Proper Implementation of Enhanced Mechanical Calibration of Dissolution Apparatus 1 and 2

White Paper

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Introduction

Mechanical calibration of Dissolution Apparatus 1 and 2 has become an increasingly popular option for pharmaceutical companies since the FDA's Guidance for Industry, *The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – Current Good Manufacturing Practice cGMP*, became official in January 2010[1]. Mechanical qualification (MQ) has been embraced for many reasons such as the belief that the qualification supports tighter tuning for the dissolution apparatus, perceptions of varying results and instrument failures from the USP Performance Verification test (PVT), and reduced time and cost of analytical instrument qualification. Unfortunately, when the enhanced mechanical qualification procedures are executed in a laboratory, the focus is often on the physical parameter measurements taken on the dissolution apparatus, and other areas of the guidance are often not addressed adequately, resulting in an incomplete qualification.

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Background

Mechanical calibration was developed by the PhRMA Subcommittee on Dissolution Calibration in order to address quality and cost concerns with chemical qualification of dissolution apparatuses[1]. The prednisone tablets were also said by the FDA to show a "...lack of sensitivity to variation and uncertainty" and led them to conclude that "...sole reliance upon reference standard tablets to evaluate the performance of USP Dissolution Apparatus 1 and 2 does not provide assurance that the apparatus is adequately calibrated as required by cGMP regulation in 211.160(b)(4). Enhanced MC is advantageous, enabling a dissolution apparatus operator to minimize the significant sources of measurement system variation identified in the recently published studies[2]."

In response to the trend to identify sources of variability by the new mechanical qualification (MQ) procedures, the USP released the latest lot of dissolution PVT 10 mg prednisone tablets with acceptance criteria focusing on accuracy and variability with the holistic PVT. Additionally, the USP published its Toolkit 2.0 which endorses many of the tighter tolerances discussed in mechanical calibration as recommendations. However, it should be noted that the official USP specifications and tolerances for Apparatus 1 and 2 are contained in the current USP <711> chapter.

Although MQ has always been a key component of PVT, a dissolution lab can choose to adopt the enhanced mechanical calibration approach outlined by the FDA and ASTM[3] standard procedures or continue performing USP PVT with the prednisone tablets, both of which fulfill GMP requirements for dissolution apparatus qualification[2].

Key parameters of mechanical calibration

The mechanical calibration procedure has five main components that must be implemented to consider a dissolution unit qualified. These components are:

(1) Enhanced mechanical measurements of the dissolution system such as RPM speed, centering, wobble, and so on.

(2) Verification of dissolution components against USP <711> - paddles, baskets, basket shafts, and vessels

(3) Preventative maintenance plan in place according to manufacturer recommendations

(4) Control of vessel variability, dissolved gasses, and vibration

(5) Prerun analyst checks before each run for component condition

Many laboratories focus on the first component, yet omission of any or all of the other four points can compromise the calibration and overall performance of the dissolution apparatus. It is important to develop a plan to address all five aspects of the enhanced mechanical qualification process to ensure that the dissolution apparatus is fit for use.

(1) Enhanced mechanical measurements

The enhanced mechanical measurements are where the greatest amount of focus is placed. The most important difference in tolerances between the requirements in USP <711> and the mechanical calibration approaches are the addition of two vessel centering measurements with tighter tolerance, shaft wobble, and vessel verticality measurements. The mechanical calibration also includes stricter tolerances for RPM speed and basket wobble.

Detailed information on how to achieve the measurements per ASTM E 2503-07 is available, and the new centering and vessel verticality measurements can be achieved with a variety of tools[4].

