Dissolution Tester

GMP 4th
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Department of Medical Sciences
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Topics

- Dissolution Testing
- Calibration of Dissolution Tester
  - Physical Parameters
  - USP Tablet Calibrators
- Maintenance
What is Tablet Dissolution?

Tablet Dissolution is a standardized method for measuring the rate of drug release from a dosage form.
Dissolution Testing

The principle function of dissolution test may be summarized as follows:

- Optimization of the therapeutic effectiveness during product development and stability assessment.
- Routine assessment of production quality to ensure uniformity between production lots.
- Assessment of ‘bioequivalence’.
- Prediction of ‘in-vivo’ availability i.e. bioavailability (where applicable)
Definition of the Dissolution Rate

\[ \frac{dw}{dt} = kS (Csat - Csol) \] \[1\]

where
\[ \frac{dw}{dt} \] = the dissolution rate
\[ k \] = a dissolution constant
\[ S \] = the surface area of the solid
\[ Csat \] = the concentration of a saturated solution
\[ Csol \] = the concentration at any given time

\[ \frac{dw}{dt} = KS \] \[2\]

Sink condition; \( Csat >> Csol \)
The dissolution procedure requires

- Apparatus
- Dissolution Medium
  (composition and amount)
- Test Conditions
- Acceptance Criteria
## Dissolution Apparatus

<table>
<thead>
<tr>
<th>Apparatus</th>
<th>USP29</th>
<th>BP2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Basket</td>
<td>Basket</td>
</tr>
<tr>
<td>II</td>
<td>Paddle</td>
<td>Paddle</td>
</tr>
<tr>
<td>III</td>
<td>Reciprocating Cylinder</td>
<td>Flow-Through Cell</td>
</tr>
<tr>
<td>IV</td>
<td>Flow-Through Cell</td>
<td>-</td>
</tr>
<tr>
<td>V</td>
<td>Paddle over Disk</td>
<td>-</td>
</tr>
<tr>
<td>VI</td>
<td>Cylinder</td>
<td>-</td>
</tr>
<tr>
<td>VII</td>
<td>Reciprocating Holder</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Solid Dosage Forms (Apparatus)</th>
<th>Transdermal Patches (Method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>-</td>
<td>Disk assembly (SSDA)</td>
</tr>
<tr>
<td>II</td>
<td>Extraction Cell</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Dissolution Medium

Typical media for dissolution may include the following:

- Water
- Diluted HCl
- Buffers in physiological pH range (pH 1.2-7.5)
- Simulated gastric or intestinal fluid (with or without enzymes)
- Surfactants (with or without acids or buffers)

such as
- polysorbate 80
- sodium lauryl sulfate
- bile salts
Dissolution Tester

Before the test, the operator must check

- the calibration date
- bath water level
- temperature (bath and vessels)
- distance of the apparatus from bottom of vessel
- rotating speed (RPM)
- time
- sampling position of the sampling probe
- automated sampling system
Calibration of Dissolution Tester

Physical Parameters

- Shaft Rotating Speed
- Wobble
- Temperature
- Shaft Alignment
- Instrument Level
- Vibration
- Shaft Centering

USP Tablet Calibrators
Calibration Instrumentation for Dissolution Tester (QA Station II)

- Temperature probe
- Setup station
- Magnetic clip
- Electronic level sensor
- Adapter (EaseAlign)
- Vibration sensor
Shaft Rotating Speed (RPM check)

Tachometer sensor

Magnetic clip

Max. allowable : $\pm 4\%$
Wobble Gauge with Basket (Shaft)

Max. allowable: ≤ 1 mm
Wobble Gauge with Basket (Basket Rim)
Wobble Gauge with Paddle

Max. allowable: $\leq 1 \text{ mm}$

Wobble gauge
Temperature Test (Bath)

Temperature probe
Temperature Test (Vessel)

Max. allowable: ± 0.5 °C
Shaft Alignment

Electronic level sensor

Max. allowable : ± 1.5 °
Vessel Table Level

Electronic level sensor

Max. allowable : ± 0.5 °
Vibration

**Sources of Vibration**

*External:*

ex. centrifuges, double-beam spectrophotometers, pumps, fume hoods, fan, air conditioner etc.

