples of tools available for measuring vessel centering/verticality, runout and level. The examples are not intended to be comprehensive representations but do include typical tools that may be used for different types of apparatuses. The recommended tolerance level for each classification has been indicated as well. It should also be noted that all of these examples can be used with dissolution systems that have full access to the shafts and vessels when engaged. For enclosed or limited access systems some of the examples may be applicable but when necessary consult the manufacturer of the dissolution system for "system specific" mechanical calibration tools.

VESSEL CENTERING / VERTICALITY TOOLS

Tolerance: Digital or analog centering/verticality tools must be accurate to 0.2mm.

Example Tools:

Fig. (1.1.). Shaft surrogate tool (analog).

Fig. (1.2.). Shaft attached tool (analog).

Fig. (1.3.). Shaft surrogate tool (digital).

Fig. (1.4.). Shaft attached tool (digital).

RUNOUT TOOLS

Tolerance: Digital or analog dial indicator must be accurate to 0.05mm.

Example Tools:

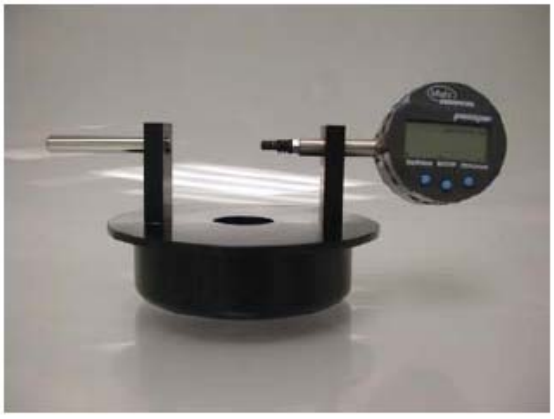

Fig. (2.1.). Vessel mounted tool with digital gauge.

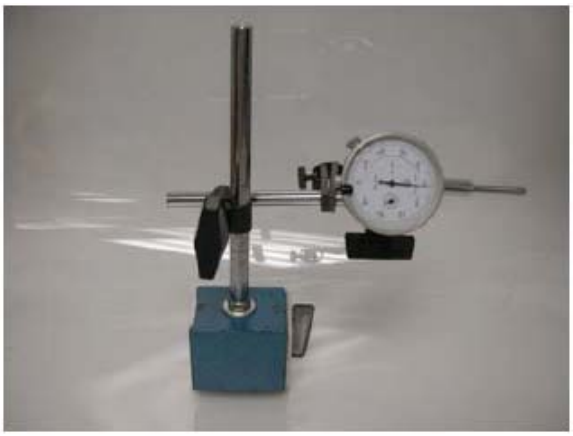

Fig. (2.2.). Support arm mounted with analog gauge. eliminate

Fig. (2.3.). Digital runout gauge.

Fig. (2.4.). Analog runout gauge.

LEVELS:

Tolerances: Digital or analog levels must be accurate to 0.1°.

Example Tools:

Fig. (3.1.). Digital Level.

Fig. (3.2.). Analog level.

VESSEL CENTERING (SECTION 4.5.4)

The ASTM standard requires the measurement of vessel centering at two different positions. Historically, this has been measured at one location only. A procedure for assessing vessel centering at two vertical positions is provided below.

Before centering a vessel you must make sure that the paddle or basket shaft is vertical.

A mechanical or digital centering device that measures centering inside the vessel is required. An example of vessel centering using two mechanical calibration tools and a dissolution apparatus that allows access to the inside of the vessel when it is in the operating position is shown in Figs. (**4.1** and **4.2**).

The paddle must be positioned about 2.5 cm above the bottom of the vessel. One centering tool is attached to the shaft about 2 mm above the top of the paddle blade. Another tool is attached to the shaft and positioned below the lip of the vessel with the probe positioned in the same direction towards the glass as the other tool. Deformities in the glass may occur near the lip of the vessel so the upper centering measurement must be taken below the lip. Each division on the tool demonstrated in Figs. (**4.1** and **4.2**) represents 1 mm. The shaft is slowly turned one complete revolution. The readings on both tools must indicate that the inside of the vessel is centered within a tolerance of 1.0 mm from the shaft in all directions as the shaft and centering tools are rotated. This procedure can also be conducted using one centering tool by first centering the vessel at the lower position then sliding the tool to the upper position and repeating the process.

