Addressing Dissolution Compliance 2017

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Dissolution and Drug Release Compendial Updates
Compendial Updates

<1724> Semisolid Drug Products – Performance Tests
<1092> The Dissolution Procedure: Development and Validation
<711> Dissolution and Cross Linking of Gelatin Capsules
<1236> Solubility Measurements
Semisolid Drug Products - Performance Tests
New USP Chapters – In Process Revision

Tests for Semisolid dosage forms

• First developed as <725> Topical and Transdermal Drug Products – Product Performance Tests published in PF 35(3) [May-Jun 2009]

• Transferred into three USP Chapters:
  - <3> Topical and Transdermal Drug Products – Quality Tests
  - <724> Drug Release
  - <1724> Semisolid Drug Products – Performance Tests
USP <3> Topical and Transdermal Drug Products – Quality Tests

USP PF 36(6) Nov-Dec 2010, In-Process Revision
official USP 35 2012

• Contains Product Quality Tests in accordance with ICH Q6A – Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and new Drug Products: Chemical Substances

• **Universal Tests**: Description, ID, Assay and Impurities

• **Specific Tests**: Physicochemical Properties, Uniformity, Water Content, Microbial Limits, Antimicrobial and Antioxidant Preservative, Sterility, pH, Particle Size
  - Ophthalmic Dosage Forms
  - Topically Applied Semisolid Drug Products
  - Transdermal Delivery Systems
USP <724> Drug Release

Existing Chapter for Drug Release.

Due to ICH, USP Apparatus 3 – Reciprocating Cylinder and Apparatus 4 – Flow Thru Cell were moved to <711> Dissolution

Contains Acceptance Tables and:

- Apparatus 5 - Paddle Over Disk
- Apparatus 6 - Rotating Cylinder
- Apparatus 7 - Reciprocating Holder:
  - Disk Sample Holder
  - Angled Disk
  - Cylinder Holder
  - Acrylic Rod
  - Spring Holder
<1724> Semisolid Drug Products - Performance Tests

Official USP 36, April 2013

Performance tests for topical dosage forms including creams, ointments, gels and lotions through various diffusion cell apparatus.

In Vitro Performance Tests:
- Vertical Diffusion Cell – Franz Cell
- Immersion Cell – Enhancer Cell
- Flow Through Cell – Apparatus 4
USP <1724> Semisolid Drug Products - Performance Tests

(1724) SEMISOLID DRUG PRODUCTS—PERFORMANCE TESTS

SCOPE

The scope of this general chapter is to provide general information for performance testing of semisolid drug products, various types of equipment employed for such testing, and potential applications of the performance testing.

PURPOSE

This chapter provides general information about performance testing of semisolid drug products, the theory and applications of such testing, information about the availability of appropriate equipment, and likely developments in performance testing of semisolid drug products. General chapter Topical and Transdermal Drug Products—Product Quality Tests (3) provides

THEORY OF THE DIFFUSION CELL
Theory of the Diffusion Cell

The diffusion cell is a reliable and reproducible means of measuring drug release from semisolid dosage forms.

A thick layer of the semisolid product under evaluation is placed in contact with a medium in a reservoir, and the latter acts as a receptor when the drug substance diffuses through the formulation, across the membrane, and into the reservoir.

Diffusion occurs across an inert, highly permeable support membrane.

The membrane is intended to keep the product and the receptor medium separate and distinct.

Membranes should offer the least possible diffusional resistance and should not be rate controlling.

Samples are withdrawn from the receptor chamber, typically at 1-h intervals over a 4–6 h period.
Vertical Diffusion Cell

Typically, amounts of the semisolid sample NLT 200 mg are used. Diffusive communication between the semisolid sample and the reservoir takes place through the support membrane. The membrane is intended to keep the drug product sample and receptor medium separate and distinct.

A heating jacket or a suitable device should be used to maintain the temperature within the cell.

The release rate experiment is carried out at 32 ± 1°, except in the case of vaginal drug products for which the temperature should be 37 ± 1°.