*Internal:*

ex. circulator for the water bath, motor

4 parameters:

- Acceleration (g)
- Frequency (Hz)
- Velocity (mm/s)
- Displacement (mm)

Max. allowable:

Displacement-Z ≤ 0.1 mils (0.00254 mm)
Shaft Centering

is dependent on two parameters:

- The position of the spindle (factory set)
- The position of the vessels

Max. allowable: ± 2 mm
Q-AIT ANALYSIS REPORT

STORAGE # 23  Dished Co.
VK7000 S/N 2-2771-3119
TEST TIME 18/05/06 12:30

POSITION: 1
SHAFT ID: 01
ACTL RPM: 050.06
WOBBLE (mm): 00.08
TEMP (°C): 37.3
SHAFT-X: 00.1
SHAFT-Y: -0.1

VIBRATION-X (g): 0.008
FREQUENCY (Hz): 100.24
VELOCITY (mm/s): 00.13
DISPLACEMENT (mm): 0.0004

VIBRATION-Y (g): 0.017
FREQUENCY (Hz): 100.19
VELOCITY (mm/s): 00.27
DISPLACEMENT (mm): 0.0008

VIBRATION-Z (g): 0.006
FREQUENCY (Hz): 108.14
VELOCITY (mm/s): 00.09
DISPLACEMENT (mm): 0.0002

END OF REPORT
<table>
<thead>
<tr>
<th>Variable</th>
<th>Maximum allowable</th>
<th>Excess Commonly Seen</th>
<th>Effect of Excess</th>
<th>Methods of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Eccentricity, Wobble, Tilt</td>
<td>± 1 mm</td>
<td>2-5 mm</td>
<td>+ 4%-8%</td>
<td>straighten shafts, use wide shaft-guide points</td>
</tr>
<tr>
<td>2. Vibration</td>
<td>0.1 mil</td>
<td>0.2-0.9 mils</td>
<td>+ 5%-10%</td>
<td>eliminate source</td>
</tr>
<tr>
<td>3. Shaft Alignment</td>
<td>1.5° to perpendicular</td>
<td>2° -7°</td>
<td>+ 2%-25%</td>
<td>adjust alignment in field</td>
</tr>
<tr>
<td>4. Shaft Centering</td>
<td>± 2 mm (compendium)</td>
<td>± 2-6 mm</td>
<td>± 2%-13%</td>
<td>center individual vessels</td>
</tr>
<tr>
<td>5. Agitation Rate, Rotating Speed (RPM)</td>
<td>± 4%</td>
<td>± 10%</td>
<td>linear</td>
<td>use better, smoother control or use synchronous drive</td>
</tr>
<tr>
<td>Variable</td>
<td>Maximum allowable</td>
<td>Excess Commonly Seen</td>
<td>Effect of Excess</td>
<td>Methods of Control</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------</td>
<td>----------------------</td>
<td>------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>6. Dissolved gas</td>
<td>deaerated</td>
<td>bubble form</td>
<td>± 50%</td>
<td>deaerate media</td>
</tr>
<tr>
<td>7. Media pH</td>
<td>accuracy</td>
<td>± 0.05</td>
<td>± 10%</td>
<td>check buffers or deaerate, calibrate the pH meter</td>
</tr>
<tr>
<td>8. Media contamination</td>
<td>ppm</td>
<td>ion, surfactants</td>
<td>substantial</td>
<td>carefully control media</td>
</tr>
<tr>
<td>9. Evaporation</td>
<td>none</td>
<td>2%-5%</td>
<td>linear</td>
<td>use vessel covers</td>
</tr>
<tr>
<td>10. Temperature</td>
<td>± 0.5 °C</td>
<td>1 °C-2 °C</td>
<td>linear</td>
<td>monitor individual vessels, allow adequate equilibrium</td>
</tr>
<tr>
<td>Variable</td>
<td>Maximum allowable</td>
<td>Excess Commonly Seen</td>
<td>Effect of Excess</td>
<td>Methods of Control</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>----------------------</td>
<td>------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>11. Flow pattern</td>
<td>no interference</td>
<td>turbulence from probes</td>
<td>substantial</td>
<td>remove probes</td>
</tr>
<tr>
<td>12. Sampling position</td>
<td>compendium</td>
<td>± 0.5 cm</td>
<td>little</td>
<td>use care</td>
</tr>
<tr>
<td>13. Filters</td>
<td>no sorbing</td>
<td>considerable blockage</td>
<td>significant</td>
<td>check sorbing</td>
</tr>
<tr>
<td>14. Detection</td>
<td>use standard</td>
<td>interference</td>
<td>considerable</td>
<td>use standard</td>
</tr>
<tr>
<td>15. Sorbing</td>
<td>none</td>
<td>considerable</td>
<td>significant</td>
<td>check materials</td>
</tr>
</tbody>
</table>
Calibration of Dissolution Tester

