Updated USP Monograph 1092
Updated USP Monograph 1092

- USP 711 (Dissolution) late 1960
- USP 724 (Drug Release) 1985
- USP 1088 (In Vitro and In Vivo Evaluation of Dosage Forms) 1995
- **USP 1092 (The Dissolution Procedure Development and Validation): Total Revision August 2015**
- USP 1094 CAPSULES—DISSOLUTION TESTING AND RELATED QUALITY ATTRIBUTES
- USP 2040 Disintegration and Dissolution of Dietary Supplements

- EP 2.9.3 Dissolution late 1960
- EP 2.9.4 Dissolution for Transdermal Systems late 1970

**Harmonization in the year 2006 between USP, EP and JP**
Updated USP Monograph 1092

• **USP 1092**
  1.1 Performing Filter Compatibility
  1.2 Determining Solubility and Stability of Drug Substance in Various Media
  1.3 Choosing a Medium and Volume
  1.4 Choosing an Apparatus

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• **ACCEPTANCE CRITERIA**
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  6.2 Delayed-Release Dosage Forms
  6.3 Extended-Release Dosage Forms
1.1. Performing Filter Compatibility

- Filtration is a key sample-preparation step in achieving accurate test results.
- The purpose of filtration is to remove undissolved drug and excipients from the withdrawn solution.
- The filter material has to be compatible with the media and the drug. Common pore sizes range from 0.20 to 70 µm, however, filters of other pore sizes can be used as needed.
- Prewetting of the filter with the medium may be necessary. In addition, it is important that leachables from the filter do not interfere with the analytical procedure. This can be evaluated by analyzing the filtered dissolution medium and comparing it with the unfiltered medium.
1.1. Performing Filter Compatibility

- The filter size should be based on the volume to be withdrawn and the amount of particles to be separated. Use of the correct filter dimensions will improve throughput and recovery, and also reduce clogging. Use of a large filter for small-volume filtration can lead to loss of sample through hold-up volume, whereas filtration through small filter sizes needs higher pressures and longer times, and the filters can clog quickly.
- Flow rate through the filter and clogging may be critical for filters used in automated systems.
1.1. Performing Filter Compatibility
1.1. Performing Filter Compatibility
1.2 Determining Solubility and Stability of Drug Substance in Various Media

- When deciding the composition of the medium for dissolution testing, it is important to evaluate the influence of buffers, pH, and if needed, different surfactants on the solubility and stability of the drug substance.
- Typical media for dissolution may include the following (not listed in order of preference): diluted hydrochloric acid, buffers (phosphate or acetate) in the physiologic pH range of 1.2–7.5, simulated gastric or intestinal fluid (with or without enzymes), and water.
- Use of Surfactants for poorly soluble drugs.
<table>
<thead>
<tr>
<th>Surfactant</th>
<th>CMC (% wt/volume)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium dodecyl sulfate (SDS), Sodium lauryl sulfate (SLS)</td>
<td>0.18%–0.23%</td>
<td>(2–4)</td>
</tr>
<tr>
<td>Taurocholic acid sodium salt</td>
<td>0.2%</td>
<td>(3)</td>
</tr>
<tr>
<td>Cholic acid sodium salt</td>
<td>0.16%</td>
<td>(3)</td>
</tr>
<tr>
<td>Desoxycholic acid sodium salt</td>
<td>0.12%</td>
<td>(3)</td>
</tr>
<tr>
<td>Cetyltrimethyl ammonium bromide (CTAB, Hexadecyltrimethylammonium bromide)</td>
<td>0.033%–0.036% (0.92–1.0 mM)</td>
<td>(5,6)</td>
</tr>
<tr>
<td>Benzethonium chloride (Hyamine 1622)</td>
<td>0.18% (4 mM)</td>
<td>(2)</td>
</tr>
<tr>
<td>Polysorbate 20 (Polyoxyethylene (20) sorbitan monolaurate, Tween 20)</td>
<td>0.07%–0.09%</td>
<td>(3,7)</td>
</tr>
<tr>
<td>Polysorbate 80 (Polyoxyethylene (20) sorbitan monooleate, Tween 80)</td>
<td>0.02%–0.08%</td>
<td>(3,7)</td>
</tr>
<tr>
<td>Caprylocaproyl polyoxyl-8 glycerides (Labrasol)</td>
<td>0.01%</td>
<td>(4)</td>
</tr>
</tbody>
</table>
1.3 Choosing a Medium and Volume

- When developing a dissolution procedure, one goal is to have sink conditions, which are defined as having a volume of medium at least three times the volume required to form a saturated solution of drug substance.