Usually a set of 6 cell assemblies are operated together at one time in a single run.

Vertical Diffusion Cell

Sampling is generally performed over a 4–6 h time period, and the volume withdrawn is replaced with stock receptor medium.

To achieve sink condition, the receptor medium must have a high capacity to dissolve the drug, and the drug concentration in the receptor medium at the end of the test ideally should be as low as possible.

For each cell, the amount of drug released (mg/cm²) at each sampling time ($t_1$, $t_2$, etc.) is determined, and the cumulative amount released plotted versus time.

The slope of the resulting line is a measure of the rate of drug release.

The test is often conducted with a group of 6 or 12 cells per test run.

The average of 6 slopes for each test and reference product is a measure of the drug release rate from the dosage form.
Vertical Diffusion Cell

**Figure 1.** Vertical diffusion cell—Model A (All dimensions are in mm. All diameters are ±0.5 mm. All lengths are ±2 mm).

**Figure 2.** Vertical diffusion cell—Model B (All dimensions are in mm. All diameters are ±0.5 mm. All lengths are ±2 mm).

**Figure 3.** Vertical diffusion cell—Model C (All dimensions are in mm. All diameters are ±0.5 mm. All lengths are ±2 mm).

Immersion Cell – Enhancer Cell

The immersion cell can be used with USP Apparatus 2 (see general chapter Dissolution <711>) with vessel volumes that vary from 100 mL up to 4 L, but the 150- or 200-mL vessels are the most commonly used.

A flat-bottom variation of the 150- or 200-mL vessel can be used to avoid the issue of dead space under the cell when it is used in a round-bottom vessel.

If analysts are going to use a 150- or 200-mL vessel with USP Apparatus 2, then the appropriate modifications must be made, including holders for the small-volume vessels and replacement of the standard paddle with the appropriate paddle.

It also may require repositioning of any automated sampling device and/or manifold.

The water bath or vessel heater should be set to have the medium temperature at 32.0 ± 0.5° or 37.0 ± 0.5°.

Before loading the cells and placing the medium in the vessel, set the paddle height, which is 1.0 ± 0.2 cm above the surface of the membrane.

Immersion Cell – Enhancer Cell

All other operational parameters, such as level, vibration, wobble, etc., should be set at the same conditions defined for USP Apparatus 2.

The small-volume condition is qualified by first using the standard Apparatus 2 setup and Performance Verification Test, Apparatus 1 and 2 (see Dissolution <711>).

Cut the membrane to an appropriate size. If necessary, soak the membrane in the receptor medium for at least 30 min before loading. If the membrane is thick, a longer soaking time period may be necessary.
Immersion Cell – Enhancer Cell

Prepare the immersion cell components as specified by the device manufacturer.

Fill the reservoir dosage area with the sample under test. Ensure that the reservoir is filled to the top in order to minimize the possibility of air bubble formation between the surface of the sample and the membrane.

A uniform surface can be obtained with the aid of a spatula.

The typical quantity of sample is between 300 mg and 2 g, depending on the type of immersion cell used.

An excess of sample is needed to obtain a steady-state drug release rate.

Immersion Cell – Enhancer Cell

Using forceps or tweezers, remove the membrane from the soaking medium and place it over the top of the sample compartment. Ensure that the membrane is free of wrinkles.

Assemble the immersion cell components as specified by the device manufacturer.

Carefully place the completed assembly into the bottom of the dissolution vessel with the membrane facing up.

The appropriate preheated medium may be preloaded in the vessel or can be added after immersion of the immersion cell to start the test.
Immersion Cell – Enhancer Cell

Samples from at least 5 time points should be obtained in the steady-state (linear) portion of the drug release profile.

The data points are cumulative and expressed as concentration per surface area, typically per cm², as a function of the square root of time.

Sampling is generally performed over a 4–6 h time period.

The slope of the line is the in vitro release rate of drug from the product.