- **Physical Parameters**
- **USP Tablet Calibrators**

- USP Prednisone Tablets RS
  (Dissolution Calibrator; Disintegrating)
- USP Salicylic Acid Tablets RS
  (Dissolution Calibrator; Nondisintegrating)
- USP Chlorpheniramine Maleate Extended-Release Tablets RS
  (Drug Release Calibrator; Single Unit)
# Tablet Calibrators

<table>
<thead>
<tr>
<th>Item</th>
<th>USP Tablet Calibrators</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prednisone (Lot O0C056)</td>
</tr>
<tr>
<td>Type</td>
<td>Disintegrating</td>
</tr>
<tr>
<td>Amount</td>
<td>10 mg/tab</td>
</tr>
<tr>
<td>Test for Apparatus</td>
<td>I and II</td>
</tr>
<tr>
<td>RPM</td>
<td>50</td>
</tr>
<tr>
<td>Dissolution Medium</td>
<td>Deaerated Water, 500 ml</td>
</tr>
<tr>
<td>Time point</td>
<td>30 minutes</td>
</tr>
</tbody>
</table>
### Tablet Calibrators (cont.)

<table>
<thead>
<tr>
<th>Item</th>
<th>USP Tablet Calibrators</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prednisone (Lot O0C056)</td>
</tr>
<tr>
<td>Max. λ (nm)</td>
<td>242</td>
</tr>
<tr>
<td>% alcohol in Std. solution</td>
<td>≤ 5 %</td>
</tr>
<tr>
<td>Packaging</td>
<td>Plastic bottle</td>
</tr>
<tr>
<td>Acceptance values (%la.)</td>
<td></td>
</tr>
<tr>
<td>Apparatus I</td>
<td>51-81</td>
</tr>
<tr>
<td>Apparatus II</td>
<td>26-47</td>
</tr>
</tbody>
</table>
USP Tablet Calibrators

Salicylic acid Tablet

Prednisone Tablet
Tablet Calibration

- Study the COA of the USP tablet calibrators
- Prepare deaerated dissolution medium
- Setup the dissolution tester
Pour the dissolution medium into the vessels and equilibrate to 37 °C, use immediately (Check and record the temperature of each vessel)

Weigh each tablet calibrators

Insert the tablet calibrators into the baskets/Drop the tablet calibrators into the vessels
Tablet Calibration (cont.)

1. Activate the spindles at the desired speed
2. Withdraw the specimens at the stated time and immediately filter
3. Recheck and record the temperature of the vessels
4. Measure the absorbance of samples and standard solutions
Standing in air of deaerated media form a natural equilibrium over a period of time. A portion of the gas is dissolved in the liquid.

