Addressing Dissolution Compliance

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Dissolution and Drug Release Compendial Updates

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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
  - Opthalmic Dosage Forms
  - Topically Applied Semisolid Drug Products
  - Transdermal Delivery Systems

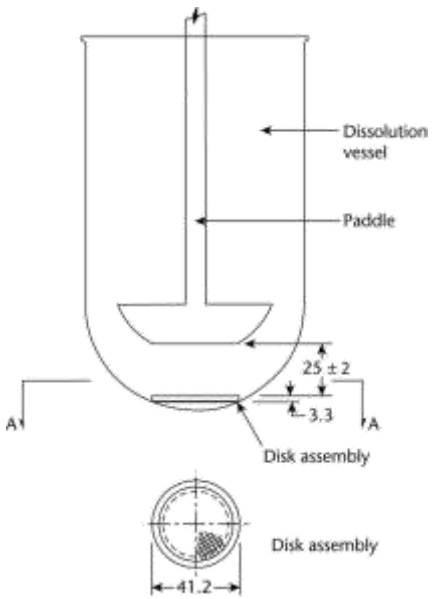
USP <724> Drug Release

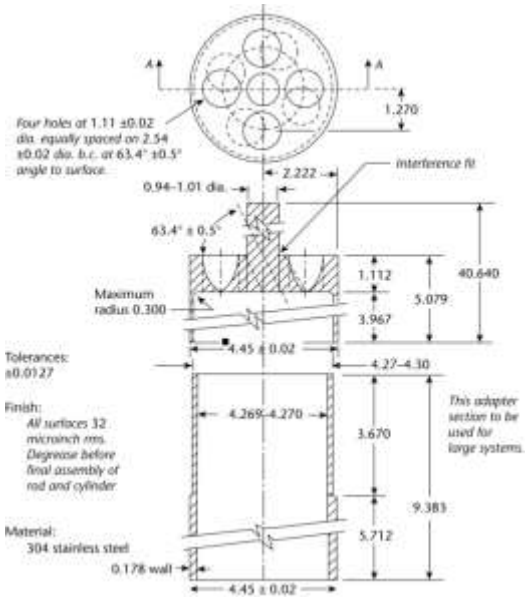
Existing Chapter for Drug Release.

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

Compendial Dissolution Apparatus

Agilent Enhancer Cell

- Vessel volume 250 mL
- Operational minimum 50 mL volume
- Transdermals, creams and ointments

Enhancer Cell Practical Demonstration Video

https://www.youtube.com/watch?v=titGXLNpCyE

USP <1092> The Dissolution Procedure: Development and Validation (USP 38 NF 33, 2015)

USP Pharmacopeial Forum – In Process Revision

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.

USP <1092> The Dissolution Procedure: Development and Validation (USP 38 NF 33, 2015)

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

USP <1092> The Dissolution Procedure: Development and Validation (USP 38 NF 33, 2015)

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

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.

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

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 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 MI."