Vessel centering is shown in literature to play a key role in vessel variability[5] and as such needs to be tightly controlled. Vessel centering measurements are taken at two locations within the vessel – one at the lower and one at the upper portions of cylinder within the dissolution vessel. Centering must be within 1.0 mm from the centerline in all directions at both locations along the shaft. Use of vessels designed for optimal centering, such as the Agilent TruAlign and TruCenter vessels, have shown improved variability and performance compared to traditional vessel types with possible deformities in the glass rim[6]. Additionally, use of centering rings from the original dissolution manufacturer for traditional vessels has attributed to tighter centering data and lower dissolution variability. Some manufactured apparatus make taking accurate measurements with

the mechanical calibration gauges very difficult. However, surrogate methods of taking these measurements with the components removed does not accurately measure vessel-to-shaft centering.

Vessel verticality is taken at two points in the vessel at 90 degrees apart, and must be within 1 degree of the vertical. Verticality can either be directly taken with a level or mathematically derived from the centering measurements[3].

Paddle and basket height is also a new measurement for most laboratories that traditionally performed the PVT test. Most laboratories set their heights through a variety of tools such as height balls and clip-on gauges, but few have actually measured that height to ensure it is correct. Height can be set incorrectly in a variety of ways such as using the height setting "hockey stick" tool at an angle or improperly using a height ball for basket height setting which will deform the bottom of the basket. Uses of a height gauge tool such as the Agilent 5010 Height/ Center Qualification Station can determine the height of the paddle or basket, and enable height optimization.

Adoption of the tighter mechanical tolerances provides better control of the dissolution apparatus and reduce variability between vessels. These mechanical tolerances are only one part of a complete mechanical calibration, however and once measured, each component must be operated in the dedicated position to which it was qualified.

(2) Verification of dissolution components

The ASTM standard and FDA SOP require that the dissolution analyst must verify or measure the dimensions of the vessels, baskets, and paddles upon receipt. The FDA states that it is the analyst's responsibility to "check the vessel, basket, and paddle dimensions on receipt" and the ASTM states that the analyst must "verify the vessel, basket, and paddle dimensions through measurement, Certificate of Analysis (COA), or Certificate of Conformity (COC)[2,3]. Component measurement and/or verification of a certificate "ensure the components are appropriate for use [3]."

The COA and COC issued by some manufacturers of dissolution components have simply not met the requirements contained in the FDA and ASTM procedures because they do not contain actual measurements of compendial specifications and tolerances. The certificates must include measurements of each component with appropriately documented measuring devices for the critical parameters outlined in USP <711>. The tools used to measure the components "shall be traceable to an accepted standard calibration source from a national or international calibration laboratory."[3] For vessels, it is additionally recommended that the inner surface of the vessel should be checked to ensure that it is smooth and regular. This can be accomplished through mechanical profiling tools or a tactile evaluation of the inner surface[4]. It is felt by the authors that tactile examination is highly subjective and not likely to discover imperfections that will affect vessel performance.

Vessels	Baskets	Basket shafts	Paddles
Internal dimension	Shaft diameter	Shaft diameter	Shaft diameter
Height	Vent hole diameter	Disk width	Blade height
Verify that the vessel is cylindrical and hemispheric	Thickness of basket/shaft adapter	Vent hole diameter	Blade thickness
	Basket height	Three clip design	Blade length
	Basket internal dimension		Bottom blade length
	Outer screen diameter		Radius on top upper blade portion
	Screen height		Radius on outer blade edge
	Outer diameter of bottom screen		Distance from shaft to blade tip at midline
	Mesh number		Difference of paddle heights at outside top along shaft

Table 1
Critical dissolution component attributes outlined in ASTM[3] standard procedures by USP <711>[4].

