
21 October 2011 – Toronto, Canada
Agenda

✓ USP
  ✓ Relation to the FDA and to the pharmaceutical and nutraceutical industry
  ✓ Hierarchy of the USP regulations
  ✓ Regulations regarding dissolution

✓ Disintegration <2040>, <701>
  ✓ Apparatus types
  ✓ Procedures
  ✓ Acceptance Criteria

✓ Dissolution <2040>, <711>
  ✓ Apparatus types
  ✓ Procedures
  ✓ Acceptance Criteria
The USP and the FDA

- Publishes
  - Best Practices and procedures
  - Apparatus Specifications
  - Monographs
  - Strength, purity, quality, packaging and labeling

- Produces the USP PVT calibration standards

- "Compendial", refers to items listed in the USP

- Enforcement
  - Best Practices
  - Inspects labs, and manufacturing facilities/processes

- Approval
  - Safety and Efficacy
  - Marketing
  - …More

- Developed a mechanical calibration with ASTM
Dissolution in USP Monographs

Compendial Dissolution is over forty years old…

- **1970:** 6 monographs
- **1975:** 12 monographs
- **1980:** 60 monographs
- **1990:** 462 monographs
- **2000:** 550 monographs
- **2005:** 647 monographs (584 Dissolution + 63 Drug Release)
- **2010:** 750 monographs (741 Dissolution + 9 Drug Release)

- **Hierarchy:** General Notices are trumped by General Chapters which are trumped by Monographs
Disintegration

- If there is no monograph, you cannot legally make a label claim that a product is in “compliance” with the USP.
- The USP encourages monographs submissions from the industry.
- Troches, chewables and extended release formulations are excluded from disintegration testing, but have other requirements.
- If a dosage form has physical dimensions less than or equal to 18 mm in the largest dimension, then Apparatus “A” is used. Otherwise, use Apparatus “B”.
In addition to the published USP, also be aware of "Revision Bulletins", which give guidance regarding coming changes.

In December of this year, <2040> will begin to require Apparatus 4 for dissolution, replacing the current disintegration test.
Disintegration: Instrumentation

- Multiple vendors
- Instrumentation is not specified in the USP
- “Apparatus” refers to the basket design, motion of the basket, and the temperature
Disintegration: Apparatus types

Apparatus A

Apparatus B
### Disintegration Procedures

<table>
<thead>
<tr>
<th></th>
<th>Time (min)</th>
<th>If Sugar Coated</th>
<th>Media</th>
<th>Disk</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncoated Tablet</td>
<td>30</td>
<td></td>
<td>Water or see monograph</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sublingual Tablets</td>
<td>30</td>
<td></td>
<td>Water or see monograph</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buccal Tablet</td>
<td>240</td>
<td></td>
<td>Water or see monograph</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard Shell Capsule</td>
<td>see monograph</td>
<td></td>
<td>0.05M Acetate Buffer pH 4.5</td>
<td></td>
<td>Need upper mesh</td>
</tr>
<tr>
<td>Plain coated Tablet</td>
<td>30</td>
<td>5 min. in 25 degree C water</td>
<td>Water or see monograph</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed Release Tablets</td>
<td>60</td>
<td>5 min. in 25 degree C water</td>
<td>Simulated Gastric TS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Enteric Coated)</td>
<td>see monograph</td>
<td></td>
<td>Simulated Intestinal Fluid TS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed Release Tablets</td>
<td>60</td>
<td></td>
<td>Simulated Gastric TS</td>
<td>No Disk</td>
<td>Mentions the use of Apparatus B</td>
</tr>
<tr>
<td>(Enteric Coated) Softshell capsules</td>
<td>60</td>
<td></td>
<td>Simulated Intestinal Fluid TS</td>
<td>With Disk</td>
<td></td>
</tr>
</tbody>
</table>

- **Acceptance Criteria**: If 1-2 fail, then run 12 more, if 3 out of 18 fail, then the test fails.
- **Use of Disks (by default)**: Vitamin-mineral (yes), botanical and dietary supplements other than vitamin-mineral, and enteric coated (no).
The USP Dissolution Apparatus Types

- USP 29 - NF 24 <711> Dissolution
  - Apparatus 1 – Basket Apparatus
  - Apparatus 2 – Paddle Apparatus
  - Apparatus 3 – Reciprocating Cylinder (not JP)
  - Apparatus 4 – Flow-through Cell Apparatus (JP - App.3)
  - Apparatus 5, 6 – Paddle over disk, rotating cylinder
  - Apparatus 7 – Reciprocating Holder