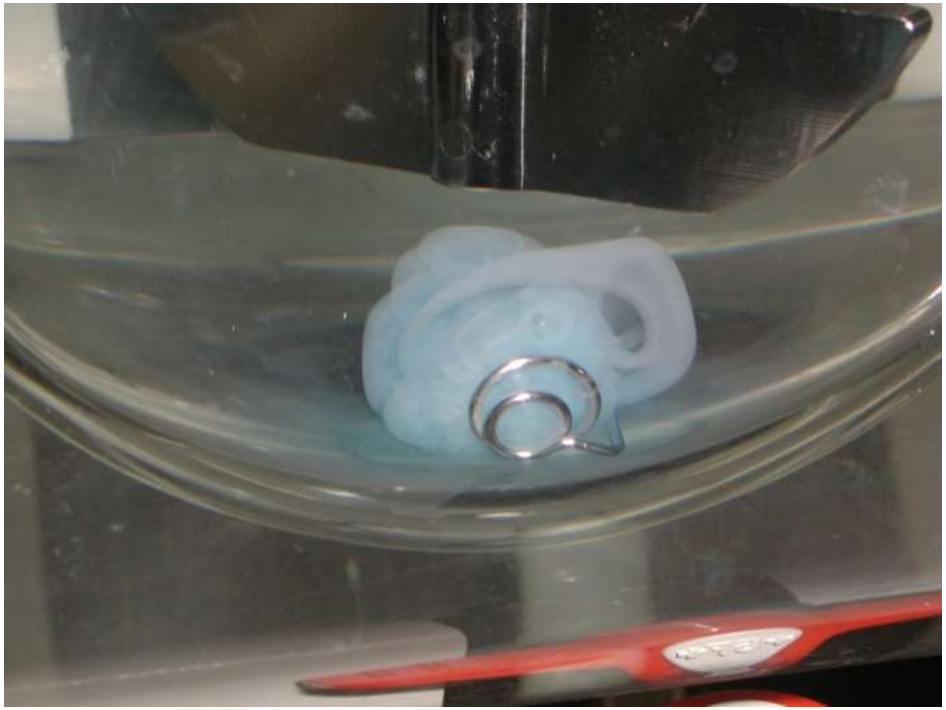
Cross-Linking of Gelatin Capsule Shells

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)

