Toolkit
Dissolution Procedure: Mechanical Calibration and Performance Verification Test
Version 1.0
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The USP Performance test with procedures and acceptance criteria for solid oral dosage forms is specified in General Chapter *Disintegration* <701> and General Chapter Dissolution <711>. These procedures are used both in drug development and quality control. They help assure consistent dosage form performance over time. Dissolution is also used increasingly as a means of documenting bioequivalence. Assurance of the integrity of the dissolution procedure is achieved through careful assembly qualification, analyst training, and use of validated analytical procedures. cGMP's speak to analytical instrumental qualification (AIQ), which includes installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). For dissolution assemblies, the mechanical calibration steps in this guide should satisfy OQ and parts of IQ. PQ may be satisfied by a performance verification test (PVT), in support of which USP makes available official USP Reference Standard Tablets (Prednisone Tablets and Salicylic Acid Tablets). The Guide contains five parts with an Appendix.

I: Mechanical Calibration
II: Performance Verification Test
III: Frequency of qualification
IV: Nomenclature
IV: References
Appendix.

I. Mechanical Calibration

Equipment Needed

Equipment should be using tools calibrated and traceable to national metrologic or other suitable standards. Users are encouraged to contact manufacturers to assure proper function and use.

Level—measures horizontal and vertical (plumb) orientation of the assembly with a sensitivity of 0.5°. A level can be checked for accuracy by the following methods.

Trueness Test--determines the suitability of a level. Place the working surface of the level on a horizontal surface. Note the reading for a digital level or position of the bubble for a spirit level. Rotate the level 180° on the horizontal plane. The reading or position of the bubble should be the same. Repeat the procedure for the opposite working surface of the level. A similar procedure can be used with vertical surfaces as a reference.

Sensitivity Test--determines the sensitivity of the level for use in operational qualification of dissolution assemblies. Place the level on a horizontal surface (vertical surface) and under one end place a feeler gauge of the appropriate thickness so that the offset at that end produces an angle of 0.5 between the surface and the surface of the level. The deviation of the position of the bubble or the reading is noticeable in comparison to that observed with no feeler strip in place. [Note an angle of 0.5° can be produced for a 6-inch (15 cm) level with and offset of 0.052″ (1.32

mm); for a 24-inch (60 cm) level the offset should be 0.209″ (5.32 mm)] The sensitivity must be determined on all surfaces of the level that will be used to determine levelness of the dissolution vessel support plate, drive unit plate, or the verticality of the stirring element shaft or vessel walls.

Tachometer—measures revolutions per minute with sensitivity less than 0.5 rpm. Tachometers may be mechanical or optical.

Vibration Meter—measures displacement, acceleration, and frequency. The sensing device should be able to be placed on both vertical and horizontal surfaces of the assembly (oriented in 'x', 'y', and 'z' directions).

Caliper—measures distance between two opposing points or surfaces. The trueness and precision of measurement by a caliper can be checked using gauge blocks. Gauge blocks are standardized materials that represent a range of distances and are used as reference distances for calibration of measuring tools.

Compass—transfers a distance from an otherwise inaccessible position to a location where the distance can be determined using the caliper . Compasses can have inward or outward-facing points to allow the transfer of inner or outer distances. The tips of the compass are adjusted to fit across the points to be measured and fixed, the compass is then removed, and the distance between the tips measured.

Centering Gauge—determines centering of the apparatus shaft within the vessel. Distances given by this gauge are checked with a caliper.

Dial Test Indicator (Runout Gauge)—determines the eccentricity of a rotating surface. Trueness and precision are checked with a caliper or gauge blocks.

Stirring Element Height Gauges—using a caliper, determines or limits the distance between the bottom of the basket or paddle and the vessel bottom.

pH Meter—see <791> pH

Thermometer—see <21> Thermometers

Feeler Gauge—these are small lengths of metal, typically of steel, of different thicknesses with measurements marked on each piece used to provide a standard thickness in the sensitivity test for the level. Gauge blocks typically represent larger thicknesses and can also be used.

Digital Protractor—determines the angle of a surface relative to horizontal or vertical.

