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Summary Report from the USP Workshop on Dissolution Testing of Capsules

Summarized on behalf of the FIP Dissolution–In Vitro Performance Focus Group by Amy R. Barker and Johannes Krämer

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The U.S. Pharmacopeia (USP) held a workshop coordinated by some USP expert panels at its headquarters in Rockville, MD, on March 24 and 25, 2014, to present and discuss the ongoing projects related to Dissolution Testing for Capsules. This paper presents a summary of the discussions held at this meeting.

CAPSULES AND CROSS-LINKING

Pharmaceutical capsule preparations consist mostly of either hard or soft gelatin shells filled with non-aqueous liquids, powders, semisolids, or solids (e.g., as multiparticulates). To a minor degree, alternative materials are being used for the manufacture of the shells.

The gelatin-containing capsule shell structure may exhibit structural changes by propagating cross-linking phenomena. This process continues during storage and may largely affect the outcome of in vitro dissolution tests. To overcome the poor hydrolysis rate of gelatin capsule shells, *USP* General Chapter <711> allows the addition of proteolytic enzymes, if needed. This is the so-called two-tier dissolution test procedure. However, the use of enzymes is complex because of the sensitivity of the biochemical reaction. Moreover, enzymatic activities expressed in units per mass are not harmonized internationally, which hinders their use. USP is currently working on a revision of its General Chapter <711> with the goal to facilitate the use of alternative proteolytic enzymes. This revision was the topic of a workshop held at USP headquarters in March 2014.

Establishing an understanding of the potential impact of capsules and cross-linking on drug product dissolution is critical not only for method development, but also for definition of appropriate specifications. Components contributing to cross-linking include the manufacturing process, the contents of the capsule (API and excipients), the composition of the capsule shell, and the environmental conditions to which the capsules and the drug product are exposed. The major component of the capsule shell is gelatin, which is a primary contributor to cross-linking. Gelatin sourcing should be tightly controlled, and the molecular weight fraction ratios should be restricted as tightly as possible so as not to contribute to either cross-linking (high molecular weight fractions) or brittleness (low molecular weight fractions). However, the presence of gelatin alone does not induce cross-linking. Components such as microcrystalline cellulose or any oxidizing agents that can degrade to aldehydes, such as formaldehyde, combined with high heat or humidity further promote cross-linking. It is necessary to understand and control each contributing factor as part of capsule and product manufacture. An additional means of minimizing the occurrence of cross-linking is to assure the most appropriate and effective packaging for the drug product. Packaging must protect the product from moisture and oxygen exposure. Development of products using hydroxypropyl methylcellulose (HPMC)-based capsules is underway, and this will eliminate the occurrence of cross-linking. Studies demonstrate that HPMC capsules experience delayed release versus their gelatin capsule-based counterparts. While there are multiple types of HPMC capsule options with different benefits, additional studies will be required to improve robustness of the capsule and to fully understand the impact of the HPMC capsules on measurements of dissolution performance.

USE OF ENZYMES TO OVERCOME CROSS-LINKING

The phenomenon of cross-linking should be evaluated as part of dissolution method development and validation. Addition of pepsin for acidic dissolution conditions or pancreatin for quasi-neutral dissolution conditions is accepted in the *USP* General Chapter <711>, but only in the national section, which is not fully harmonized with the *Japanese Pharmacopoeia* (*JP*) and the *European Pharmacopoeia* (*Ph. Eur.*). For instance, *USP* <711> describes how to determine addition of enzyme for overcoming cross-linking as part of dissolution methodologies. However, the Use of Enzymes in the Dissolution Testing of Gelatin Capsules Expert Panel is in the process of updating the *USP* general chapter to suggest different enzymes depending on the pH of the medium. As part of this effort, <1094> will also be revised to include discussions of theory and troubleshooting as well as common quality attributes for enzymes. To further assist with a general understanding of cross-linking as well as determination of enzyme activities, a stimulus article will be published by the expert panel. Other compendia such as the *European Pharmacopoeia* allow for the use of enzymes when justified and authorized by the competent authority (*Ph. Eur.* Chapter 5.17), yet the *Japanese Pharmacopoeia* does not accept addition of enzymes to overcome cross-linking, but rather recommends the use of succinated gelatin, which is does not cross-link, for the capsule shell.

DISSOLUTION METHOD

If high variability is observed including some atypically low dissolution results at S_1, it is necessary to confirm the

issue of cross-linking prior to progressing to Tier 2 testing with the addition of enzyme. If cross-linking is confirmed, Tier 2 testing will begin at S_1. Enzymes should only be required for the first part of the dissolution test. If pretreatment before dissolution testing is the selected option, it must be validated and the time must be included in the total time of the test. For modified-release products that include coatings such as enteric coatings or coated spheroids in capsules, the occurrence of cross-linking is likely. Specific coating contributors to cross-linking include solvent-based coatings, peroxide residues, or incomplete drying.

Case studies were presented to demonstrate examples of cross-linking. The differences between a "good" capsule with rapid dissolution (escape of a bubble followed by dispersion of powder and other materials) and a cross-linked capsule (appearance of a pellicle on the outside with cloudiness in the media or appearance of a pellicle on the inside of the capsule with swelling and distortion) were presented and discussed. The necessity of a clear understanding of the extent of cross-linking and definition of the testing path for an affected batch at the first occurrence of cross-linking as well as subsequent stability timepoints was discussed. Options of enzyme addition versus presoaking were presented, and there were multiple opinions of the benefits of each.