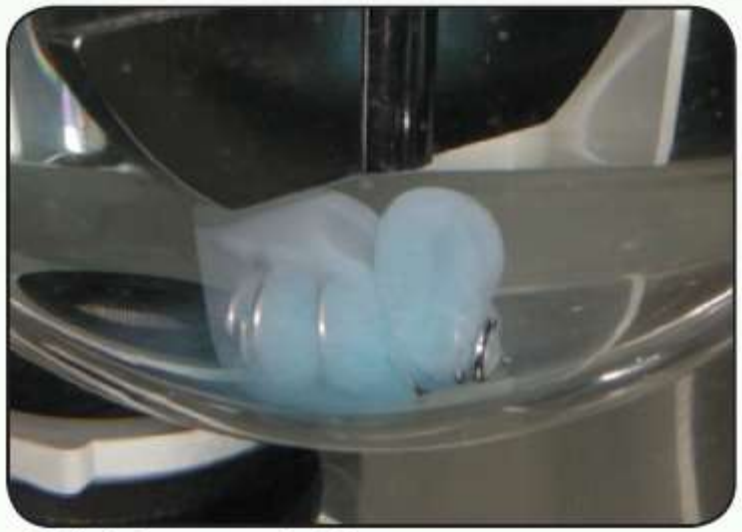
Gelatin Structure

- 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



Pellicle Formation Problem

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

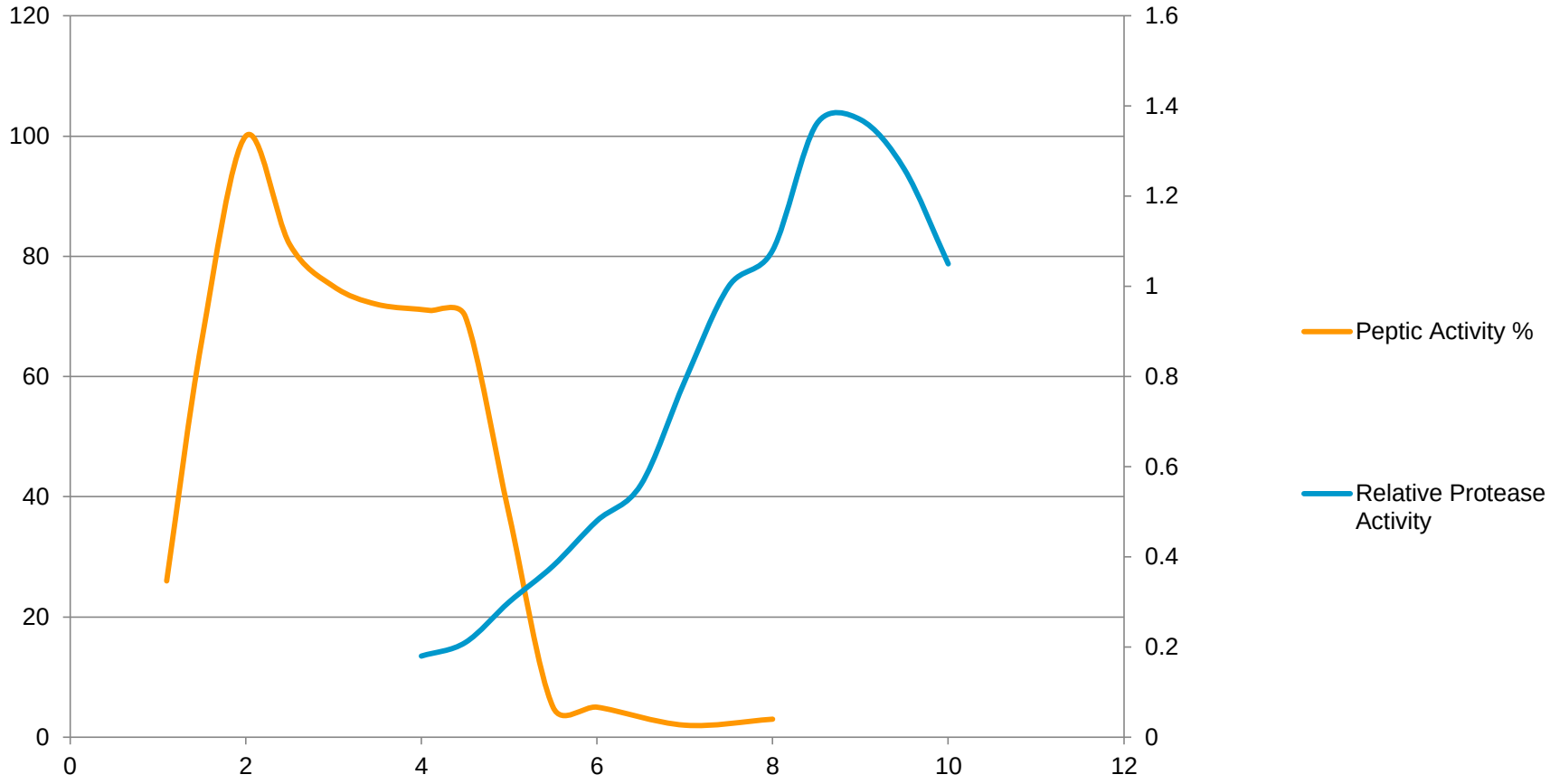
Success with USP <711>

- 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 2-8C

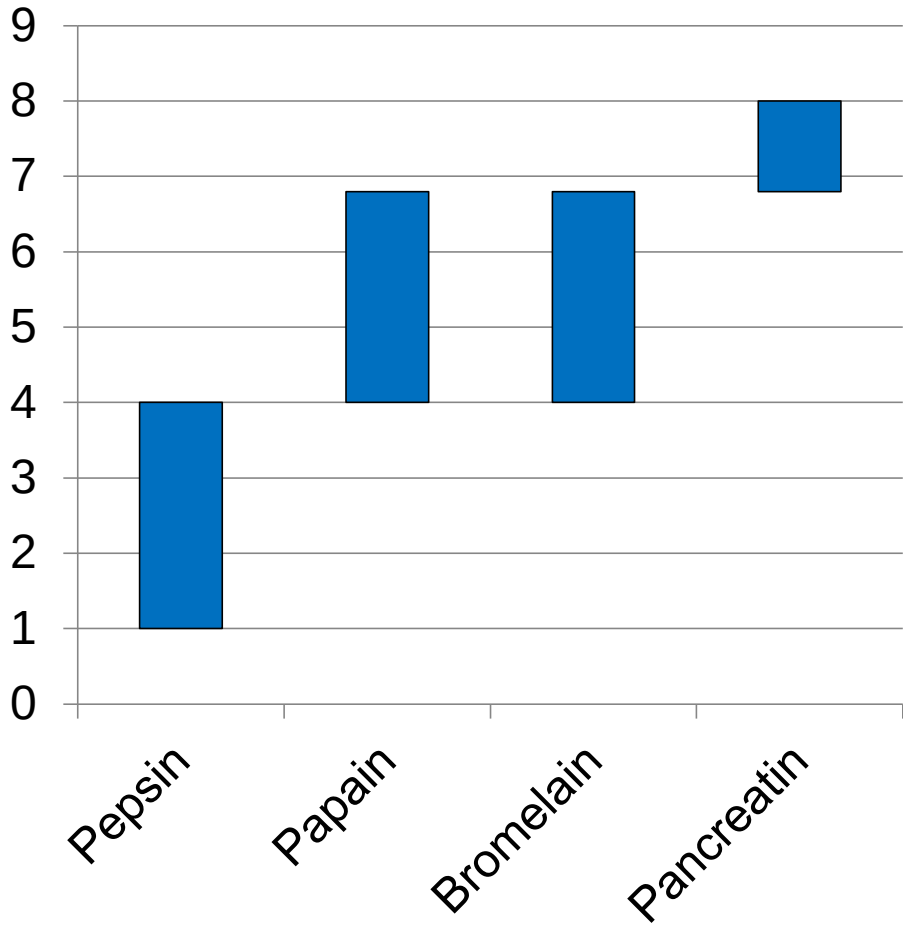
Bromelain

- 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 2-8C

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.

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