1. Environment

Bench tops (1.1)[1]—Bench tops used to support dissolution equipment must be level, sturdy and provide an high inertial mass to limit vibration. Disturbances such as the placement of large volume solution containers may produce transient vibration but should not affect the levelness of the surface. A rough estimate of the levelness of the bench top is the tendency for a metal sphere

[1] Numbers in parenthesis refer to Appendix section.

to remain where it is placed on the surface. Bench top surface tilt of up to 1° in two directions can be compensated by leveling devices provided with modern assemblies.

Vibration (1.2)—minimize vibration sources on the bench top to the extent possible. Vibration from any essential pieces of equipment, such as water circulators for the bath, should be dampened with foam padding or similar material. All non-essential vibration producing equipment should be moved from the bench occupied by the dissolution tester. A vibration meter can be used to measure the vibration level on the motor head plate, bench top, and base plate. The vibration of the environment is measured with the test assembly motor and water bath circulation system turned off. Generally, frequency values below 200 Hz have significant impact on dissolution results. Displacement values below 0.1 mils (0.0254 mm) are achievable and are considered acceptable in the frequency range from 0 to 200 Hz on the bench top, vessel support plate and drive unit head plate. The mechanical components of the assembly may contribute vibration that should be measured during the periodic OQ. Before each test begins the surrounding area should be observed to detect and eliminate obvious sources of vibration. Sources of vibration include but are not limited to: ultrasonic baths, centrifuges, shaker apparatuses, chillers, ovens, fume hoods, tap density testers, pumps, production equipment, stairwells, fork lifts, construction, other laboratory equipment, and trains and automobile traffic. Avoidable sources of vibration such as opening/closing of doors or heavy foot traffic should be discouraged during testing. The contribution of the test assembly drive train to the total vibration can be a diagnostic enabling decisions regarding maintenance.

Air Currents (1.3)—are laboratory design attributes as well as incidental occurrences. Air currents delivered by heating and air conditioning systems can adversely affect the temperature of the dissolution medium in the apparatus, cause temperature gradients in the water bath, or within the dissolution media in bathless systems. Efforts should be made to minimize air current fluctuations during testing periods.

2. Assembly

Apparatus Position Within The Assembly (2.1)— All vessels, shafts, baskets (if applicable) and paddle blades (if applicable) should be uniquely identified, documented, and kept in the same position in the same test assembly for all dissolution runs. Apparatus positions on the baseplate of the dissolution test assembly should be numbered systematically. Numbering counterclockwise starting from the back left position is a possible approach (Figure 1).

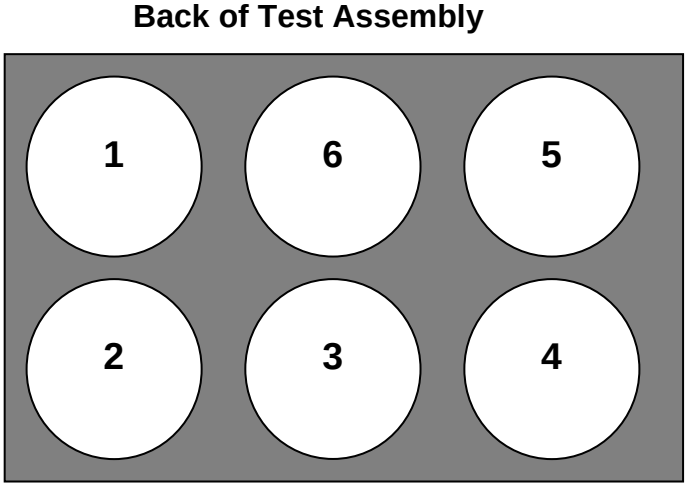

Figure 1. Possible numbering scheme for apparatus positions in a test assembly

Vessel Support Plate (**Baseplate)** (2.2)—supports and precisely positions the vessels used for dissolution testing. The baseplate must be level (nmt 0.5° deviation from horizontal). Levelness is determined in at least two orthogonal directions (at an angle of approximately 90°), spanning a representative surface. The measurement is made on the machined surface that provides support to the vessels. If possible, temporarily remove attachments that protrude from the machined surface to allow the placement of the level. The manufacturer may need to perform this measurement where the design of the assembly does not permit it without disassembly. Measure the levelness of the base plate of the tester in two orthogonal directions using a digital level that has been calibrated. Values must be 0.5° or less. It is recommended to attempt a vessel support plate adjustment to achieve a reading closer to 0.0° in both directions. Measurement is by spirit or electronic level not less than 24 inch (60 cm) in length and calibrated as described under *Equipment Needed* above. Where the clear area of the baseplate does not allow a 24 inch distance for the longer level, a 6 inch level (15 cm) can be used. Check the test assembly for stability. Adjust levelness of the baseplate, if necessary, usually by rotating adjusting screws on the feet of the support and frame assembly. Typically part of the structure is a bull's eye level, similar to what is used on most analytical balances. This tool is used to check the level of the head plate (supporting the drive mechanism, as well to ensure that co-planarity exists. Many assemblies are built in such a way that monitoring more frequently than at the time of the PVT is not necessary. Confirmation of the levelness of the test assembly for use after mechanical qualification by periodic level checks is recommended. The condition of the vessel support plate should be evaluated and found to be uniform, even, and not distorted or misshapen. The vessel support plate should remain planar when burdened with filled vessels.