- The use of enzymes in the dissolution medium is permitted, in accordance with Dissolution 711, when dissolution failures occur as a result of cross-linking with gelatin capsules or gelatin-coated products.
1.3 Choosing a Medium and Volume

A (0.40 : 1)
1.4 Choosing an Apparatus

- For solid oral dosage forms, Apparatus 1 and Apparatus 2 are used most frequently.
- Some changes can be made to the compendial apparatus; for example, a basket mesh size other than the typical 40-mesh basket (e.g., 10-, 20-, or 80-mesh) may be used when the need is clearly documented by supporting data. Care must be taken that baskets are uniform and meet the dimensional requirements specified in 711.
- **Peak Vessels do not comply with USP.....can be used for research and development.**
1.4 Choosing an Apparatus

- A noncompendial apparatus may have some utility with proper justification, qualification, and documentation of superiority over the standard equipment. For example, a small-volume apparatus with mini paddles and baskets may be considered for low-dosage strength products.
- A rotating bottle or dialysis tubes may have utility for microspheres and implants, peak vessels, and modified flow-through cells for special dosage forms including powders and stents.
1.4 Choosing an Apparatus
2.1 Deaeration

The significance of deaeration of the dissolution medium should be determined because air bubbles can act as a barrier to the dissolution process if present on the dosage unit or basket mesh and can adversely affect the reliability of the test results. Furthermore, bubbles can cause particles to cling to the apparatus and vessel walls. Bubbles on the dosage unit may increase buoyancy, leading to an increase in the dissolution rate, or may decrease the available surface area, leading to a decrease in the dissolution rate.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Speed (rpm)</th>
<th>Buffer/Conditions</th>
<th>NBL</th>
<th>Test Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine Besylate/Valsalartan</td>
<td>Tablet II (Paddle)</td>
<td>75</td>
<td>Phosphate Buffer, pH 6.8</td>
<td>1000</td>
<td>06/06/2013, 07/21/2011</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>For Oral Suspension II (Paddle)</td>
<td>50</td>
<td>Water (degassed)</td>
<td>900</td>
<td>06/06/2013, 07/21/2011</td>
</tr>
<tr>
<td>Amphetamine ER</td>
<td>Capsule II (Paddle)</td>
<td>50</td>
<td>750 ml of dilute HCl, pH 1.1 for the first 2 hours, then add 200 ml of 200 mM phosphate buffer, and adjust to pH 6 (w/ HCl or NaOH) for the remainder</td>
<td>750</td>
<td>06/06/2013, 07/21/2011</td>
</tr>
<tr>
<td>Aspirin/Dipyridamole</td>
<td>Capsule I (Basket)</td>
<td>100</td>
<td>0.01 N HCl for first hour, 0.1 M Phosphate Buffer, pH 5.5, thereafter</td>
<td>0-1 hrs: 900 mL. 900 mL thereafter</td>
<td>06/06/2013, 07/21/2011</td>
</tr>
</tbody>
</table>

2. METHOD DEVELOPMENT

- Peak Vessels are available
- Alfuzosin Holder
- Felodipine Basket
- Dispensation Releaser for Nanoparticles containing Testmaterial
- New PTWS 1220 12+2 Vessel Dissolution Tester
- New Automatic Media Addition System
Method Development, Software structure
• Method development, Calibration

Dilution curve requires at least two spectra to be measured.

The concentration curve is absorbance at the specified wavelength as a function of concentration.

The concentration curve can be displayed while creating the calibration. Changes of wavelength or data will immediately be reflected in the chart. The chart is empty if the calibration is invalid.
2.2 Sinkers

Table 2. Wire Sinkers Used With Common Capsule Shell Sizes

<table>
<thead>
<tr>
<th>Capsule Shell Size</th>
<th>Length of Wire (cm)</th>
<th>Diameter Size (cm)</th>
<th>Cork Bore Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>#0, elongated</td>
<td>12</td>
<td>0.8</td>
<td>4</td>
</tr>
<tr>
<td>#1 and #2</td>
<td>10</td>
<td>0.7</td>
<td>3</td>
</tr>
<tr>
<td>#3 and #4</td>
<td>8</td>
<td>0.55</td>
<td>2</td>
</tr>
</tbody>
</table>

Sinkers are often used to adjust the buoyancy of dosage forms that would otherwise float during testing with Apparatus 2.