At the end of the test period, dismantle the cell and examine the contents for anything unusual that could explain any anomalous data (e.g., leaks, bubbles, etc.).
Immersion Cell – Enhancer Cell
Immersion Cell – Enhancer Cell

USP <1724> Semisolid Drug Products – Performance Tests,
US Pharmacopeial Convention, USP 39, 2016
Flow-Through Cell

The membrane, which may be soaked in the receptor medium beforehand, is loaded in the membrane ring using the provided tool. The membrane should be large enough to overlap the top edge of the reservoir body with a diameter of 18 mm.

The sample is loaded into the reservoir. The other side of the tool can be used to hold the reservoir while loading the sample.

If necessary, the excess of sample can be removed using a spatula. Screw the membrane ring onto the sample reservoir. Ensure that the membrane is free of wrinkles while screwing.

Remove the semisolid sample adapter from the tool, and slide it into the cylindrical part of the 22.6-mm cell with the membrane facing downward.

Vertical positioning within the cell can be adjusted using the tablet holder scoring, if desired (see Figure 9).

If the lower position is chosen, release can be higher due to the proximity to the flow inlet. The prepared cell is inserted in a heating jacket.

Flow-Through Cell

Figure 8. Adapter for topical dosage forms in USP Apparatus 4 (All dimensions are in mm).

Figure 9. Vertical positioning of the insert using the tablet holder scoring (all dimensions are in mm).

Troubleshooting

Many of these issues are discussed in the USP <1724> Semisolid Drug Products – Performance Testing Chapter:

Deaeration
Sample Preparation in Various Cells
Starting the Test
Variable Test Results
Membrane Selection
Calculation
Comparison...
SOURCES FOR MEMBRANES
Ideal Membrane Characteristics

Minimize resistance to drug transport

- High porosity
- Minimal thickness
- No drug binding
Examples of Membranes Used in In Vitro Tests

- Regenerated Cellulose (Dialysis membrane)
- Silastic membrane - polydimethyl siloxane
- Fluoropore FHLP hydrophobic membrane
- Ethylene vinyl acetate (Cotrans 9702)
- Skin (human, rat, rabbit, porcine, mice)
- Cuprophan
- Carbosil
- Polysulfone
- Tuffren
3-M Drug Delivery Systems:
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We will respond to your email request in 24 - 48 business hours.
Chapter 1092 addresses the development and validation of dissolution methods, with a focus on solid oral dosage forms. Many of the concepts presented, however, may be applicable to other dosage forms and routes of administration.

The organization of 1092 follows the sequence of actions often performed in the development and validation of a dissolution test.
1) PRELIMINARY ASSESSMENT (FOR EARLY STAGES OF PRODUCT DEVELOPMENT/DISSOLUTION METHOD DEVELOPMENT)

   1.1 Performing Filter Compatibility
   1.2 Determining Solubility and Stability of Drug Substance in Various Media at 37
   1.3 Choosing a Medium and Volume
   1.4 Choosing an Apparatus
2) METHOD DEVELOPMENT

2.1 Deaeration
2.2 Sinkers
2.3 Agitation
2.4 Study Design
   2.4.1 Time Points
   2.4.2 Observations
   2.4.3 Sampling
2.5 Data Handling
2.6 Dissolution Method Assessment
USP <1092> The Dissolution Procedure: Development and Validation (USP 38 NF 33, 2015)

3) ANALYTICAL FINISH

3.1 Sample Processing
3.2 Filters
3.3 Centrifugation
3.4 Analytical Procedure
3.5 Spectrophotometric Analysis
3.6 HPLC
USP <1092> The Dissolution Procedure: Development and Validation (USP 38 NF 33, 2015)

4) AUTOMATION

4.1 Medium Preparation
4.2 Sample Introduction and Timing
4.3 Sampling and Filtration
4.4 Cleaning
4.5 Operating Software and Computation of Results
4.6 Common Deviations from the Compendia Procedures That May Require Validation
4. AUTOMATION

Automated dissolution systems may be configured in various ways and degrees. The elements of test preparation, initiation, sampling and timing, and cleaning all can be automated. Fully automated systems are available, as are systems where individual steps, such as media preparation or sampling, are automated. This section will discuss operational steps that can be automated. The level of complexity for automation depends on whether the instrument configuration is open or closed loop and also whether the analytical device is coupled online or offline. 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. The decision on the configuration usually depends on the number of samples to be processed and the time required for their analysis.