Motor and Transmission (2.3)
Inspection, cleaning and lubrication (2.3.1)—ensures the proper operation of moving parts of the test assembly. As part of routine maintenance, inspection, cleaning obviously fouled components and, if necessary, lubrication should be performed for all components (i.e., drive belts, spindle assemblies) of the dissolution assembly. Note: this may not be possible for all dissolution test assemblies. Use a minimal amount of lubricant (silicone, waxes, grease) as excess lubricant attracts dirt. Consult assembly manufacturer for correct lubricant and lubrication procedure. While inspecting the drive belt assembly check for proper tension and look for signs of excessive wear on the belts. If possible, rotate the spindle assemblies while observing the belts to ensure proper function. Individual laboratories may assign the maintenance to a special group or individual. Major adjustments may require the intervention of the vendor.

Rotation speed (2.3.2)—is a critical mechanical attribute of the motor and drive system. All manufacturers provide a rotation speed indicator and control mechanism. The provided equipment should be checked against an external calibrated tachometer. Measure the rotation speed of all stirring element shafts using the calibrated tachometer. All measured speeds should be within ± 1 rpm of the set value and should not fluctuate considerably during the measurement.

Wobble and Centering (2.4)
Basket (2.4.1) **—** provides the motion of the dissolution medium and sample during dissolution testing. The straightness of the element shaft is assessed from the deviation of the point of contact

with the probe of the dial test indicator (runout gauge) as the shaft is rotated through 360° with the stirring element removed from the test assembly (Figure 3). This measurement is called intrinsic wobble. The basket and shaft are placed on a set of two v-blocks (device for allowing rotation of a shaft in a fixed position, Figure 2). The shaft is supported for a distance of not less than 80% of its length (tip to top basket attachment flange). Measure intrinsic wobble at the midpoint of the portion of the shaft supported by the v-blocks. Intrinsic wobble is less than 0.5 mm. The total wobble produced from the intrinsic wobble in addition to the contribution from the drive assembly is measured at the bottom basket rim (see Figure 1 in <711> Dissolution) with the stirring element installed. The total wobble contributes to the centering measurement. Total wobble should be less than 1.0 mm.

Paddle (2.4.2) — provides the motion of the dissolution medium and sample during dissolution testing. The straightness of the element shaft is assessed from the deviation of the point of contact with the probe of the dial test indicator (runout gauge) as the shaft is rotated through 360° with the stirring element removed from the test assembly (Figure 3). This measurement is called intrinsic wobble. The paddle and shaft is placed on a set of two v-blocks (device for allowing rotation of a shaft in a fixed position, Figure 2). The shaft is supported for a distance of not less than 80% of its length (tip to top of paddle blade). Measure intrinsic wobble at the midpoint of the portion of the shaft supported by the v-blocks. Intrinsic wobble is less than 0.5 mm.

The total wobble produced from the intrinsic wobble in addition to the contribution from the drive assembly is measured at a point on the shaft just above the paddle blade and with the stirring element installed. The total wobble is part of the centering measurement. Total wobble is less than 1.0 mm when measured 1 cm above the paddle blade.