For all products, method development is the critical phase for defining cross-linking issues as well as the path for QC testing. In addition, if enzyme addition is recommended as an option during method development, media stability and method specificity in the presence of enzymes should also be evaluated and validated. If HPLC is the analytical tool for quantitation, then dilutions, turbidity, and any additional filtration requirements should be specified as part of the method. Options such as automation may improve random error issues that occur as part of dissolution testing, and different modes of detection may be explored to reduce sample preparation variability. In all of these cases, method validation must be performed to demonstrate the method is validated for its intended use. Dissolution method development and validation are presented in *USP* <1092>, which is under revision. There may be a difference between testing leveraged in product development versus applicable methods for routine quality control (QC) testing. Biorelevant media may apply more during development, while more traditional media or compendial based apparatus would apply for QC testing. Methods for QC should be understood and validated to be appropriately discriminating to detect manufacturing changes that would impact in vivo performance. While

Workshop speakers and moderators (left to right): Faye Han, Chris Moreton, Om Anand, Matt Richardson, Edward Shneyvas, Ewart Cole, Jian-Hwa Han, Madhusudan Vudathala, Michael Cutrera, Natalia Davydova, Vivian Gray, Erika Stippler, Jianmei Kochling, Margareth Marques, Greg Martin, Tom Langdon, Stephen Tindal, Jerry Wang, Jeff Schwartzenhauer, Steven Meyerhoffer, and Rakhi Shah. (Not pictured: Johannes Krämer and John Duan.) Photograph provided by Vivian Gray.

dissolution development and testing requirements for nutraceuticals are similar to those for innovator products, additional testing requirements are described in <2040> and include disintegration and rupture testing. Different testing for tablets versus capsules, vitamins, minerals, and botanicals are described in <2040>, which is currently under revision to include options for more uses of the rupture test as well as options for uses of different apparatus and appropriate modifications.

REGULATORY PERSPECTIVES

In Japan, the use of enzymes to overcome cross-linking is not accepted. The rationale as well as a clinical study reference paper (*Iyakuhin Kenyu*, **2001**, *32* (12), 804–813) were presented to facilitate communication of the compendial position differences. Regulatory authorities in the United States and the European Union are more harmonized because both accept the addition of enzymes. However, the degree of justification and requirements for acceptance as part of a new drug registration may differ. It is typical that tiered compendial methodology may be successful for immediate-release and delayed-release capsule products as a means to overcome cross-linking. In the case of modified-release products, additional method development and validation conditions may be required. In addition, for modified-release products, it is necessary to understand the potential for dose-dumping for all product strengths as well as to acquire the appropriate correlation, such as multimedia testing, for biowaivers. For liquid-filled capsule nutraceuticals, the rupture test may be proposed in place of dissolution as long as no organic additives are required to perform the test.

After an appropriate dissolution method is defined, it is important to establish a relevant specification. When a discriminating dissolution method is registered, completeness of dissolution may be the most relevant for establishing the specification. In this scenario, the method development report should describe the rationale for media selection, as well as the specific rationale for any additions of surfactants and enzymes to the media. When determining a discriminating specification, an understanding of inter- versus intra-batch contributions to any observed variability is important. In addition, specification determinations should consider the dissolution profile, averages at tested timepoints, variability at tested timepoints, and potential changes on stability. As part of specification setting, IVIVC data should be considered. If IVIVC data are not available, the relationship of data to clinical batches must be understood. After a discriminating dissolution test method with its respective specification is approved, it is expected that any manufacturing changes produce product that sufficiently matches the data of the batches from which the method and specification were set.

SPEAKER SUMMARY FOR USP WORKSHOP PROGRAM

USP Workshop on Dissolution Testing of Capsules
March 24-25, 2014, USP Headquarters, Rockville, Maryland

Date	Speaker	Topic
24 Mar 2014	James De Muth, Ph.D.	USP Welcome and Overview of the Revision Process
	Matt Richardson, Ph.D.	Manufacture of Hard Capsules
	Madhusudan Vudathala, M.Pharm.	Manufacture of Soft Capsules
	Michael Cutrera, M.S.	Causes of Crosslinking in Gelatin Caps
	Jian-Hwa Han, Ph.D.	Crosslinking and Dissolution Testing
	Richard Moreton, Ph.D.	Modified Release Capsules
	Stephen Tindal	Packaging Issues
	Vivian Gray	USP Revisions on <711> and <1094>
	Thomas Langdon	Use of Enzymes in Dissolution Testing
25 Mar 2014	Hu Wang, Ph.D.	Case Studies – Pre-Soaking and Packaging
	Johannes Kraemer, Ph.D.	Case Studies – Automation and Biorelevant Testing
	Jeff Schwartzenhauer, M.S.	Case Studies – Liquid-filled Soft Gelatin Capsules
	Edward Shneyvas, MBA, Ph.D.	Dissolution vs. In-Vivo Absorption for Dietary Supplements
	Natalia Davydova, Ph.D.	Revisions to <2040>
	Gregory Martin, M.S.	Validation and Verification of Use of Enzymes
	Jian-Hwa Han, Ph.D.	Evaluating the Use of HPMC Capsules in Drug Product Development
	Om Anand, Ph.D.	Dissolution Testing for Generic Drug Products-Capsules: an FDA Perspective
	John Duan	The Effect of Gelatin Cross-Linking on Capsule Dissolution in New Drug Applications–FDA Experience