Automation may require deviations from the pharmacopeial specifications of the instruments, such as incorporation of an integrated outlet on the bottom of the vessel for cleaning and replacement of medium.

Operational steps that are not part of the compendial procedure should be validated. Deviations from the standard procedure described in (711), such as use of sampling probes or fiber-optic probes, should be validated against the standard procedure.
4.3 Sampling and Filtration

Autosampling is a useful alternative to manual sampling, especially if the test includes several time points. The transfer and filtration of sample solutions from the dissolution instrument to the analytical unit may be undertaken via tube connections or via robotic devices operated in a stepwise procedure. Sample volumes may be removed from the dissolution medium and not returned (consumptive sampling), or the sample volume may be returned to the dissolution medium (recirculated sampling).

There are many brands of autosamplers, including semi-automated and fully automated systems. Routine performance checks, cleaning, and maintenance, as described in the pertinent standard operating procedures or metrology documents, help to ensure reliable operation of these devices.

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. If filters are used that are different from those used for manual sampling, then these different filters should also be evaluated separately. 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. Sampling probes should pull the sample from the sampling zone. Instruments for which the sampling occurs through the hollow shaft should be designed with a means to adjust the depth of the inlet aperture to allow conformance with this requirement. The programmed sampling volume depends on the dead volume of the tubing, cuvettes, and other devices and has to be adjusted accordingly.

A recirculated sampling alignment can be operated either by discharging the tubing contents into the vessel after each sampling or by allowing the tubing to remain filled with solution in the intervals between sampling points. In the latter case, the dead volume and carryover effects are important considerations.

The need for sample volume replacement should be considered. In consumptive sampling with multiple sampling time points, the withdrawn volume may be replaced with an equal volume of fresh medium. 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 re-
placement 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.

Interaction of dissolved drug substance with the sampling and transfer devices is an important consideration. When adsorption of the dissolved drug substance occurs, it most often involves surfaces of the dissolution apparatus or sampling filters and tubing. Adsorption may be pH dependent in the case of charged, dissolved drug substance. Adsorption of the dissolved drug to the parts of the sampling device should be assessed using a typical sample solution (dissolution sample from the product or drug substance with formulation matrix) with known concentration. The typical design is a cross-validation with aliquots of the same sample solution passing and bypassing the sampling device (including the sampling probe, filter, tubing, valves, and pump). There is no general recommendation that may give preference to any kind of material or equipment construction (e.g., glass or specific polymers). See section 5.7 Considerations for Automation for more information.

In addition to the information in section 2.4.3 Sampling, connections of pumps and tubing may be sources of contamination in automated systems. Interferences with the spectroscopic analytical procedures, which are commonly used for dissolution testing, are less of a concern. However, interferences must be evaluated if the product under investigation contains low-dose metal salts, as do some dietary supplements.

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. Depending on the type of polymer and its crystallinity and density, leaching of constituents, mainly plasticizers, may occur. Leachables can interfere with the analytical procedure. The concentration leached to the sample solution usually depends on the surface, the temperature, the exposure time, the hydrodynamic conditions, and the composition of the media.
4.6 Common Deviations from the Compendial Procedures That May Require Validation

Some common areas of deviation from compendial procedures include the following:

- Sample introduction relative to start of spindle rotation
- Residence time and positioning of sampling probes
- Recirculated versus consumptive sampling
- Sample volume replacement in consumptive sampling.
USP <1092> The Dissolution Procedure: Development and Validation (USP 38 NF 33, 2015)