For materials, use 316 stainless steel wire, typically 0.032 inch/20 gauge, or other inert material and wind the wire around cylinders of appropriate diameter (e.g., cork borers) for an appropriate number of turns to fit the capsule shell type.
2.2. Sinkers
2.3 Agitation

- For immediate-release capsule or tablet formulations, Apparatus 1 (baskets) at 50–100 rpm or Apparatus 2 (paddles) at 50 or 75 rpm are used commonly. Other agitation speeds are acceptable with appropriate justification. Rates outside 25–150 rpm for both the paddle and the basket are usually not appropriate because of mixing inconsistencies that can be generated by stirring too slow or too fast. Agitation rates between 25 and 50 rpm are generally acceptable for suspensions.
2.4 Study Design, 2.4.1 time points

- For immediate-release dosage forms, the duration of the dissolution procedure is typically 30–60 min; in most cases, a single time point specification is adequate for pharmacopeial purposes.
- Industrial and regulatory concepts of product comparability and performance may require additional time points, which may also be required for product registration or approval.

Monograph with Method description for Biowaivers:
www.fip.org/bcs_monographs
So-called infinity points can be useful during development studies. To obtain an infinity point, the paddle or basket speed is increased at the end of the run (after the last time point) for a sustained period (typically, 15–60 min), after which time an additional sample is taken. Although there is no requirement for 100% dissolution in the profile, the infinity point can be compared to content uniformity data and may provide useful information about formulation characteristics during initial development or about method bias.

Pharma Test Features Infinity Tests
2.4 Study Design, 2.4.1 time points
Media Addition for „Half Change“ Dissolution Tests

Pharma Test automated Media Addition Station
2.4 Study Design, 2.4.1 time points

Media Addition for „Half Change“ Dissolution Tests

Pharma Test automated Media Addition Station
2.4 Study Design, 2.4.1 time points

• According to the Biopharmaceutics Classification System referred to in several FDA Guidances, highly soluble, highly permeable drugs formulated into very rapidly dissolving products need not be subjected to a profile comparison if they can be shown to release 85% or more of the drug substance within 15 min. For these types of products, a one-point test or disintegration will suffice. However, most products do not fall into this category. Dissolution profiles of immediate-release products typically show a gradual increase reaching 85%–100% at about 30–45 min.

• If the f2 similarity factor is to be used, multiple time points for the dissolution test are required, with at least two time points with mean percent dissolved (typically for n = 12) below 85% dissolved and only one point above 85% for both products (16). Therefore, the addition of early time points may be useful.
## BIOWAIVER Requirements/BCS System

<table>
<thead>
<tr>
<th>Class</th>
<th>Solubility</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Highly soluble</td>
<td>Highly permeable</td>
</tr>
<tr>
<td>II</td>
<td>Poorly soluble</td>
<td>Highly permeable</td>
</tr>
<tr>
<td>III</td>
<td>Highly soluble</td>
<td>Poorly permeable</td>
</tr>
<tr>
<td>IV</td>
<td>Poorly soluble</td>
<td>Poorly permeable</td>
</tr>
</tbody>
</table>
### Solubility Permeability BCS classification

<table>
<thead>
<tr>
<th>Solubility</th>
<th>Permeability</th>
<th>BCS classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>high</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(e.g. Propranolol)</td>
</tr>
<tr>
<td>low</td>
<td>high</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(e.g. Glibenclamide)</td>
</tr>
<tr>
<td>high</td>
<td>low</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(e.g. Atenolol)</td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(e.g. Azathioprine)</td>
</tr>
</tbody>
</table>

2.4 Study Design, 2.4.1 time points
Comparative Dissolution Tests ie Biowaiver and Stability Tests using f2

Pharma Test 12 + 2 Vessel Dissolution Tester PTWS 1220
And PTWS D620 (Double Motor)
PTWS 1220 and PTWSD620 (12+2 Vessel Dissolution Tester)

Advantages:
- f2 Tests always require the Test of 12 Tablets
- Same Testtime, Same Temperature, Same Stirrer Speed, Same Sampling Times for all 12 Tablets
- Staggered Start is possible to allow timeshifted Teststart
- Mechanical Calibration According to all Pharmacopoeia, Only one Protocol for IQ, OQ, PQ and other Validation Documents are needed.
- Automation with only one Set of Equipment such as Pumps and Spectrophotometer. Only One Software Package. And only one Set of Validation Documents for the additional Instruments
- Wider Range for Prednisone Test according to USP (Only one Test is required for 12 Vessel Bathes)
- With PTWSD620 high degree of Flexibility. 6 Front Row Vessels and 6 Back Row Vessels are driven by a individual Motors.
- Minimum Space required
- Convenient Price compared to 2 Dissolution Instruments with 6/8 Vessels
2.4.2 Observations