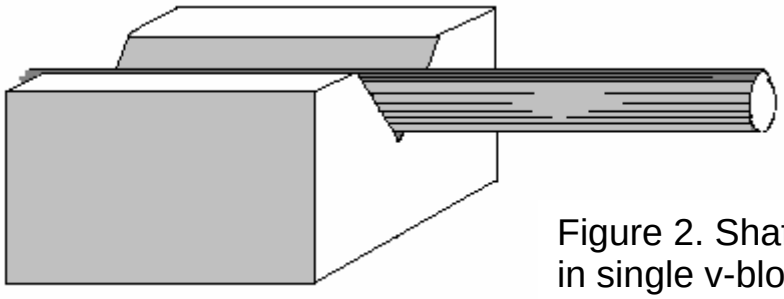

Figure 2. Shaft lying in single v-block

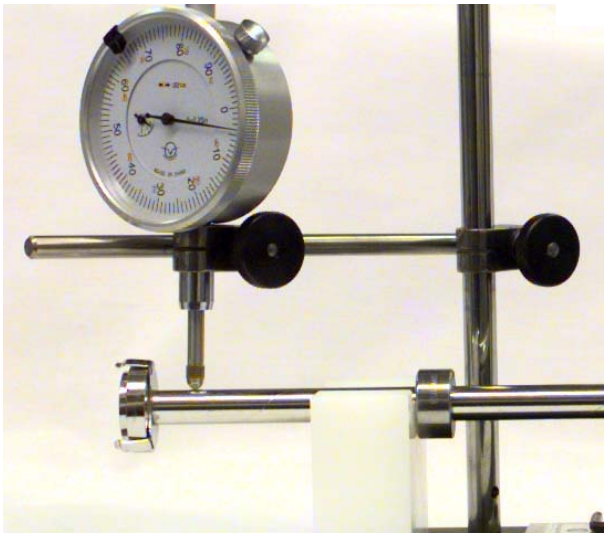

Figure 3. Dial test indicator (runout gauge) showing probe in contact with shaft held at one end by v-block. Note that measurement procedure is normally performed on the midpoint of the shaft held between v-blocks.

Centering (2.4.3)—is the estimate of coincidence of the axis of the stirring element shaft with the axis of the vessel. Determine the centering of the stirring element shaft within the vessel. This optimal condition will exist when the distance from the surface of the shaft to the inner vessel surface is determined to be constant when the shaft is rotated. In practice the ideal will not likely be achieved. Measure the centering using a dial test indicator fixed on the shaft at any position above the basket-flange or paddle wings if the stirring element shaft and the vessel walls are determined to be vertical. Other controls can be applied. Alternatively a caliper may be used to measure the distance. Measurement of the distance is made at several points representing not less than four positions (no more than 90° apart, Figure 4). The difference between the largest and smallest measurements must not be more than 2.0 mm.

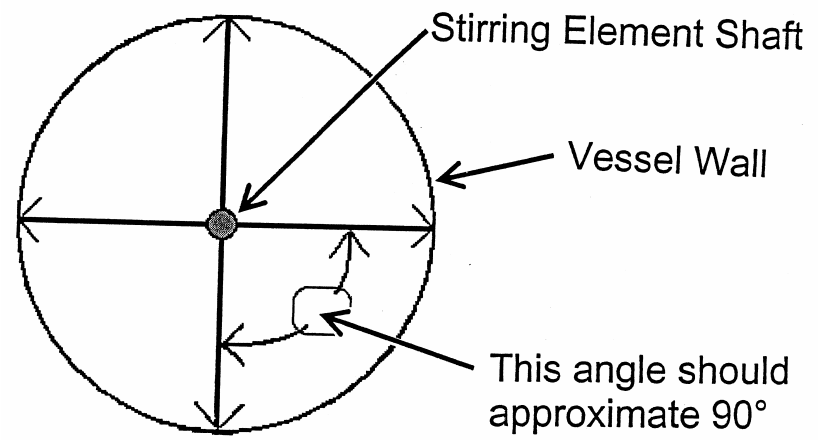

Figure 4. Centering measurement. Four readings are used and that the angle between measurements should not exceed 90°.

Conformance (2.5)
Basket (2.5.1)—Observed dimensions must conform to <711> Dissolution, Figure 1. These should be determined upon receipt and at other suitable intervals due to the tendency of baskets to deform due to mishandling, and also as a result of the reaction of the basket mesh with acid media. The material of construction is vulnerable to acidic media causing surface etching. The diameter of wires composing the basket mesh may change and the mesh openings may also increase as a result. The dimensional conformance of the basket mesh can be estimated using an optical micrometer to check the wire dimensions and the opening size. The magnifying power of the micrometer allows for a check of the wire condition as well.