5) VALIDATION

5.1 Specificity/Placebo Interference
5.2 Linearity and Range
5.3 Accuracy/Recovery
5.4 Precision
  5.4.1 Repeatability of Analysis
  5.4.2 Intermediate Precision/Ruggedness
  5.4.3 Reproducibility
5.5 Robustness
5.6 Stability of Standard and Sample Solutions
5.7 Considerations for Automation
USP <1092> The Dissolution Procedure: Development and Validation (USP 38 NF 33, 2015)

6) ACCEPTANCE CRITERIA

6.1 Immediate-Release Dosage Forms
6.2 Delayed-Release Dosage Forms
6.3 Extended-Release Dosage Forms
6.4 Multiple Dissolution Tests
6.5 Interpretation of Dissolution Results
   6.5.1 Immediate-Release Dosage Forms
   6.5.2 Delayed-Release Dosage Forms
   6.5.3 Extended-Release Dosage Forms

7) REFERENCES
Workshop for Dissolution Testing of Capsules
Revision of <711> Dissolution: 24-25 March, 2014

The development of dissolution procedures for capsules is most challenging mainly for cross-linked gelatin capsules and capsules with lipophilic fillings. The USP Dosage Forms Expert Committee has created Expert Panels to suggest improved compendial approaches to these challenges. The Panels are also interested in concerns and quality attributes of capsules with shells made from other materials.

This workshop aims to discuss manufacturing, formulation, storage, and packaging conditions that could have an impact in the dissolution testing of any type of capsules (gelatin, starch derivatives, cellulose derivatives) containing any type of filling (solid, semisolid, liquid, dispersion, etc.). USP activities regarding the revision of relevant USP–NF General Chapters will also be discussed.
Pellicle

- Swollen, very thin, tough, rubbery, water-insoluble membrane.
- Acts as a barrier to dissolution and restricts release of the drug.
- Not disrupted easily by gentle agitation.
- Addition of enzymes either pancreatin or pepsin will digest the denatured gelatin.
- USP allows to add enzyme to dissolution medium when specification failures are observed.
Current Harmonized Pharmacopeia Requirement:

“For hard or soft gelatin capsules and gelatin coated tablets that do not conform to the Dissolution specifications, repeat the test as follows:

- Where water or medium with a pH of less than 6.8 is specified as the Medium in the individual monograph, the same Medium specified may be used with the addition of purified pepsin that results in an activity of 750,000 Units or less per 1000 mL – For media with a pH of 6.8 or greater pancreatin can be added to produce not more that 1750 USP Units of protease activity per 1000 mL.”
Workshop for Dissolution Testing of Capsules
Revision of <711> Dissolution: 24-25 March, 2014

Topics:

- Manufacture of hard and soft capsules, including nongelatin capsules, and capsules containing lipophilic filling
- Causes of crosslinking in gelatin capsules (formulation, storage conditions, etc)
- Modified release capsules
- Use of enzymes in the dissolution testing of crosslinked gelatin capsules
- Dissolution testing of dietary supplements
- Revisions to USP–NF General Chapters <711> Dissolution, <1094> Capsules—dissolution Testing and Related Quality Attributes, and <2040> Disintegration and Dissolution of Dietary Supplements
- Validation and verification of dissolution procedures using enzymes
- Discussion of case studies
Agenda

- Gelatin and Cross-Linking
- USP Procedure pre-40(6)
- 40(6) Revisions to USP <711> and <2040>
- Failures
- Prevention of Cross-Linking
What is Gelatin?

- Hydrolyzed form of collagen
- Collagen is obtained from various animal by-products
- Used as a gelling agents in a variety of applications:
  - Food
  - Cosmetics
  - Photography
  - Pharmaceuticals
What is Cross-Linking?

Cross-linking is the “formation of strong chemical linkages beyond simple hydrogen and ionic bonding between gelatin chains.”