- Visual observations and recordings of product dissolution and disintegration behavior are useful because dissolution and disintegration patterns can be indicative of variables in the formulation.
- For visual observation, proper lighting (with appropriate consideration of photo-degradation) of the vessel contents and clear visibility in the bath are essential. Formulation or manufacturing process.
- It is important to record observations of all six vessels to determine if the observation is seen in all six vessels,
2.4.2 Observations

Deaerated

Not Deaerated

Note the cone shapes and amount of flowing particles!
Observations are:

• Uneven distribution of particles throughout the vessel
• Air bubbles on the inside of the vessel or on the apparatus or dosage unit
• Dancing or spinning of the dosage unit
• Adhesion of particles to the paddle or the inside of the basket
• Observation of the disintegration rate
• Whether the dosage form lands in the vessel center or off-center, and if off-center, whether it sticks there
2.4.3 Sampling

• For manual sampling, use chemically inert devices (e.g., polymeric or glass syringes, and polymeric or stainless steel cannula), a filter, and/or a filter holder

• The sampling site must conform to specifications in 711

• Replacement is not preferred because the dosage unit may be disturbed during delivery of the media. However, replacement may be necessary if maintaining sink conditions is a challenge. With replacement, the volume used in the calculations remains the same throughout the time points, but there is some drug substance withdrawn with each sample that will need to be accounted for in the calculations.
2.4.3 Sampling

- Outer Tube
- Inner Tube
- ITM Temperature Sensor
2.4.4 Cleaning

• Importance is placed on evaluation of the cleaning process between tests.
• Residues on the vessels can affect the results (e.g., adsorbed residues may dissolve and alter subsequent media properties or interfere with the sample analysis), and effective cleaning will return them to a suitable state.
• Vessel Washer
2.4.4 Cleaning

• New Vessel Washer

Easy-Ease of Use. It’s small and compact size in addition with small weight makes the apparatus easy to move.

Comfortable use through its touch-screen display and its silent operation.

Versatile instrument that can be used with all 1 liter USP dissolution vessels, as well as for 2 liters and 500ml vessels, including plastic vessels and special dissolution vessels like rimless vessels.

On-site cleaning makes unnecessary vessel removal, avoiding vessels repositioning, breakage and recalibration.

Fast cleaning operation, typically 20 seconds per vessel highly increasing laboratory dissolution testing capacity.

Efficient and homogeneous vessel cleaning.

Standard Validated Method included with calibrating tablets.
3.1 Sample Processing

- After the samples are withdrawn from the dissolution medium, they may require additional processing to make them suitable for the analytical methodology
- Filtration for UV-VIS, HPLC
3.4 Analytical Procedure

The usual assay for a dissolution sample employs either a spectrophotometric procedure or a liquid chromatographic procedure. Spectrophotometric determination may be direct or may provide the detection for HPLC. Spectrophotometric determination is used often because results can be obtained faster, the analysis is simpler, it is easier to automate, and fewer solvents are needed.
3.5 Spectrophotometric Analysis

- Direct spectrophotometric analysis may be performed on samples that are manually introduced to the cuvette
- Samples may be automatically introduced into the spectrophotometer
- Cells with path lengths ranging from 0.02 cm to 1 cm are typically used
3.5 Spectrophotometric Analysis

EP 2.2.25

Control of absorbance. Check the absorbance using suitable filters or a solution of potassium dichromate R at the wavelengths indicated in Table 2.2.25-2, which gives for each wavelength the exact value and the permitted limits of the specific absorbance. The table is based on a tolerance for the absorbance of ± 0.01.

For the control of absorbance, use solutions of potassium dichromate R that has been previously dried to constant mass at 130 °C. For the control of absorbance at 235 nm, 257 nm, 313 nm and 350 nm, dissolve 57.0-63.0 mg of potassium dichromate R in 0.005 M sulphuric acid and dilute to 1000.0 ml with the same acid. For the control of absorbance at 430 nm, dissolve 57.0-63.0 mg of potassium dichromate R in 0.005 M sulphuric acid and dilute to 100.0 ml with the same acid. Suitable certified reference materials may also be used.