The mesh sides of the basket cylinder should approach a 90° angle with respect to planes containing the basket end rings. Although gross deviations will be obvious to visual inspection, this can be confirmed by comparison with a machinist's square when both are placed on a planar surface such as a bench top.

Frequency of these determinations of basket integrity should be no less often than the PVT.

Paddle (2.5.2)—Observed dimensions must conform to Figure 2 in <711>. This is determined on receipt from the supplier. The condition of the surfaces of the paddle such as the wings and shaft should be free of defects including scratches, and shredded coating material.

Vessel (2.5.3)—contain the dissolution medium, allow observation of the sample and also provide a hydrodynamic boundary for the moving fluid. The accurate assessment of the performance of a dosage form can only be made with a vessel of standardized geometry, which is clean, not etched or scratched, and positioned so that the boundary presented by its inner walls presents a consistent condition to the flowing medium. Inner diameter when measured at any depth within the cylindrical portion must not vary by more than 1 mm. At any depth the diameters measured at 90° orientation must not vary by more than 1 mm. For the basket and paddle apparatus, the cylindrical portion of the inner vessel surface must be vertical (not less than 0.5° from vertical) when it is suspended from the baseplate. If the vessel is immersed in an isothermal bath, the bath fluid should be clear to allow observations to be made. Vessels conform to dimensional requirements of <711> Dissolution.

Vessel symmetry and dimensional attributes that may have influence over the observed dissolution rate are the following.

Axis: datum line describing the ideal center of revolution of the inner cylindrical surface of the vessel.
Cylinder inner diameter: measurement across the cylindrical portion of the vessel and through the axis.
Cylinder circularity: a condition of the inner surface of the vessel cylinder where all points of the surface that are intersected by a plane perpendicular to the vessel axis are equidistant from the axis.
Cylindricity: a condition of the inner surface of the vessel cylinder in which any point of the surface is equidistant from the axis.
Perpendicularity: angular relationship between the plane containing the points on the lower surface of the vessel support flange and the axis.
Center: datum point describing the center of revolution of the inner spherical surface of the vessel.
Spherical radius: distance from the points on the inner surface of the spherical portion of the vessel to the center.
Circularity of the hemisphere: a condition of the inner surface of the spherical portion of the vessel where all points of the surface intersected by any plane containing the center are equidistant from the center.
Concentricity between center of the hemisphere and the axis of the cylinder: a condition where the center lies on the axis.
Flatness of bottom surface of flange: a condition of the bottom surface of the flange where all of the points lie in a plane relative to each other.

Temperature Control (2.6)
Water bath (2.6.1)—provides a reproducible environment for the dissolution process. The assembly will have a temperature control mechanism integrated in its design. The heating efficiency is also an important attribute of the temperature control. Determine the time that the water bath filled with room temperature water can be brought to the operating temperature, about 37°. This will be characteristic for the particular test assembly and may be recorded and used to assess the condition of the heater and circulator over time. Logbooks should be kept for all test assemblies where the maintenance, repairs and qualification information is tracked.
The accuracy of the temperature control and output is an important operational variable. The operator will set a temperature for the bath, typically a few tenths of a degree higher than the test

temperature intended for the dissolution medium. This is done to counteract heat loss by the dissolution test medium to the stirring element for example. The accuracy of the control and output device will be determined by measuring the temperature of the water bath with a calibrated thermometer. Any difference between the set point or output and the measured temperature should be recorded. The difference should not be more than ±0.1°. The efficiency and stability of the temperature control of the water bath can be determined by observing the temperature of the water bath as it is heated following bath cleaning. The time taken for the bath to reach operating temperature should be recorded.

Bathless systems (2.6.2)—are assessed by the ability to heat and maintain temperature of dissolution medium. Evaluation of the time required to bring medium from room temperature to 37°, for each vessel position should be made. The relationship of the intended or set temperature to that measured in the medium should be documented as well as the precision of temperature measured for all vessel positions. Medium temperature should agree with set point within ±0.1°.

Abbreviated Mechanical Checks (2.7)—are performed as a subset of the full performance of the mechanical calibration procedures listed in this document. The full performance of the mechanical calibration procedures requires a considerable expenditure of resources but should take place no less than quarterly. The abbreviated mechanical checks are run just prior to execution of a dissolution procedure. The purpose of the abbreviated mechanical checks is to ensure that no gross changes in operational qualification variables have occurred that would compromise the quality of the test. The checks include: visual inspection of the condition of the vessels, water bath, baskets, and paddles; centering, and water bath and vessel medium temperature. The speed of a single position stirring element should also be checked at this time. Documentation of the results of these checks will serve to support the quality of dissolution testing data obtained.