- Reaction is generally irreversible
- Renders gelatin insoluble
- Reaction catalyzed by a number of chemical and environmental factors

*From USP Stimuli to the Revision Process, Use of Enzymes in the Dissolution Testing of Gelatin Capsules and Gelatin-Coated Tablets – Revisions. USP-PF 40(6)*
Gelatin Structure

- Protein with some potentially reactive side chains
- Often will form helices, etc.
- Can form covalent and hydrogen bonds between itself and another chain
- Cross-linking can occur in collagen as condensation products between aldehydes and amines, or between two aldehydes
- Gelatin more prone to cross-linking than collagen
Cross-Linking Impact

Capsule shell opening is delayed or stopped by pellicle formation on the internal or external gelatin surface

- Visually confirmed with seeing thin membranes or gelatinous masses
- Cross-linking amount can be determined by other methods – NMR, UV/Fluorescence Spectroscopy, MRI, Near IR Spectroscopy
Cross-Linking Impact

Lower and/or incomplete dissolution in vitro

In severe situations, can lead to problems in vivo as well

Cross-linking most commonly seen in stability testing

Pictures used courtesy of Vivian Gray, 2014
Current USP Approach to Cross-linking
USP <711>

“For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the Dissolution specification, repeat the test as follows.”

- Media < pH 6.8 – repeat test with addition of purified pepsin (<750,000 units/L)
- Media ≥ pH 6.8 – repeat test with addition of pancreatin (<1750 USP units of protease activity/L)
Pepsin

- Digestive enzyme in stomach which converts proteins to peptides
- For cross-linking, this is used to clean gelatin proteins in places other than cross-linking site and allow rupture
- Typically obtained from glandular layer of hog stomach
- Peak activity at pH 2, good activity to ~pH 4.5
Pancreatin

- Mixture of digestive enzymes created by exocrine cells of pancreas
- Typically porcine/bovine origin
- Has good protease activity
- Peak Activity at pH 6.8, good between 6-8
Success with USP <711>

- Pepsin activity generally felt sufficient to deal with mild to moderate cross-linking
- Pancreatin able to handle mild cross-linking
Limitations with USP <711>

- No good enzymes for pH 4-6.8
- Surfactant/Enzyme incompatibility
  - SLS and other surfactants can denature enzymes
  - Other enzymes can enhance activity
- Pancreatin levels too low?
Enzyme Activity in mid-range
Proposed Changes to <711>
Key Changes

- New Enzymes!
  - Papain
  - Bromelain
- Pre-treatment Option
- Increase in Pancreatin Levels
- Clarifications
When Enzymes are to be Used

<711> changed to indicate the enzymes are to be used only when:

- Product contains gelatin
- Product does not meet dissolution specification
- Evidence of cross-linking is observed

Prior to this, no evidence of cross-linking was required
Cross-Linking Evidence

Defined in USP <1094> Liquid-Filled Capsules – Dissolution Testing and Related Quality Attributes PF 38 (1)

• Observations (Gelatinous mass, pellicles, swelling w/o rupture)
• Instrumental Techniques (C13-NMR, FTIR, MRI, etc.)
• Switching capsule shells with fresh
Failure with Cross-Linking

If cross-linking is seen, and failure occurs you DO NOT need to continue testing until the last stage.
Papain

- Derived from unripe green papaya
- Commonly used as meat tenderizer, dietary supplement, etc.
- Digests protein substrates more extensively than pancreatin
- Optimal pH between 6-7 for most substrates, pH 5 for gelatin
- Powder stable 2 years at 2-8°C
Bromelain

• From Pineapple Stems
• Used commonly as meat tenderizer, anti-inflammatory agent, leather tanning, etc.
• Optimal pH 5-7, stable from pH 3.0-6.5
• Powder stable 1.5-3 years at 2-8°C
Papain and Bromelain in Dissolution

• Both suitable for use between pH 4-6.8
• Papain used in activity of NMT 550,000 Units/L
  • Activity determination explained in Papain monograph, under Assay
• Bromelain used in activity of NMT 30 gelatin-digesting units (GDU)/L of dissolution media
  • Activity determination determined in Reagent Specifications, Bromelain
Enzyme Choice

- Pepsin now clarified for use with pH ≤ 4.0
- Pancreatin for use with pH ≥ 6.8
- For pH 4.0 – 6.8, you can use either Papain or Bromelain
Points of Consideration