When centering a vessel around a basket shaft, the tool is placed about 2 mm above the top of the shaft's basket holder with the bottom of the basket positioned about 2.5 cm above the bottom of the vessel bottom. Centering must be done at both the lower and upper positions. If the vessel is not centered at both levels, adjustments can be made by rotating the vessel inside the vessel plate, moving the vessel sideways within the vessel plate or placing shims under one side of the lip of the vessel or vessel centering collar. If the vessel cannot be centered at both levels, check the vessel for deformities and replace or consult the apparatus manufacturer.

Fig. (4.1.). Vessel Centering measurements.

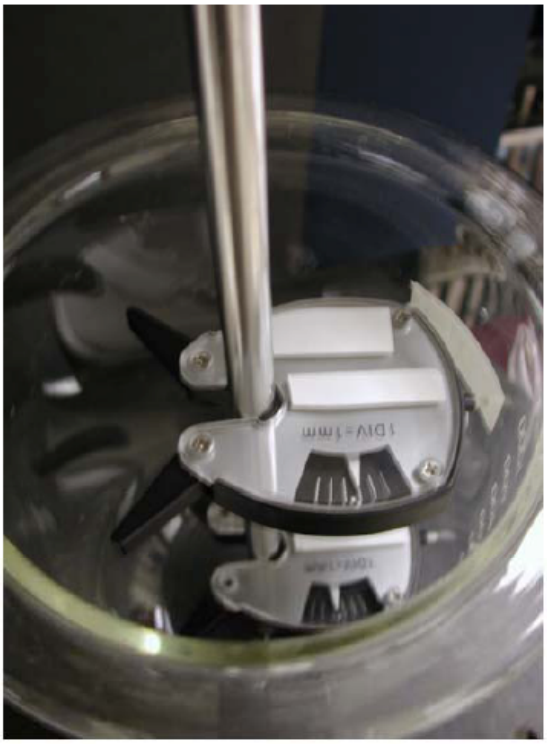

Fig. (4.2.). Vessel Centering (close-up).

Digital centering tools can also be used to measure centering by placing the device at the lower and upper positions of a vessel and repeating the process described above. Pictures of digital centering tools are shown in Figs. (**4.3**, **4.4** and **4.5**).

Fig. (4.3.). Digital Centering Tool – Varian.

Fig. (4.4.). Digital Centering (alternate view).

Some centering tools require that the paddle or basket shaft be removed and replaced by the shaft of the centering device (see Figs. **1.1** and **1.3**). The centering gauge is attached to the shaft and the shaft extends above the apparatus head. Positioning of the measurement point is achieved by adjusting the shaft height. This type of tool can be used for apparatus designs that do not allow access to the interior of the vessel when the apparatus head is in the operating position.

VESSEL VERTICALITY (SECTION 4.5.5)

This parameter has not historically been measured. Vessel verticality can be determined using a mechanical centering tool or a digital level. This section provides a description of how to measure verticality using either a digital level or the vessel centering measurements as denoted in the prior section.

Fig. (4.5.). Digital Centering tool – Sotax.

Verticality - Using a Digital Level

A small digital level can be used to measure vessel verticality. This is done by placing it on the straight inside wall of the vessel above the spherical bottom and below the lip of the vessel. This is then repeated at a second position on the inside vessel surface that is approximately 90º from the first measurement. [Note: There are some digital levels that are suitable for shaft measurements however, they are not of an appropriate size to allow vessel verticality measurements to be acquired in a suitable manner.

Verticality - Using Vessel Centering Measurements

Before determining vessel verticality you must ensure that the paddle or basket shaft is vertical as described in ASTM E 2503-07 Section 4.5.2, "Paddle and Basket Shaft Verticality".

When using centering tools, like the ones shown in Figs. (**1.1** - **1.4**), measurements must be made at two vertical positions. There are two options for obtaining these measurements as follows: (1) Either two tools are positioned on the shaft with the probes positioned in the same direction for simultaneous measurement (Fig. **4.1**) or (**2**) the measurement can be conducted sequentially by repositioning the tool.

