Compendial Dissolution: Theory and Practice

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Compendial dissolution testing

- Dissolution apparatus
- Pharmacopeial harmonization
- Acceptance criteria for dissolution testing
Dissolution Test

- An API has to be released from the dosage form and has to dissolve in the physiological fluid in order to be available for absorption

Factors influencing dissolution

- Active pharmaceutical ingredient
  - Solubility
  - Intrinsic dissolution
  - Stability

- Pharmaceutical dosage form
  - Site of release
  - Mechanism of release
Dissolution: Relevant USP General Chapters

- General Chapters—mandatory requirements
  - <701> Disintegration
  - <711> Dissolution
  - <724> Drug Release

- General Chapters—informational
  - <1087> Apparent Intrinsic Dissolution – Dissolution Testing Procedures for Rotating Disk and Stationary Disk
  - <1088> In Vitro and In Vivo Evaluation of Dosage Forms
  - <1090> Assessment of Drug Product Performance – Bioavailability, Bioequivalence, and Dissolution
  - <1092> The Dissolution Procedure: Development and Validation
Mandatory Chapters

<16> Automated Methods of Analysis
<21> Thermometers
<31> Volumetric Apparatus
<41> Weights and Balances
<621> Chromatography (HPLC)
<791> pH
<851> Spectrophotometry and Light-Scattering (UV-Vis Spectroscopy)
Harmonized between USP, Ph. Eur. and JP

USP: <711> Dissolution
- Descriptions of Apparatus 1, 2, 3 and 4 for testing of solid oral dosage forms
- Apparatus Suitability, Procedure, and Interpretation of results including acceptance criteria

Ph. Eur.: 2.9.3 Dissolution Test for Solid Dosage Forms
- Descriptions of Apparatus 1, 2, 3 and 4
- Acceptance Criteria
- Guidance on dissolution testing and qualification and validation
JP: General Tests Processes and Apparatus
6.10 Dissolution Test

- Descriptions of Apparatus for solid preparations for internal use
  - Basket Method (Apparatus 1),
  - Apparatus for Paddle Method (Apparatus 2), and
  - Apparatus for Flow-Through Cell Method (Apparatus 3)

- Procedure and Interpretation including acceptance criteria
USP Apparatus 1 - Basket

- **Vessels**
  - Glass or other inert, transparent material
  - Cylindrical with hemispherical bottom
  - 1L nominal capacity
  - USP only: 2L or 4L

- **Basket**
  - 40 mesh (wire openings of 0.36 – 0.44 mm)
  - Gold coating of 2.5μm is allowed

- **Stirring**
  - Rotating stirrer
  - Typical speeds: 50-100 rpm

- **Dosage form placed in the basket**
Drug products tested
- Solid dosage forms
  - Floating
  - Disintegrating and non-disintegrating
    - Single units (e.g. tablets)
    - Multiple units (encapsulated beads)
- Generates cumulative dissolution results
USP Apparatus 1 - Basket

- pH change by media addition or replacement
- Disadvantages
  - Formulation may clog the screen
  - Small disintegrated particles fall out
USP Apparatus 2 - Paddle

- **Vessels**
  - Same as for Apparatus 1

- **Stirring blade and shaft**
  - Metallic, or suitably inert and rigid
  - May be coated

- **Agitation**
  - Rotating stirrer
  - Typical speeds: 50-75 rpm
- Dosage form should remain at the bottom centre of the vessel
- Sinkers used for floating dosage forms
Drug products tested
  - Solid dosage forms
    • tablets
    • capsules
  - Particulates
    • suspensions
    • powders
Generates cumulative dissolution results
USP Apparatus 2 - Paddle

- pH change by media addition
- Disadvantages
  - Floating dosage forms require sinker
  - Cone formation may be problematic
  - Positioning of the dosage form in the vessel
Cone formation

- is a typical problem for disintegrating products
  - especially if hydrophobic
- fluid interchange only at surface
  - center of cone may be saturated solution
- increasing rotation speed may overcome problem

- A PEAK vessel with an inverted cone molded into the bottom was developed to eliminate the potential for cone formation (non-compendial)
USP Apparatus 2 - Paddle

Particle Image Velocimetry

Computational Fluid Dynamics

Low shear region
Sinkers

- A small, loose piece of nonreactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float

- Alternative sinker devices
Stationary basket

*e.g.*; Felodipine Extended-Release Tablets, USP

Palmeri basket for suppositories
Paddle/ Basket Dissolution Apparatus

- **Advantages**
  - Widely accepted apparatus for dissolution testing
  - Apparatus of first choice for solid oral dosage forms
  - Easy to operate
  - Standardized
  - Robust
  - Broad experience

- **Disadvantages**
  - Fixed (limited) volume
  - Simulation of gastrointestinal transit conditions not easily possible
USP Apparatus 3 - Reciprocating Cylinder

- **Vessels**
  - Cylindrical flat-bottomed glass
  - about 325 ml capacity

- **Glass reciprocating cylinders**
  - Inert fittings
  - Screens at the top and bottom of the cylinders
Reciprocating agitation
- Usual speed 5 to 35 dips/min
- Through 10 cm vertical distance