II. Performance Verification Test

The Reference Standard Tablets used in the PVT should be stored as described in the certificate.

Medium (3.1)—The PVT for baskets and paddles uses a specific medium for each of the supplied official USP RS Tablets. The medium is deaerated. Volume is measured to within ± 1% specified.

Prednisone Tablets (3.1.1)—use deaerated purified water
Medium deaeration using the USP procedure is recommended. Other deaeration procedures are permissible, but they should be demonstrated to be equivalent to the USP procedure. This can be verified using a dissolved gas meter. For testing with USP Prednisone Tablets RS, a dissolved oxygen level of not more than about 6 ppm has been shown to be acceptable. (If nitrogen sparging is used, the dissolved oxygen level will not be an adequate measure.) Dissolution test results for other drug products may not show the same sensitivity to dissolved gas content.

Salicylic Acid Tablets (3.1.2)—transfer a 41-g portion of monobasic potassium phosphate into a 6-L volumetric flask, and dissolve in 5.8 L of purified water. Add portions of sodium hydroxide solution 50% (w/w) to obtain a pH of 7.4 ± 0.05. Dilute this solution with water to volume and mix. Readjust the pH , if necessary, with sodium hydroxide solution or phosphoric acid. The formula may be adjusted to produce a volume other than 6 liters. The medium is deaerated prior to use.

USP Deaeration procedure **(**3.1.3)—Heat an appropriate volume of the medium to approximately 45°. Vacuum filter through a 0.45-µm membrane filter (Millipore HVLP, or equivalent). Continue to stir medium under vacuum for an additional 5 minutes, with stirring (the measured vacuum should be less than 100 mbar). Transfer the heated, degassed solutions gravimetrically to each of the vessels and allow to equilibrate to 37.0° ± 0.5° in the tester. Degassed media should be handled and used with care. The dissolved gas content will tend to increase and procedures that increase the mixing of the dissolution medium or increase the area of contact between the atmosphere and the medium will tend to increase the rate of re-equilibration. A minimal time should be planned for thermal equilibration of the medium when in the test assembly. Not more than 30 minutes should be allowed for the medium to reach the test temperature to minimize re-aeration. The dissolved gas content will increase on standing and during the test so promptness in initiating and completing the run is essential.

Medium Temperature (3.1.4)—is confirmed in each vessel prior to the start of any testing and upon its completion. Confirm that the medium has reached the allowable range of the test temperature by determining that no change occurs over a 2-3-minute interval.

Start of PVT (3.2)
Scope (3.2.0)—is for apparatus placed in all positions.

Baskets (3.2.1)— the test is considered to start when the basket is in position and in motion. The position for testing is with the bottom of the basket between 23 and 27 mm above the bottom of the vessel. Floating dosage forms observed in the baskets may show reduced dissolution rates due to adherence of air bubbles and the resulting decrease in surface area presented to the medium. Record the start time of the dissolution test and/or use a calibrated timing device. Carefully note any visual observations of the dissolution test, such as basket wobble, air bubble formation, unusual particle behavior, floating tablets, etc.

Paddles (3.2.2)—the test is considered to start when the tablet has come to rest at the bottom of the vessel and the paddle rotation has begun. The bottom of the paddle blade is not less than 23 mm and not more than 27 mm from the bottom of the vessel. Close attention should be given to starting the testing promptly and introducing the tablet into the medium in a standardized manner, e.g., along the vessel wall or at the center of the vessel along the paddle shaft. The most reproducible conditions will exist with the sample settled directly under the paddle shaft (e.g., on the vessel axis).

Timing (3.2.3)—Record the start time of the dissolution test and/or use a calibrated timing device. The type of starting procedure must allow for sample collection and filtration of all positions within the current ± 2% tolerance limit for time (± 36 seconds for a 30 minute run). A staggered start is recommended for Apparatus 2 runs, if possible on the tester.

Observations (3.2.4)—Carefully note any visual observations of the dissolution test, such as basket wobble, air bubble formation, unusual particle behavior, floating tablets, etc.