Description of part

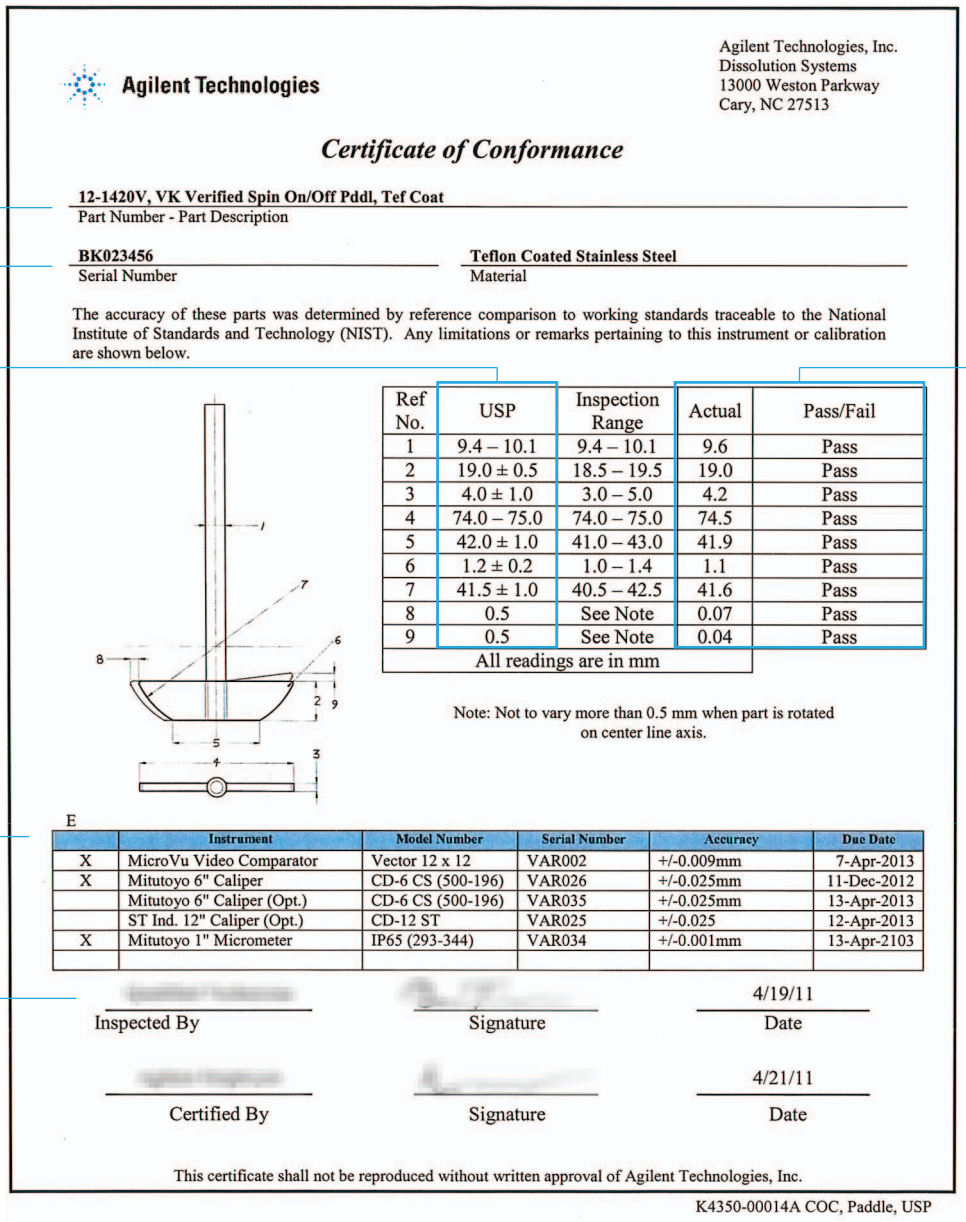
Serial number of part

Required measurement parameters and specifications

As-found values and pass/fail indication

NIST-traceable measurement tools used

Technician performing measurements



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Agilent Technologies, Inc.
Dissolution Systems
13000 Weston Parkway
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Certificate of Conformance

12-1420V, VK Verified Spin On/Off Pddl, Tef Coat
Part Number - Part Description

BK023456
Serial Number

Teflon Coated Stainless Steel
Material

The accuracy of these parts was determined by reference comparison to working standards traceable to the National Institute of Standards and Technology (NIST). Any limitations or remarks pertaining to this instrument or calibration are shown below.