Dosage form is placed in the cylinder

Cylinder moves horizontally to different rows of vessels
Drug products

- Solid dosage forms (mostly non-disintegrating)
  - Single units (e.g. tablets)
  - Multiple units (e.g. encapsulated beads)
- Originally used for extended release products, particularly beads in capsules

Generates fractionated dissolution results
Advantages
- Programmable to run dissolution in different media and at different speeds at various times
- Attempt to simulate pH changes in the GI tract e.g. pH 1, pH 4.5, pH 6.8

Disadvantages
- Not suitable for dosage forms that disintegrate into small particles
- Surfactants cause foaming
- Small vessel volume
- Media evaporation for tests of long duration
**Example Conditions for Extended Release Testing**

<table>
<thead>
<tr>
<th>Row</th>
<th>GI Position</th>
<th>pH</th>
<th>Speed - DPM</th>
<th>Time - Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Stomach</td>
<td>1.2</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Duodenum</td>
<td>4.5</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Small Intestine - Proximal</td>
<td>6.4</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Small Intestine - Medial</td>
<td>6.8</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Small Intestine - Distal</td>
<td>7.2</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Colon</td>
<td>7.4</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

*Drug Release Characteristics of Different Mesalazine Products Using USP Apparatus 3 to Simulate Passage Through the GI Tract, Sandra Klein, Markus W. Rudolph, Jennifer B. Dressman, Dissolution Technologies, Volume 9, Issue 4, November 2002*
Mesalazine Dissolution in USP Apparatus 3
USP Apparatus 4 - Flow Through Cell

Filter
Laminar Flow
Glass Beads

Heating Coil
Syringe Pump
Media Reservoirs

Collection
• Various cell designs
  – Compendial
    • 12 mm
    • 22.6 mm diameters
  – For special dosage forms (not harmonized)
    • Lipophilic solid dosage forms i.e. suppositories (2.9.42)
    • Powders, granules (2.9.43)

• Flow rates
  – 4, 8, 16 mL/min compendial
  – Alternative 2-32 ml/min
USP Apparatus 4 - Flow Through Cell

- **Operation**
  - Open system: continuous flow
  - Closed system: recirculate media

- **Media change by exchange of reservoirs**
  - Generates fractionated dissolution results
Drug products
- Solids: tablets, capsules, implants, powder, granules
- Semisolids: suppositories, soft gelatin capsules, ointments
- Liquids: suspensions
Disadvantages
- Limited experience with use of the apparatus - no USP monographs
- Pump precision influences the results

Advantages
- Volume of media not limited
- Suitable for poorly soluble drugs
- Gentle hydrodynamic conditions
USP <724> Drug Release

- Since harmonization - general statement
- Sub-section for Transdermal Delivery Systems
  - Apparatus 5, 6 and 7 including
  - Procedure and Interpretation for each apparatus

\[
\text{〈724〉 DRUG RELEASE}
\]

This test is provided to determine compliance with drug-release requirements where specified in individual monographs. Use the apparatus specified in the individual monograph. Replace the aliquots withdrawn for analysis with equal volumes of fresh \textit{Dissolution Medium} at the temperature specified in the monograph or,
Ph.Eur. 2.9.4 “Dissolution Test for Transdermal Patches”
– Disk Assembly Method (using stainless steel disk assembly corresponding to App. 5)
– Cell Method (using extraction cells)
– Rotating Cylinder Method (using stainless steel cylinder corresponding to App. 6)

JP: no methods described for transdermal delivery systems
USP Apparatus 5 - Paddle Over Disk

- Uses paddle and vessel assembly from Apparatus 2 with the addition of a stainless steel disk assembly
- Temperature: 32°C
- Speed: typically 50 rpm
- Drug Products
  - Transdermal patches
    - Matrix transdermal patches can be cut to the size of the disk assembly
USP Apparatus 6 - Cylinder

- Uses vessel assembly from Apparatus 1
  - Replaces basket and shaft with a stainless steel cylinder stirring element
- Temperature: 32°C
- Dosage unit is placed on the cylinder with release side out
- Drug products
  - Reservoir transdermal patches
USP Apparatus 7 - Reciprocating Holder

- Similar to Apparatus 3 but with different dimensions
- Temperature: 32°C (for transdermal dosage forms)
- Various devices to hold transdermal patches, tablets, capsules, implants
- Speed: 20-50 dpm
- Reciprocation through 2 cm
Special Dosage Forms

- Chewing Gum Apparatus – Ph. Eur.
  - Intensity and frequency of shearing forces generally have an affect on the drug release from the gum
Chewing Gum Apparatus

- **Advantages**
  - Good simulation of the masticatory activity
  - Easy to use

- **Disadvantages**
  - Apparatus not commercially available
  - Limited experience
  - Limited volume
Apparatus for Medicated Chewing Gum

- Not compendial
As described in PF35(3) May-June 2009
Donor and receptor area
Temperature: 32°C
Vertical Diffusion Cell – not compendial

- Drug products
  - Semisolid dosage forms
  - Development of transdermal delivery systems
- Samples are periodically withdrawn from sampling port
Vertical Diffusion Cell – not compendial
The USP monograph provides information about the test procedure for a specific drug product.