- Storage the tablet calibrators in the original package.
- Sampling probe that enter the media only during sampling in order to avoid flow disturbances.
- Ensure that no sample absorption onto the filter.
- Carefully sampling the specimens.
Automated sampling system should be calibrated parallel with manual analysis

It may be useful to weigh the tablet calibrators before and after a run to answer the failure of the test

Air bubbles can interfere with the test results, especially air pocket inside the basket may lower the dissolution rate of salicylic acid tablet by much as 50%

Visual observations are often helpful for understanding the source of the variability
Tablet Calibration

“There are many reasons that a tablet calibration test may fail. The items in the checklist may or may not be the reason for a failed test. Deaeration and vibration are two of the largest contributors to failure.”
Influence of Release Gases

The bubbles that appear in media as the equilibrium is disturbed may

- ↑ buoyancy  →  ↑ dissolution rate
- ↓ available surface area  →  ↓ dissolution rate
- associate with aggregate particles  →  random concentrations of the particles in the solvent stream
- collect at the screen on the basket  →  changing the effective porosity of the mesh
- cling the particle to the apparatus and vessel walls
- influence on pH of the media
Deaeration Methods

- Helium flushing
- Sonicating + Vacuum
- Automated media degasser (ex. DosaPrep®)
- Warming to 41 °C + filtering + Vacuum
## Deaeration Methods (cont.)

<table>
<thead>
<tr>
<th>Method</th>
<th>% Reduction in dissolved oxygen (approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP23 (heating to 45 °C plus filtration and vacuum)</td>
<td>85 ± 11%</td>
</tr>
<tr>
<td>Filtering only at room temperature</td>
<td>65 ± 3%</td>
</tr>
<tr>
<td>Boiling (heating to 100 °C)</td>
<td>50 ± 3%</td>
</tr>
<tr>
<td>Ultrasound and vacuum degassing</td>
<td>95 ± 2%</td>
</tr>
</tbody>
</table>

![Graph showing % Reduction for different methods](chart.png)
Deaeration Method (USP29)

Heat the medium, stirring gently, to approximately 41 °C

Immediately filter through 0.45 μm or less filter, under vacuum with vigorous stirring

Continue stirring under vacuum for 5 additional minutes
Carefully transfer the medium into the container with tightly closure until full

Allow to cool and measure 500 or 900 ml (or whatever the method calls for) volumetrically

Gently pour medium into the dissolution vessel and equilibrate to 37 °C, use immediately
Maintenance

- Careful cleaning is required to ensure there is no contamination between tests.
- Handling the basket and shaft/ paddles with care
- Visually inspect the bath water weekly for algae or other foreign material.
- Water in the bath is reasonable clean to ensure that the circulating pump is also clean.
- Do not allow dissolution media sit on the system. Clean up dissolution media whenever it is spilled on the system.
## Maintenance Schedule

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>After each test</td>
<td>Clean up system</td>
</tr>
<tr>
<td>Weekly</td>
<td>Inspect:</td>
</tr>
<tr>
<td></td>
<td>- circulating water pump</td>
</tr>
<tr>
<td></td>
<td>- bath water</td>
</tr>
<tr>
<td>Monthly</td>
<td>Replace bath water</td>
</tr>
<tr>
<td>Frequency</td>
<td>Procedure</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Every 6 months</td>
<td>- Check temperature calibration</td>
</tr>
<tr>
<td></td>
<td>- Calibration the system</td>
</tr>
<tr>
<td></td>
<td>- Inspect guide rods and spindle bearings</td>
</tr>
<tr>
<td>Annually</td>
<td>Inspect:</td>
</tr>
<tr>
<td></td>
<td>- belts</td>
</tr>
<tr>
<td></td>
<td>- Idler pulleys</td>
</tr>
<tr>
<td>Every 2 years</td>
<td>Replace belts</td>
</tr>
</tbody>
</table>
Causes of Variables

- Formulation and Manufacturing Process
  Example:
  - poor content uniformity
  - process inconsistencies
  - a reaction taking place at different rates during dissolution
  - excipient interactions or interference
  - film coating
  - capsule shell aging
  - hardening or softening of the dosage form on stability

- Routine testing of the product
  - analytical
  - formulation
  - processing perspectives
References

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2.เมตตา ตรีบูรณะ. 2541. การทดลองการละลายตัวของยา. กองยา กรมวิทยาศาสตร์การแพทย์.
3.นิคพาพรรณ เรืองฤทธินัย. 2538. การบูรณาการและการปรับเทียบเครื่อง Dissolution. กองวิเคราะห์ยา กรมวิทยาศาสตร์การแพทย์.
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