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Specific absorbance $A_{1\text{cm}}^{1\text{per cent}}$</th>
<th>Maximum tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>235</td>
<td>124.5</td>
<td>122.9 to 126.2</td>
</tr>
<tr>
<td>257</td>
<td>144.5</td>
<td>142.8 to 146.2</td>
</tr>
</tbody>
</table>
3.5 Spectrophotometric Analysis
Requirements EP, USP, FDA, ASTM Spectrophotometer

![Spectrophotometer Analysis Graph]
### Spectrophotometric Analysis

**Requirements EP, USP, FDA, ASTM Spectrophotometer**

**Messergebnisse:**

Während der Messungen wurden die folgenden Werte ermittelt:

<table>
<thead>
<tr>
<th>Typ</th>
<th>Nominale $K_2Cr_2O_7$-Konzentration (Nominal Concentration of $K_2Cr_2O_7$)</th>
<th>Seriennummer (Serial Number)</th>
<th>Wellenlänge (Wavelength)</th>
<th>Optische Dichte (Abs)</th>
<th>Berechnete Spezifische Absorption ($A1%1\text{cm}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>667-UV60</td>
<td>60 mg/l</td>
<td>0318</td>
<td>235 nm</td>
<td>0.7462 $\pm$ 0.0050</td>
<td>124.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>257 nm</td>
<td>0.8685 $\pm$ 0.0050</td>
<td>144.61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>313 nm</td>
<td>0.2925 $\pm$ 0.0050</td>
<td>48.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>350 nm</td>
<td>0.6472 $\pm$ 0.0050</td>
<td>107.76</td>
</tr>
<tr>
<td>667-UV600</td>
<td>600 mg/l</td>
<td>0231</td>
<td>430 nm</td>
<td>0.9593 $\pm$ 0.0050</td>
<td>15.97</td>
</tr>
</tbody>
</table>
When using 2mm, 5mm or 10 mm kuvettes?

If the concentration and the Absorbance of the solution is too high for a measurement with a spectrophotometer it’s possible to dilute the sample or to take a smaller pathlength of the küvette.

**Law of Lambert Beer:**

\[ A = e \times b \times c \]

Where \( A \) is absorbance

- \( e \) is the extinction coefficient (the molar absorptivity with units of L mol\(^{-1}\) cm\(^{-1}\))
- \( b \) is the path length of the sample - that is, the path length of the cuvette in which the sample is contained.
- \( c \) is the concentration of the compound in solution, expressed in mol L\(^{-1}\)

Most of the spectrophotometers have an Absorbance measurement limit of ~1,2. If you take a look on the Equation the only possibility to change the Absorbance is to change \( b \) (the pathlength) or \( c \) (concentration by dilution) because \( e \) is a constant.
3.5 Spectrophotometric Analysis
3.5 Spectrophotometric Analysis

- Using a validated analytical finish, standard solutions are typically prepared in dissolution media and analyzed at just one concentration, either at 100% of the dosage strength or the selected Q value because linearity of the analytical finish has been established.
4. AUTOMATION

- Online analysis returns the sample aliquot to the test system, as in the case of spectrophotometry with flow-through cuvettes. Offline analysis removes the sample aliquot from the dissolution medium for subsequent analysis, typically by HPLC, where the analysis consumes the sample.
What is an Offline Automated System?
An offline automated dissolution system includes a dissolution bath, a pump and a fraction collector.
4. AUTOMATION/ Offline Systems

- Offline with DSR and CAT
What is a Online Dissolution System?

A closed loop or online dissolution system includes a dissolution bath, a pump and a spectrophotometer with a multiple cell changer.
4. AUTOMATION/Online Systems
4.1 Medium Preparation

- Automated media preparation systems typically dispense the volume of medium into the vessel by monitoring either the weight or volume.
- If deaeration of the medium is required, the level of deaeration should be specified.
- The concentration of the dissolved oxygen can be used to evaluate the efficiency of deaeration procedures discussed in section 2.1 Deaeration.
4.1 Medium Preparation

Factors Influencing the PQ Result - Deaeration

- The Influence of Dissolved Oxygen

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Absorbance</th>
<th>% Dissolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaeration</td>
<td>1</td>
<td>0.358</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.370</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.413</td>
</tr>
<tr>
<td>Non-deaeration</td>
<td>4</td>
<td>0.613</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.589</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.576</td>
</tr>
</tbody>
</table>

>50% increase between non deaerated and deaerated media

*) This value is out of range: Note that this study was carried out when the Prednisone LOT POE203 ranges were: 37 - 70% for Apparatus 2 (paddles)
4.1 Medium Preparation
Factors Influencing the PQ Result - Deaeration