Ref No.	USP	Inspection Range	Actual	Pass/Fail
1	9.4 – 10.1	9.4 – 10.1	9.6	Pass
2	19.0 ± 0.5	18.5 – 19.5	19.0	Pass
3	4.0 ± 1.0	3.0 – 5.0	4.2	Pass
4	74.0 – 75.0	74.0 – 75.0	74.5	Pass
5	42.0 ± 1.0	41.0 – 43.0	41.9	Pass
6	1.2 ± 0.2	1.0 – 1.4	1.1	Pass
7	41.5 ± 1.0	40.5 – 42.5	41.6	Pass
8	0.5	See Note	0.07	Pass
9	0.5	See Note	0.04	Pass

All readings are in mm

Note: Not to vary more than 0.5 mm when part is rotated on center line axis.

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	Instrument	Model Number	Serial Number	Accuracy	Due Date
X	MicroVu Video Comparator	Vector 12 x 12	VAR002	+/-0.009mm	7-Apr-2013
X	Mitutoyo 6" Caliper	CD-6 CS (500-196)	VAR026	+/-0.025mm	11-Dec-2012
	Mitutoyo 6" Caliper (Opt.)	CD-6 CS (500-196)	VAR035	+/-0.025mm	13-Apr-2013
	ST Ind. 12" Caliper (Opt.)	CD-12 ST	VAR025	+/-0.025	12-Apr-2013
X	Mitutoyo 1" Micrometer	IP65 (293-344)	VAR034	+/-0.001mm	13-Apr-2103

[redacted] Inspected By — [redacted] Signature — 4/19/11 Date

[redacted] Certified By — [redacted] Signature — 4/21/11 Date

K4350-00014A COC, Paddle, USP

Figure 1
Example of a Certificate of Conformance (COC).

A COA/COC or in-house measurements must include measurements of the critical attributes in Table 1. The measurements should also be accompanied with the tools used and their calibration due dates to ensure conformance.

Use of a certificate without the individual measurements of each serialized vessel, paddle, and basket for all measurements listed in Table 1, does not meet the requirements of FDA and ASTM mechanical qualification guidelines. It is the burden of the dissolution laboratory and analyst to ensure that all critical measurements of these components were taken with traceable, calibrated tools, and that these measurements are properly documented to adhere with the appropriate guidance. Declarations of manufacturing conformity alone do not meet the mechanical qualification criteria and only indicate that appropriate quality control and engineering design is in place, and declares that components are manufactured to USP specifications. It cannot guarantee conformance of individual components.

Agilent offers verified components with individual certificates of each component that meet the requirements listed in ASTM and FDA guidance. These components can be purchased from Agilent with new equipment or as accessories or replacements to existing equipment.

(3) Preventive maintenance plan

Preventive maintenance plans need to be developed, implemented, and documented according to the mechanical calibration procedures. The preventative maintenance plan should follow the recommendations of the dissolution apparatus manufacturer and take into account the frequency of instrument use.

Preventative maintenance is typically done at six-month intervals or by a number of spindle hours run. Preventative maintenance should encompass all aspects of the dissolution apparatus, not only to lubricate and maintain, but also to inspect for any current problems with the unit including areas of excessive wear that could cause a future performance issue.

Procedures should include periodic checks inside the drive unit to ensure there is no excessive belt wear, fraying, and so on, and that the tension is appropriate. The spindles themselves should also be manually rotated to ensure that they move smoothly. Any points that require lubrication should also be checked and the appropriate lubricant applied. Use of a non-recommended lubricant can cause a buildup of dust or other issues resulting in potential excessive vibration. Sealed bearings may be irreversibly damaged when light machine oils are applied to sealed bearing assemblies, which unintentionally dissolve the grease and eventually render the apparatus inoperable.

Temperature probes should be checked to ensure they are within proper tolerances against NIST-traceable devices, typically within 0.2 °C.

Electric boards, wires, and so on, should also be checked to ensure that they are clean, free of corrosion, and connections are intact.