The USP monograph provides the acceptance criteria which the drug product must meet.

Results of a compendial dissolution test do not prove bioavailability or bioequivalence.
Multiple dissolution tests are allowed in a USP drug product monograph
  – The test to which the drug product complies must be stated on the label

The sponsor of the original monograph will submit a dissolution test along with other tests, procedures and acceptance criteria

Another manufacturer of the same drug product may submit an alternate dissolution test
  – Usually for extended release drug products
The USP monograph provides information about conditions and procedures of the tests for a specific drug product.

The USP monograph provides the acceptance criteria which the drug product must meet to be accepted:
- Q values for Immediate Release products (single time-point)
- Tolerances are given in acceptance tables for multiple time-points

Dissolution tests in USP reflect the dissolution conditions approved by FDA for products sold in the USA.

In some circumstances, different marketed products using different formulations (excipients and/or process) may require different dissolution conditions.
Interpretation of Dissolution Results

USP <711>

- Perform the analysis as directed in the individual monograph
- Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to the accompanying Acceptance Table
Interpretation of Dissolution Results

- Continue testing through the three stages unless the results conform at either S1 or S2.
- The quantity, \( Q \), is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.
- The 5%, 15%, and 25% values in the Acceptance Table are percentages of the labeled content so that these values and \( Q \) are in the same terms.
## Immediate-release dosage forms

### Acceptance Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of units tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>6</td>
<td>Each unit is not less than Q + 5%.</td>
</tr>
<tr>
<td>S2</td>
<td>6</td>
<td>Average of 12 units (S1 + S2) is equal to or greater than Q, and no unit is less than Q-15%.</td>
</tr>
<tr>
<td>S3</td>
<td>12</td>
<td>Average of 24 units (S1 + S2 + S3) is equal to or greater than Q, not more than 2 units are less than Q-15%, and no unit is less than Q-25%.</td>
</tr>
</tbody>
</table>
## Immediate-release dosage forms

### Acceptance Table for a Pooled Sample

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of units tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>6</td>
<td>Average amount dissolved is not less than $Q + 10%$.</td>
</tr>
<tr>
<td>S2</td>
<td>6</td>
<td>Average amount dissolved ($S1 + S2$) is equal to or greater than $Q + 5%$.</td>
</tr>
<tr>
<td>S3</td>
<td>12</td>
<td>Average amount dissolved ($S1 + S2 + S3$) is equal to or greater than $Q$.</td>
</tr>
</tbody>
</table>
## Extended-release dosage forms

### Acceptance Table 2

<table>
<thead>
<tr>
<th>Level</th>
<th>Number of units tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>6</td>
<td>No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.</td>
</tr>
<tr>
<td>L2</td>
<td>6</td>
<td>The average value of the 12 units (L1 + L2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.</td>
</tr>
</tbody>
</table>
## Extended-release dosage forms

### Acceptance Table 2

<table>
<thead>
<tr>
<th>Level</th>
<th>Number of units tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3</td>
<td>12</td>
<td>The average value of the 24 units (L1 + L2 + L3) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.</td>
</tr>
</tbody>
</table>
## Interpretation of Dissolution Results

### Delayed-release dosage forms

**Acid Stage - Acceptance Table 3**

<table>
<thead>
<tr>
<th>Level</th>
<th>Number of units tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>6</td>
<td>No individual value exceeds 10% dissolved.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average of the 12 units (A1 + A2) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.</td>
</tr>
<tr>
<td>A2</td>
<td>6</td>
<td>Average of the 24 units (A1 + A2 + A3) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.</td>
</tr>
<tr>
<td>A3</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>
## Extended-release dosage forms

### Buffer Stage - Acceptance Table 4

<table>
<thead>
<tr>
<th>Level</th>
<th>Number of units tested</th>
<th>Acceptance Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>6</td>
<td>Each unit is not less than $Q + 5%$.</td>
</tr>
<tr>
<td>B2</td>
<td>6</td>
<td>Average of 12 units ($B1 + B2$) is equal to or greater than $Q$, and no unit is less than $Q-15%$.</td>
</tr>
<tr>
<td>B3</td>
<td>12</td>
<td>Average of 24 units ($B1 + B2 + B3$) is equal to or greater than $Q$, not more than 2 units are less than $Q-15%$, and no unit is less than $Q-25%$.</td>
</tr>
</tbody>
</table>
Upcoming One-day course:

Dissolution: Theory and Best Practices

Date: October 27, 2011
Location: USP Headquarters, Rockville, MD

For more information and complete course listings, visit http://www.usp.org/education/pe/courses.html

For questions, contact USP Pharmacopeial Education at PharmEd@usp.org
Questions