%Dissolution of Prednisone Test with Deaeration and Non-Deaeration

<table>
<thead>
<tr>
<th>Vessel</th>
<th>% Dissolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>103</td>
</tr>
<tr>
<td>5</td>
<td>103</td>
</tr>
<tr>
<td>6</td>
<td>103</td>
</tr>
</tbody>
</table>
4.1 Medium Preparation
Factors Influencing the PQ Result - Deaeration

Deaerated

Not Deaerated

Note the cone shapes and amount of flowing particles!
4.1 Medium Preparation
Factors Influencing the PQ Result - Deaeration

Effects of Deaeration Methods on Dissolution Testing in Aqueous Media: A Study Using a Total Dissolved Gas Pressure Meter

ZONGMING GAO, TERRY W. MOORE, WILLIAM H. DOUB, B.J. WESTENBERGER, LUCINDA F. BUHSE
Food and Drug Administration, Center for Drug Evaluation and Research, Division of Pharmaceutical Analysis, St. Louis, Missouri 63101

Received 30 December 2005; revised 14 February 2006; accepted 21 February 2006
Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/...
4.1 Medium Preparation

Factors Influencing the PQ Result - Deaeration
4.1 Medium Preparation
Factors Influencing the PQ Result - Deaeration

Figure 1. Effect of dissolved oxygen concentration on percent prednisone dissolved in 30 min.

Nithyanandan et al. (USP), Dissolution Technologies 2006, 15-18
4.1 Medium Preparation

Factors Influencing the PQ Result - Deaeration

Pharma Test
PT-DDS4 Media Preparator
20l, preheated, dosed and deaerated media
4.1 Medium Preparation

DDS4 Media Preparation System
4.1 Medium Preparation

Factors Influencing the PQ Result - Deaeration

Diagram of a process including labels such as "Inlet", "dosage", "circulation", "drain", "evacuation/ breather", and other numbered parts 1 to 14.
Samples should be inserted in the vessel in a reproducible way. Automated sample introduction and aliquot withdrawal provide an advantage over manual sampling because the automated techniques can reduce the variability in the vessel-to-vessel timing of the test intervals.
• Sampling probes may or may not remain in the vessel throughout the entire run. Sampling probes or fiber-optic probes can disturb the hydrodynamics of the vessel; therefore, adequate validation should be performed to ensure that the probes are not causing a significant change in the dissolution rate.

• The position of the pharmacopeial sampling zone for Apparatus 1 and Apparatus 2 is midway from the top of the stirring element to the medium surface and depends on the medium volume.

• The sampling volume may be critical if, in total, it exceeds 1% of the stated volume of dissolution medium required by the procedure. If it can be shown that replacement of the medium is not necessary, the volume change must be part of the calculation of results. See section 2.5 Data Handling.
• Carryover may occur when subsequent samples are affected by residues or conditions of previous samples; the effect of the first sample or condition “carries over” to the second. In liquid handling, residues of liquids previously in the sample solution may contaminate subsequent sample solutions. Dissolution media containing surfactants or lipids may present problems. Carryover may occur for successive samples taken over a multiple time-point test, as well as at the beginning of a new test due to the cleaning solution. This topic is discussed in section 4.4 Cleaning.

• In addition to the information in section 2.4.3 Sampling, connections of pumps and tubing may be sources of contamination in automated systems.
• Liquid transfer usually is undertaken via polymeric tubing. Inert materials such as polytetrafluoroethylene (PTFE) sometimes cannot be used because of their mechanical properties. Where flexible tubes are required, for example in peristaltic pumps or for coiling in a small radius, polypropylene (PP) or high-density polyethylene (HDPE) may be the preferred materials.

4.3 Sampling and Filtration
4.3 Sampling and Filtration
In addition to the information in section 2.4.4 Cleaning, automated systems have specific cleaning issues. For example, evaluation of the effectiveness of purging and rinsing between sampling times and within-run condition of the tubing is recommended. Also it is important to evaluate the cleaning process between tests. In addition to the information in section 2.4.3 Sampling, connections of pumps and tubing may be sources of contamination in automated systems.
4.4 Cleaning
4.5 Operating Software and Computation of Results

• The software systems for data evaluation and instrument operation must be validated as per 21 CFR 11 (17). This means that the software data need to be secured.

ARGUS/Dissolution Software
- 21 Part 11 compliant
- Electronic Signature
- User-Hierarchy
- Audit Trail
- Password Protections
4.5 Operating Software and Computation of Results/ 21 CFR Part 11
At least one role must be assigned to an account. To remove a role, the appropriate entry must be selected in the list "Roles".