- Enzyme interaction with media/formulation should be confirmed with samples through method development
- Enzyme(s) should be shown to be effective vs. cross-linked samples
  - Tier 1 vs. Tier 2 with same stressed samples (see USP <1094>)
  - Confirm performance of enzyme(s) to give proper results
  - Use enzyme with best activity
- Validation of a method should include enzyme use where appropriate
Changes to USP <2040> Disintegration and Dissolution of Dietary Supplements

- Similar revisions to USP <711> regarding new enzymes, higher pancreatin, presoaking, etc.
- Chewable tablets now require IR dissolution testing (not related to cross-linking)
- Rupture or Disintegration may be more sensitive test, should be determined on a method to method basis
What if failure still occurs w/ enzyme?

- If failure is still seen with enzyme, then you fail.
- It is not permissible to add additional enzymes or other techniques with a validated method.
<1236> Solubility Measurements

USP PF 43 (2)
In-Process Revision
March 2017
USP <1236> Solubility Measurements

Accurate determination of the aqueous solubility of pharmaceutical materials is important for understanding both quality control and drug delivery issues for pharmaceutical formulations.

Accurate measurements of aqueous solubility of the API is affected by:

- **Physicochemical properties**: surface area, particle size, crystal form
- **Media properties**: pH, polarity, surface tension, surfactants, co-solvents, salts
- **Measurement parameters**: temperature, time, agitation method
USP <1236> Solubility Measurements

Sections include:

• Thermodynamic Equilibrium and Solubility

• Methods of Estimating Aqueous Solubility

• Factors Affecting Solubility and Solubility Measurements
  • Effects of: Salts and Counter-Ions, Co-Solvents, Surfactants, Complexing Agents and Surface Energy (nanoparticles)

• Experimental Methods
  • Saturation Shake Flask Method – This method should be used when equilibrium solubility needs to be determined. Other methods may be used to evaluate apparent solubility, but are not considered suitable for evaluation of true equilibrium solubility.
USP <1236> Solubility Measurements

Shake Flask Method (triplicate):

- **Sample preparation**: stoppered flask with 1-2 mg/ml in excess of the estimated solubility
- **Equilibration of solution**: 24 hours minimum, temp control ±0.5°C, clarify, dilute to within range of analytical method
- **Analysis**: HPLC preferred because it can detect instability by resolving drug-related impurities
- **Reporting of solubility results**: solubility at the final timepoint of consistent results
USP <1236> Solubility Measurements

Methods for Determination of Apparent Solubility

• Potentiometric Titration
• Turbidimetry (DMSO)
• Miniaturization, High-Throughput, and Automation in Solubility Measurement – necessary for using ads little compound as possible
Methods for Determination of Apparent Solubility (cont.)

- Solubility measurements in Bio-Relevant Media (at 37.0 ±0.5°C). Media composition tables for:
  - Human Fasted-State Simulated Gastric Fluid (FASSGF)
  - Human Fed-State Simulated Gastric Fluid (FESSGF)
  - Human Fasted-State Simulated Intestinal Fluid (FASSIF)
  - Human Fed-State Simulated Intestinal Fluid (FESSIF)
  - Human Simulated Colonic Fluid (SCOF)
References

- USP PF 38(1) – <1094> Liquid-Filled Capsules – Dissolution Testing and Related Quality Attributes
- USP PF 40(6) - <711> Dissolution and <2040> Disintegration and Dissolution of Dietary Supplements
- USP PF 40(6) – Stimuli to the Revision Process: Use of Enzymes in the Dissolution Testing of Gelatin Capsules and Gelatin-Coated Tablets – Revisions
- USP PF 24(5) – Collaborative Development of Two-Tier Dissolution Testing for Gelatin Capsules and Gelatin-Coated Tablets Using Enzyme Containing Media
- USP Workshop of Dissolution Testing of Capsules, March 24-25 2014, Rockville, MD
QUESTIONS?