In addition to the checks of the system above, the water bath should also be cleaned, and refilled to the proper operating level with the addition of an algaecide approved for heater/circulator systems. Most algaecides will prevent buildup for three to four weeks before another cleaning is necessary.

(4) Control of vessel variability, vibration, and dissolved gasses

One of the major concerns about the mechanical calibration procedure is that it is unable to determine unacceptable levels of vessel variability, vibration, or dissolved gasses. The prednisone PVT tablet has demonstrated sensitivity to these parameters, so many laboratories are hesitant to transfer to the mechanical calibration alone until there are specifications, tolerances and procedures to measure and quantify them. Each of these parameters can be controlled to a degree and will help properly qualify the dissolution apparatus. FDA states manufacturers "should take appropriate measures to control the following recognized sources of significant variability in dissolution testing[2]." This means that the laboratory must have written and validated procedures in plance to measure and control these sources of significant variability.

Vessels

Vessel variability is one on the most important aspects of the dissolution test to control, and is cited as the greatest cause of variability in the dissolution environment[7]. Vessel variability can lead to very high %CV values with the USP PVT as shown when vessels from various manufacturers are used on the same apparatus[6]. To reduce vessel variability, the same supplier should be used for all of the vessels on the dissolution unit. In addition, the COCs for the vessels should be reviewed not only to meet the USP criteria, but also to assess the variability of that set of vessels. Vessels should also be examined prior to each run for their condition and cleanliness; this is discussed in more detail in the pre-run analyst checks section.

Vibration

The only requirement for vibration in the USP, FDA, and ASTM procedures is that "no significant vibration" should be present. The original PhRMA collaborative study suggested the maintenance of a calibrating tablet until a definitive vibration specification is developed. Although an FDA-led collaborative effort is underway to determine a vibration specification and tolerance, no such specification is available for vibration at the time of this publication.

Vibration is a very significant force in dissolution and can cause variable results and, depending on the source of vibration, it may affect paddle and basket analysis differently. It is difficult to set a vibration limit for a variety of reasons. Vibration is virtually the quantification of chaos with respect to cancelling and additive effects of sine waves, and vectors associated with the direction of wave forms. Frequency and amplitude variations also must be considered. Vibration can be sustained or intermittent, so it is not clear what cumulative vibration is acceptable, nor what limit there is for an intermittent effect. As a result, vibration must be controlled as much as possible in order to preserve the dissolution environment.

Sustained vibration is typically caused by issues within the dissolution apparatus, a defective water bath circulator, or nearby equipment. The dissolution apparatus and circulator vibration can be controlled through proper preventative maintenance, particularly looking at the belts and spindles for wear, and performing proper lubrication of the system. The dissolution apparatus must not be closely associated with equipment known to vibrate such as fume hoods, vacuum pumps, shakers, ultrasonic cleaners, and even a radio playing music. Intermittent vibration should also be controlled as much as possible. The dissolution apparatus should be in a location of the laboratory where it is not susceptible to vibration from heavy foot traffic, slamming doors or near walls where heavy machinery is running in an adjacent room. Even highways, railroads, and construction have drastically affected dissolution apparatus performance. Vibration can also be controlled to a degree using shock absorbing pads under the feet of the dissolution apparatus which will help limit vibration from the environment from impacting the performance of the dissolution test. Please remember vibration may be transmitted long distances through the bench top itself.

Dissolved gasses

Dissolved gasses are identified as another important aspect to be properly controlled during the dissolution test. Dissolved gasses can lead to considerable variability, and can alter hydrodynamics, distribution of particles in the media, and several other effects. A proper degassing scheme such as vacuum degassing at 41 °C through a 0.45 µm filter in USP <711> should be implemented in order to reduce dissolved gasses below 6 ppm O_2.[9] Alternative approaches for degassing media include helium sparging, sonication under vacuum, and media preparation devices. When using a non-USP degassing method, the media should be checked using a total dissolved gasses meter to ensure the proper level of deaeration has occurred.