Sampling (3.3)—Withdrawal of the sample and filtration of the sample aliquot concludes the test interval. After 30 minutes of testing and with rotation continuing, withdraw a portion of the dissolution medium from each vessel. Withdraw from a zone midway between the surface of the dissolution medium and the top of the basket or top of the paddle blade, not less than 1 cm from the vessel wall.
Filter each sample immediately through a syringe filter (0.45-µm Millipore Millex ® -HV PVDF, or equivalent), discarding the first 5 mL portion of filtrate. Cool the filtered dissolution samples

to ambient temperature prior to UV analysis (sample and standard solutions are at the same temperature). Do not centrifuge the sample. A separate unused filter and clean syringe should be used for each vessel.

Automated Sampling (3.3.1)—If used, automated sampling methods and alternate filter probes should be validated against the manual sampling method. Variables include, carry over from system surfaces exposed to test solution, dwell time for on-line spectrophotometric analysis, and filter interference. Ideally, sampling probes will retract from the dissolution medium when not in use.

Analytical Procedure (3.4)— for sample solutions is by Ultra-Violet Spectrophotometry in comparison with the absorbance of the appropriate reference standard material dissolved in dissolution medium. Prepare two independent standard preparations, a working standard and a control standard. Prepare the standards on the day of use. An example procedure for standard preparation for testing with 10-mg Prednisone Tablets RS is as follows:

> Transfer about 25 mg of USP Prednisone RS to a 25.0 mL volumetric flask. Dissolve in approximately10 mL alcohol with sonication. After cooling to ambient temperature, dilute to volume with alcohol. Dilute the stock solution 5.0 mL/500.0 mL with purified water.

Perform UV measurements at the wavelength of maximum absorption (for prednisone, 242 nm, for salicylic acid, 296 nm) using a quartz cell with a 1.0 cm path-length. Using Beer's law, the calculated absorptivities of the working and control standards should be in agreement with historic values and within 1% of each other. [For 127 standard solutions prepared by six different chemists over a five month period beginning in September 2005 the absorptivity of prednisone working standard solutions was 43.6 ± 0.6 AU cm^2 mg^{-1} (mean ± SD) measured at 242 nm .]

III. Periodicity

USP recommends the following periodicity associated with mechanical calibration and performance verification testing procedures.

1. Abbreviated Mechanical Checks: prior to dissolution procedure
2. Full mechanical calibration: three month intervals
3. PVT: six month intervals. Both Apparatuses 1 and 2 need not be evaluated if only one Apparatus is used in the test assembly.
4. PVT when an assembly is installed, moved or repaired.
5. For bioequivalence studies: mechanical calibration and PVT prior to and following execution of a study.

IV. Nomenclature

Apparatus: The basic unit for the in-vitro performance testing of dosage units. The apparatus consists of a container (vessel) for the dosage unit and dissolution medium, a device for promoting motion of the dissolution medium (stirring element), temperature control and support

to hold the vessel and stirring element in a fixed orientation. Typically, multiple apparatuses are grouped in a dissolution test assembly.

Stirring Element: A paddle, rotating basket and shaft, or other device for promoting the movement of dissolution medium relative to the dosage unit under test.

Position: Location within a dissolution test assembly where a particular apparatus is employed.

Assembly: A combination of multiple apparatuses providing common temperature control, controlled unified motion of stirring elements, and providing the opportunity for simultaneous or individual start of the apparatuses.

Vessel Support Plate (Baseplate): The structural element of the test assembly that positions and provides support for the vessels during testing.

Drive Unit Plate: Support structure for the drive mechanism for stirring elements. The moving parts of the drive unit are protected from contamination by a cover that also provides protection against injury to the operator. The drive unit cover will not be typically considered to represent a suitable surface on which the level of the drive unit plate can be determined.

Dissolution System: test assembly connected to sampling and filter unit without chemical analysis such as UV/VIS or HPLC.

Run: Common terminology for the dissolution sample preparation procedure. May include multiple sampling intervals, but is concluded by the withdrawal of the samples at the final specified time point.