- Ph. Eur. 2.9.3 Dissolution Test for Solid Dosage Forms

- JP General Tests - Processes and Apparatus 6.10 Dissolution Test
Dissolution: Apparatus types

Apparatus 1 and 2
Dissolution: Apparatus types

Apparatus 1 and 2
<711> Dissolution: Apparatus types

Apparatus 3
Disintegration: Apparatus types

Apparatus 4
Dissolution Requirements

<table>
<thead>
<tr>
<th>USP Class</th>
<th>Combination of Vitamins or Minerals Present</th>
<th>Dissolution Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Oil-Soluble Vitamins</td>
<td>not applicable</td>
</tr>
<tr>
<td>II</td>
<td>Water-Soluble Vitamins</td>
<td>one index vitamin; folic acid (if present)</td>
</tr>
<tr>
<td>III</td>
<td>Water-Soluble Vitamins with Minerals</td>
<td>one index vitamin and one index element; folic acid (if present)</td>
</tr>
<tr>
<td>IV</td>
<td>Oil- and Water-Soluble Vitamins</td>
<td>one index water-soluble vitamin; folic acid (if present)</td>
</tr>
<tr>
<td>V</td>
<td>Oil- and Water-Soluble Vitamins with Minerals</td>
<td>one index water-soluble vitamin and one index element; folic acid (if present)</td>
</tr>
<tr>
<td>VI</td>
<td>Minerals</td>
<td>one index element</td>
</tr>
</tbody>
</table>

☑️ Vitamin A (if present) – for tablets only
Dissolution Requirements

✓ Vitamin A: App 2 with actinic vessels
✓ Folic Acid:
  ✓ Test 1
    ✓ App 1: capsules
    ✓ App 2: tablets
✓ Test 2:
  ✓ App 3
✓ Note: …and you still need to do the index vitamin and/or mineral testing
Dissolution Requirements

✓ Dissolution conditions for index water soluble vitamins and index minerals:
  ✓ Test 1:
    ✓ App 1: capsules
    ✓ App 2: tablets
  ✓ Test 2: (not for minerals)
    ✓ Apparatus 3

✓ Note: You must still test for Folic acid if present.

✓ Rupture Test for soft shell capsules:
  ✓ Now App 4 lipidic cell application
Questions?
Instrument development...
Semi-automated closed-loop system
In the lab...
The Flow Cell

- The test sample is located in a small-volume cell through which solvent passes at 37 °C.
- The eluate is filtered upon leaving the cell.
- The eluate is analyzed directly (on-line) with a spectrophotometer and/or collected in a fraction collector (off-line).
Open and Closed Loop Configurations

- **Open System** – uses, continuously, fresh media pumped through the cell. A known part of the eluate is analyzed and the rest of the flow goes to waste. Very easy pH change possible.

- **Closed Loop System** – after the cell the media is returned and then re-circulated for each cell.
Open loop Off-line: flow direction

Fraction collector can be replaced by a UV-Vis to have an Open loop On-line with a splitting valve
When do we use an Open Loop System?

✓ For poorly soluble compounds, low dosage forms to maintain the sink conditions

✓ Easy pH change for pH sensitive release products

✓ IVIVC studies that require multiple pH changes

✓ Any method that requires an automated media change
Closed loop On-line: flow direction
When do we use a Closed Loop System?

- Need to work with any fixed volume, less than 400 mL or more than 1000 ml of media. An official USP method for small volume (as low as 5 mL depending on the cell).
- Low amount of drug to detect
- Dissolution of unique dosage forms (powders, pellets, suspensions, suppositories, soft gelatin capsules, implants, drug-eluting stents, microspheres, gels and creams…).
- Solves product build up, sticking, floating, sampling problems of paddle method.
USP chapter 711

Fig. 4. Large cell for tablets and capsules (top) Tablet holder for the large cell (bottom) (All measurements are expressed in mm unless noted otherwise.)

Fig. 5. Small cell for tablets and capsules (top) Tablet holder for the small cell (bottom) (All measurements are expressed in mm unless noted otherwise.)
European Pharmacopeia

Figure 2.9.3.5. – Flow-through cell
Dimensions in millimetres

SAMPLING AND EVALUATION
In the case of the paddle apparatus and the basket apparatus, withdraw at the prescribed time, or at the prescribed intervals or continuously, the prescribed volume or volumes from a position midway between the surface of the dissolution medium and the top of the basket or blade and not less than 10 mm from the vessel wall.

In the case of the flow-through apparatus, samples are always collected at the outlet of the cell, irrespective of whether the
USP 4 flow cells
Questions?