Once the media is prepared, heated, and degassed, it should be poured into the dissolution vessels immediately. As media is left to sit, it will begin to absorb gasses from the environment. Pouring of the media into the vessels should be done as gently as possible to prevent re-aeration of media, and weighing of the media may further help prevent reaeration since you can directly pour media from the source to the vessel.

The main point is that deaeration must be performed sufficiently so when it is measured and poured into the vessel, the level of dissolved gasses still remains well below the level of saturation, which will prohibit bubbles from forming on the vessel and paddle surface and within the mesh of the basket. Deaeration is often overlooked as a critical component of dissolution integrity. Particles rotating around a surface coated with bubbles will experience increased agitation resulting in higher dissolution results. Bubbles forming within the basket mesh will often suppress dissolution results. In either case, dissolved gasses must be removed from media when it is shown to interfere with the test[8].

(5) Prerun analyst checks

The final part of the mechanical calibration procedure is to perform on-going checks of the dissolution unit each time before testing. These checks should ensure the paddles, baskets, basket shafts, and vessels are all clean and in good condition. The analyst will also need to make sure that the vessel temperature is measured each time, and that vibration is not present.

Unfortunately, this may be one of the most subjective portions of the proper execution of MQ. If analysts are not properly trained to recognize equipment problems such as peeling paddle shafts, dented or misshapen baskets or scratched vessels, variability will persist and the MQ may not succeed in detecting sources of variability. These important observations must be properly performed and documented to provide the greatest assurance that the apparatus integrity is maintained. Prior to each run, analysts need to perform appropriate examination and documentation to meet this requirement.

Paddles examination

Paddles should be examined to ensure that they are in appropriate condition for use. Stainless steel paddles tend to be very durable, however, one should check to ensure that there are no defects and that there is no discoloration of the paddle due to corrosion from hydrochloric acid and other dissolution media. PTFE-coated paddles and similarly composed paddles need to be more closely examined for flaking and peeling of the surface which can alter the surface area of the paddle and also provide a site for cross contamination between runs.

Basket examination

The basket should be examined in several ways to ensure proper shape and cleanliness. Since baskets are quite fragile, it is recommended that they be checked prior to each use for excessive wobble, dents, and so on. Wobble can be checked each run visually by rotating the baskets at a low RPM prior to lowering them into the media. If wobble appears to be high, then the analyst can measure with an appropriate run-out gauge. The basket should be checked for dents as well, both on the sides of the basket and the bottom mesh.

Basket cleanliness should be checked as well, especially at the seams between the upper and lower metal rims and the mesh. The baskets should be free of frayed wires and not exhibit any rust spots. Baskets can be effectively and gently cleaned by placing them in a beaker of alcohol and sonicating for five minutes and then allowing them to air dry before placing them in a protected container.

Care should be taken at the beginning of the run to ensure that air is not trapped beneath the basket which restricts flow through the basket and lowers performance.

Vessel examination

The vessel should be inspected when dry to ensure that it is "free of scratches, cracks, pits, and residue[1]". Vessel scratches, cracks, and pits tend to occur in the hemispheric portion of the vessel due to dropped shafts, rough height setting procedures, and so on`. The rim of the vessel should also be inspected closely, as defects in this area can result in compromised vessel centering and verticality. If residue is present, use of alcohols for scummy residue or diluted nitric acid for scaling or other buildup can be used to restore the vessel. The upper portion of the vessel should be "examined to ensure that any material from the waterline mark of the media used in previous tests has been removed [4]."

Conclusion

The mechanical calibration procedure can be a viable alternative to the USP PVT. However, a laboratory must ensure that they are not merely taking measurements of the various physical parameters, but also putting the other procedures and controls in place as required by cGMP. A dissolution apparatus that has been checked through a series of measurements, along with a set of verified components and other laboratory controls, will help maintain low variability and ensure data integrity has been preserved.

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