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Appendix

Mechanical Calibration and Performance Verification Test for Dissolution Test Assemblies Employing Apparatuses 1 (Baskets) and 2 (Paddles)—Quick Outline

Environment

1.1 Bench tops: Level (surface tilt nmt 1°); sturdy and massive

1.2 Vibration: Minimize sources on the bench; measure vibration level on drive unit, vessel support plate, and bench top (frequency values below 200 Hz and displacement above 0.1 mils (0.0254 mm); be aware and limit transient sources (such as door slams and heavy foot traffic) 1.3 Air Currents: Heating/cooling systems and incidental drafts may create temperature gradients

Assembly

2.1. Apparatus position within the Assembly: Dedicated positions for apparatus (stirring elements, and vessels; designate numbering or other identifiers.

2. 2 Vessel Support Plate (Baseplate): Surface level (not more than 0.5° from horizontal in two directions 90° apart); adjust if necessary; surface planar and not noticeably deformed when supporting full vessels

2.3 Motor, and Transmission

2.3.1 Inspection, Cleaning, and Lubrication: Moving parts inspected, cleaned, lubricated (follow manufacturer's instructions and use recommended lubricants)

2.3.2 Rotation Speed: Each shaft position checked by external tachometer (within 1 rpm); compare tachometer output to integrated meter; daily check for one position

2.4 Wobble and Centering

2.4.1 Basket: Installed in drive assembly the wobble should not exceed 1.0 mm at the bottom basket rim (Position "A" in Figure 1 <711> Dissolution).

2.4.2 Paddle: Installed in drive assembly the wobble should not exceed 1.0 mm on shaft within 1 cm of paddle blade.

2.4.3 Centering: Each vessel position; shafts positioned in vessels as for testing; measurement is distance from shaft to inner vessel wall; made in two diametric positions (wall to shaft, shaft to wall, across vessel) that are oriented at about 90° to each other (not more than 2.0 mm difference among measurements)

2.5 Conformance

2.5.1 Basket: Dimensions as given in Figure 1, <711> Dissolution; wire mesh examined for condition using optical micrometer; sides of basket 90° to plane of end rings; at time of use, evaluate for gross defects.

2.5.2 Paddle: Dimensions as given in Figure 2, <711> Dissolution; at time of use examine for scratches and peeling coating

2.5.3 Vessels: Dimensions as given in <711> Dissolution; diameter constant at various depths (measure in two directions 90° apart, no more than 1 mm difference for all measurements); flange should sit on vessel support plate with no gaps and should be stable; when installed on vessel support plate, inner vessel walls should be vertical (no more than 0.5°); at time of use, vessel walls should be visually inspected for scratches and films.

2.6 Temperature Control

2.6.1 Water Bath (if applicable): Time to reach set temperature; accuracy of output device (temperature output should agree with calibrated thermometer to ±0.1°)

2.6.2 Bathless system: Evaluate as described for water bath

Performance Qualification (PVT)

Performance Verification Test

3.1 Medium: Use dearated medium; volume measured to within 1% specified.

3.1.1 Prednisone Tablets: Purified water; deaeration to oxygen level of 6 ppm; <711> Dissolution gives recommended procedure; medium re equilibrates so once deaerated prompt use is recommended; do not allow temperature to fall below test temperature once deaerated;

3.1.2 Salicylic Acid Tablets: Phosphate Buffer pH 7.4

3.1.3 USP Deaearation Procedure: Filtered and stirred under vacuum; avoid re-equilibration to saturation

3.1.4 Medium Temperature Individual vessels monitored before and after each dissolution run; All vessels are within allowable range of test temperature; Temperature stable in each vessel (not more than 0.1° change over 2 to 3 minute interval)

3.2 Start of PVT

3.2.1 Baskets: Basket lowered to position (25 ± 2mm from vessel bottom); rotation started (observe rpm); timing initiated

3.2.2 Paddles: Paddles in position (25 ± 2mm from vessel bottom); sample settles to bottom (directly under paddle shaft); rotation started (observe rpm); timing initiated

3.2.3 Timing: Tolerance for total time from basket in position and rotating to sampling is ±2%

3.2.4 Observations: Document observations

3.3 Sampling: With rotation continuing, withdraw aliquot midway from medium surface and top of basket or top of paddle blade; filter immediately (syringe filter, 0.45-µm Millipore Millex ® HV PVDF, or equivalent; discard first 5 mL filtrate); resident sampling probes not ideal

3.3.1 Automated Sampling: Validated; probes should not remain in medium during test

3.4 Analytical Procedure: Temperature of sample and standard solutions the same; preparation of standard monitored by having a second independent ‘check standard’