Permissions are hierarchically grouped. The following symbols exist:
- no permission in this group
- at least one permission in this group
- all permissions in this group
- export a template record
- sign a template record for release
- approve a template record
- review a template record
- print a template record
- delete a template record

Show dependencies

Add New User
Roles & Permissions
Roles
Analyst

Add Role
Remove role
21 CFR Part 11: Electronic Signature
5. VALIDATION

- Validation for both parts of the dissolution procedure, the analytical finish and the dissolution step.
- Validation of the analytical finish will evaluate the attributes, linearity and range, precision, specificity, accuracy/recovery, robustness, and stability of the sample and standard solutions.
- Validation of the dissolution step requires the use of a well-characterized dosage form.
- Manufacturers should document the appropriate acceptance criteria for their products in pertinent Standard Operating Procedures (SOPs) or in validation protocols.
Mechanical Calibration:

**FDA:** Guidance Published in January 2010

**USP:** Dissolution Toolkit for mechanical calibration: Published March 2010
<table>
<thead>
<tr>
<th></th>
<th>USP</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed Test</td>
<td>50 and 100 rpm +/- 1rpm</td>
<td>50 and 100 rpm +/- 2rpm</td>
</tr>
<tr>
<td>Wobble Test Shaft</td>
<td>1cm above the paddle &lt; 1mm</td>
<td>2cm above Paddle &lt; 1mm</td>
</tr>
<tr>
<td>Wobble Test Basket</td>
<td>Bottom Basket &lt; 1mm</td>
<td>Bottom Basket &lt; 1mm</td>
</tr>
</tbody>
</table>
Temperature Test

<table>
<thead>
<tr>
<th>USP</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 °C +/- 0.5°C (0.4°C Range e.g. 36.7 – 37.1 °C)</td>
<td>37°C +/- 0.5%</td>
</tr>
</tbody>
</table>

Vessel Centricity

<table>
<thead>
<tr>
<th>USP</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Vessel, max 2cm under the vessel surface. +/- 2mm</td>
<td>2 Positions (2mm and 80mm above the paddle) +/- 1mm</td>
</tr>
</tbody>
</table>

Shaft Verticality

<table>
<thead>
<tr>
<th>USP</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 2 Positions 90° +/- 0.5°</td>
<td>At 2 Positions 90° +/- 0.5°</td>
</tr>
</tbody>
</table>
5. VALIDATION/Mechanical Calibration

**Shaft Verticality**
Measure at 2 different points. Tolerances are $90° \pm 0,5°$) Measured with a digital level

**Vessel Verticality**
Also measured with a digital level. Tolerances are $90° \pm 0,5°$
<table>
<thead>
<tr>
<th></th>
<th>USP</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hight Check</td>
<td>25mm +/- 2mm</td>
<td>25mm +/- 2mm</td>
</tr>
<tr>
<td>Volume</td>
<td>+/- 1%</td>
<td>-</td>
</tr>
<tr>
<td>Vessel Verticality</td>
<td>At 2 Positions 90 +/- 0.5°</td>
<td>At 2 Positions 90 +/- 1°</td>
</tr>
<tr>
<td></td>
<td>USP</td>
<td>FDA</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Deaeration</td>
<td>….dissolved gases should be removed prior to testing… USP 711</td>
<td>Medium should be degassed …less than 60% saturation of total dissolved gases….</td>
</tr>
<tr>
<td>Vibrations</td>
<td>…Table should have a high inertial mass to limit vibration…</td>
<td>..There should be no significant Vibrations in the dissolution apparatus or Medium…</td>
</tr>
</tbody>
</table>
5. VALIDATION/Mechanical Calibration
5. VALIDATION/Mechanical Calibration
Certificate of Participation
from the United States Pharmacopeial Convention

In recognition of

Pharma Test AG

for participation in the USP collaborative study Prednisone Tablets.
USP expresses sincere appreciation to Pharma Test AG for its participation in the public standards-setting process in support of the USP mission: To improve the health of people around the world through public standards and related programs that help ensure the quality, safety, and benefit of medicines and food.