The difference in the readings at the two vertical positions is the amount that the vessel is out of verticality over the distance between the two probes. From this measurement and the vertical distance between the two gauge probes, the vessel verticality can be determined in degrees.

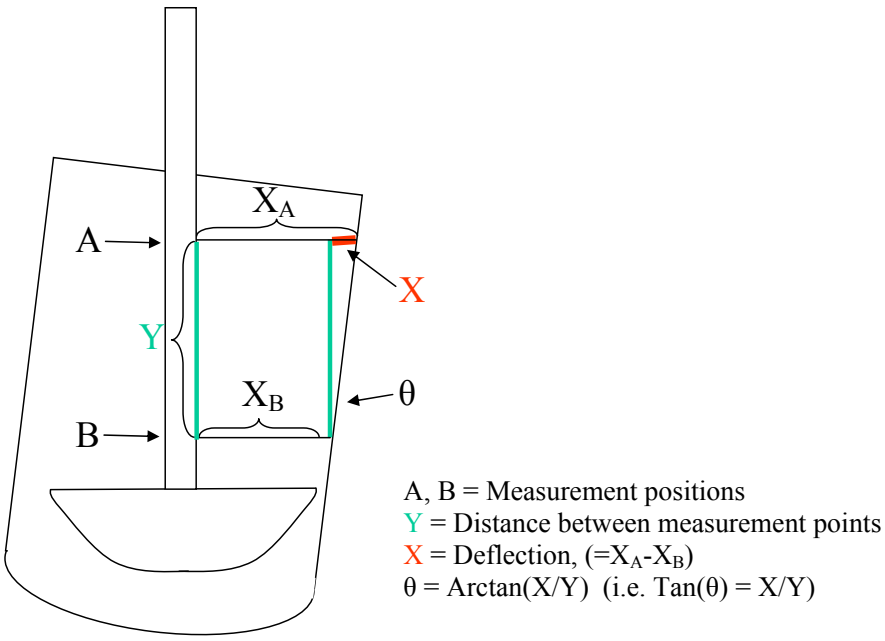

Fig. (5.1.). Graphical representation.

As an example, if the reading at the lower position indicates that the vessel is perfectly centered, the reading at the upper position shows the vessel to be 1 mm out of center and the measured distance between the two gauge positions is 65 mm, the calculation would be:

Degrees out of verticality = Arctan (1mm/65mm) = Arctan (0.0154) = 0.88°.

The Arctan of a number can be found in trigonometry books, the Handbook of Chemistry and Physics or the Chemical Rubber Company tables, and other standard mathematical reference books. Alternatively, handheld calculators or computer spreadsheet programs, such as Microsoft Excel, or online calculators, such as http://www. analyzemath.com/Calculators_2/arctan_calculator.html,

A graphical representation of this measurement is shown below.

The amount of deflection allowable depends on the vertical distance between measurements. These distances may vary according to the size of the dissolution vessel and lengths of the shafts.

Presented below in Table **1** are maximum deflections allowable for different vertical distances. This may be helpful in establishing criteria for less commonly used vessels such as 100 mL or 2 Liter vessels.

Table 1. Maximum Allowable Deflections for Given Distances

Shaft Distance (cm)	Deflection (mm) for 1 Deg off Vertical
5	0.9
10	1.7
15	2.6
20	3.5
25	4.4
30	5.2

Vessel verticality must be determined in the vessel at two positions that are approximately 90º apart. First determine verticality on the right or left side of the vessel then repeat by moving the tools to a position that is in front or back of the vessel that is 90º from the original measurement. The tolerance is ≤ 1.0º from vertical at both positions.

OPERATION (SECTION 4.6)

As is indicated in the ASTM procedure, the stated parameters should be evaluated prior to operation of the dissolution test. A documented verification of these parameters can be a significant preventative measure to further reduce/eliminate aberrant data investigations and improve the quality and efficiency of the testing process.

Vessel Examination

During routine execution of dissolution testing, the practices used in sampling, vessel cleaning, and maintenance can impact the overall condition of the vessels. The utilization of vessels with defects and/or residual material from a prior test can negatively impact the variability of results obtained.

The vessel bottom should be checked for any foreign material that may be adhered to the vessel from a prior test (e.g. cellulose, gelatin, etc) and/or to assure that no fractures/chips have occurred from routine handling/cleaning of the shafts and vessels.

The flange/lip area of the vessel can also be easily damaged in routine handling. Defects in these areas may affect the vessel levelness and verticality.

The sides of the vessel should also be examined to ensure that any material from the "waterline" mark of the media used in previous tests has been removed.

Basket Examination

A deformed basket can dramatically affect the results obtained. A basket wobble check performed at the bottom of the basket is a critical check to assure proper performance. With routine operation of dissolution equipment, baskets can be relatively easily distorted during equipment clean-up and set-up which may cause the wobble to significantly increase. It is recommended that a visual confirmation is conducted to assure that the basket condition has not changed since the last wobble check.

Typically, the mesh baskets are subject to becoming disfigured *via* the routine process of attachment or removal from the shafts. The bottom of the basket can become offset from the top of the basket, which will produce significant wobble as measured by a runout gauge on future tests. Mesh baskets are also prone to small tears at the upper and lower rims.

The shaft of the basket should be examined to assure the clips/o-rings are suitably cleaned and not bent or twisted which will cause perturbation of the hydrodynamics in the vessel.

Paddle Examination

Typically, paddles are durable pieces of equipment that can tolerate a significant amount of handling, cleaning, and routine use without experiencing any defects. However, based on the composition of the respective paddles and the components utilized in the formulations, an additional visual examination should be made to detect any defects caused by sampling or cleaning prior to the next dosage form being tested.

It is important to assure proper cleaning and the absence of defects in the paddles. Defects in these areas can allow excipient carry-over into the next test and/or alter the flow dynamics within the vessel. A common area for defects is along the bottom of the actual blade of the paddle. Defects in this area can be caused by routine handling, or improper storage or cleaning of the apparatus.

Vessel Temperature

Vessel temperature is an important attribute of the dissolution test. The temperature effects can vary significantly

depending upon the formulation being tested. Verification of this important parameter should not rely on overall bath temperatures or water circulator displays. The actual vessel temperature can be impacted by room air currents, the flow pattern of water within the bath, and/or initial temperature of media.

Vibration

This aspect can also have a significant effect on the results obtained. The current criteria of "significant" is not quantified, however, it is essential to assure the environment, which includes the mechanical drive units, does not impart vibration which could impact the outcome of the tests. For example, construction in a nearby area or significant building facilities such as air handlers or manufacturing equipment could impart a vibration effect to the testing equipment. Awareness of changes in the nearby environment that could negatively impact the dissolution test results is noteworthy to assure consistency.

CONCLUSION

This guidance provides practical information to enable the timely implementation of ASTM E 2503-07 "Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus" as the routine procedure to demonstrate acceptability of dissolution equipment prior to routine operation. The tools denoted in this guidance are for reference only as other appropriate tools may be suitable to achieve the same tolerances.

There is significant detail included regarding "vessel verticality", which has more stringent requirements in the ASTM document that should enable a rigorous application of that measurement.

As stated in the Guidance for Industry issued by the FDA in January 2010, a compendial product must meet the dissolution requirements for its USP monograph whether mechanical calibration or the USP calibrator tablet approach is used (section 501(b) of the Federal Food, Drug, and Cosmetic Act (21.U.SC. 351(b)). The practices described herein will facilitate the application of an appropriately rigorous mechanical calibration method suitable for both compendial and non-compendial articles and will allow the user to satisfy the cGMP requirement for instrument calibration under CFR 211.160(b)(4).

WEBLINKS

http://www.fda.gov/cder/guidance/7232dft.htm

REFERENCES

[1] FDA. Guidance for Industry: The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice (CGMP). January 2010.

[2] American Society for Testing and Materials (ASTM). E 2503-07. Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus 2007.

[3] FDA, "Mechanical Calibration of Dissolution Apparatus 1 and 2," DPA-LOP.002 June 2, 2006.

[4] Code of Federal Regulations, Title 21, Food and Drugs (General Services Administration). Washington, DC. 1 April 2007, Part 211.160(b)(4).

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