Barbara J. Jones, Ph.D.
Vice President

Roger L. Williams, M.D.
Chief Executive Officer
Vibration Effects on Dissolution Tests with USP Apparatuses 1 and 2

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ABSTRACT: Dissolution testing is of primary importance for drug formulation and quality control. Many sources of variability are accounted for in the apparatus' mechanical calibration process; the effect of vibration on dissolution tests is not well understood in that the test's tolerance for environmental vibration with respect to magnitude or frequency is largely unknown. In this study, USP Apparatuses 1 and 2 were used. Dissolution profiles were obtained for both disintegrating and nondisintegrating tablets. In separate experiments, a lab vacuum pump or a lab mixer, both commonly used in laboratories, was used to generate vibration during dissolution runs with vibration parameters being recorded at a location close to the dissolution vessels. Disintegrating tablets were found to be sensitive to induced vibrations with both the paddle and basket methods. Average dissolution results for nondisintegrating tablets were not sensitive to the studied vibrations; however, variability of the results increased in some cases. The dissolution profiles suggest that the vibration effects on paddle and basket methods occur...
5. VALIDATION/Performance Verification Test

Figure 4. Vibration effects on paddle dissolution test using disintegrating 10 mg prednisone tablets (with a vacuum pump as induced vibration source).
5. VALIDATION/Performance Verification Test

**Figure 5.** Vibration effects on paddle dissolution test using disintegrating 10 mg prednisone tablets (with a mixer as induced vibration source).
## Factors affecting the PVT PQ results:

<table>
<thead>
<tr>
<th>Type</th>
<th>Rating</th>
<th>Influence degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>not too significant</td>
<td>linear</td>
</tr>
<tr>
<td>Speed</td>
<td>significant</td>
<td>10-30%</td>
</tr>
<tr>
<td>Vibration</td>
<td>significant</td>
<td>10-40%</td>
</tr>
<tr>
<td>Centricity</td>
<td>reasonable</td>
<td>± 5-15%</td>
</tr>
<tr>
<td>Dissolved Gas</td>
<td>significant</td>
<td>± 50%</td>
</tr>
<tr>
<td>Media pH</td>
<td>reasonable</td>
<td>± 5-10%</td>
</tr>
<tr>
<td>Media Contamination</td>
<td>significant</td>
<td>± 20-45%</td>
</tr>
<tr>
<td>Sampling Position</td>
<td>not too significant</td>
<td>1-3%</td>
</tr>
</tbody>
</table>
5. VALIDATION/Performance Verification Test

Certificate

PREDNISONE TABLETS

<table>
<thead>
<tr>
<th>USP Catalog No.:</th>
<th>1559505</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP Lot No.:</td>
<td>R031Y0</td>
</tr>
</tbody>
</table>

(10 mg nominal prednisone content per tablet)

FOR DISSOLUTION PERFORMANCE VERIFICATION TEST (PVT)

Period of validity: This certificate of USP Prednisone Tablets Lot R031Y0 is valid through September 30th, 2016.

The USP Prednisone Tablets RS is provided for use in the Performance Verification Test for USP Apparatus 1 and 2 in the
Table 1. Performance Verification Test (PVT) limits (values apply only to Lot R031Y0)

<table>
<thead>
<tr>
<th>Apparatus</th>
<th># of vessels</th>
<th>Single-Stage</th>
<th>Two-Stage</th>
<th>1st Stage of Two Stages</th>
<th>2nd Stage of Two Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GM*</td>
<td>%CV</td>
<td>GM*</td>
<td>%CV</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>51-80</td>
<td>11</td>
<td>55-74</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td></td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td></td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>27-41</td>
<td>6.4</td>
<td>29-38</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td></td>
<td>6.3</td>
<td>4.8</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td></td>
<td>6.2</td>
<td>6.2</td>
<td>na</td>
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<tr>
<td></td>
<td>12</td>
<td></td>
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<tr>
<td></td>
<td>14</td>
<td></td>
<td>6.2</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

* Percent of the labeled amount of prednisone dissolved at 30 minutes at 50-rpm

Data set size for single and two stage testing

<table>
<thead>
<tr>
<th>Number of positions in test assembly</th>
<th>Single stage test</th>
<th>First stage of two-stage test</th>
<th>Second stage of two-stage test (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>12</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

[Note that for twelve position test assembly only the single stage test is performed.]
6.ACCEPTANCE CRITERIA / 6.5.1 immediate-release dosage forms

- Once the Q value is established, the dissolution test is a staged test of three levels. In the first level of testing called S1, six dosage forms are tested. Each dosage form must be Q+ 5% (absolute percentage points) dissolved at a specified time. For example, the time and tolerances in a monograph would be:

  - Time: 30 min
  Tolerances: NLT 80% (Q) of the labeled amount of “drug substance” is dissolved.

- If the Q value for a 200-mg label claim (LC) immediate-release tablet is specified as 80% and the time point is 30 min, then NLT 85% LC (170 mg) of the drug substance in each tablet must be dissolved at 30 min.

- Filtration for UV-VIS, HPLC
Thank you 😊

Pharma Test AG Group
Pharmag
J&M