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Method Development and Validation for Online UV-Dissolution Methods Using Fiber-Optic Technology

Online fiber-optic and multicell UV-dissolution systems have become increasingly used in the pharmaceutical industry. Fiber optics offers many advantages over traditional manual sampling and auto sampling options. Rapid timepoint collection is one of the main benefits of a fiber-optic UV system. Frequent timepoints allow profiling of immediate release dosage forms that traditional methods do not allow, as well as better characterization of modified release dosage forms.

Cary 60 UV-Visible Spectrophotometer with Fiber-Optic Multiplexer

Another advantage of fiber optics is the ability to analyze samples in real time. This is a benefit for samples with poor stability where the samples could otherwise degrade prior to analysis. Real-time analysis also allows for better interpretation and understanding of the dissolution process, as observations can be taken simultaneously with analysis. This will assist formulation development activities by providing more detailed data and quicker turnaround times.

Fiber optics, similar to other automated systems, can also improve precision of the dissolution process. The sampling area is consistent in all vessels, as is timing of the analysis in each vessel. Additionally, software greatly reduces analyst time by performing calculations in 21 CFR Part 11 environments and automatically creating reports that document the complete dissolution analysis and statistics.

Use of fiber optics requires proper validation to ensure that it does not create a bias against a manual method as stated in USP <1092> Dissolution Method Development and Validation. Validation should include, but may not be limited to cleaning validation, hydrodynamic interference and proving the ability to correct for particulates. Determination of parameters for a successful validation require:

- Surveying the dissolution process.
- Establishing the steps that differ between a manual and automated method.
- Ensuring each of those steps maintains accuracy and precision.

Challenges for Fiber-optic Methodology

Proper validation of a fiber-optic system must take into account all changes from a manual method and ensure these differences have not created bias. USP <1092> advises several areas for validation which will encompass both the dissolution process and analytical finish.[1]

Interchangeable Fiber-optic Tips

Statements from USP <1092>

The disturbance of the hydrodynamics of the vessel by sampling probes should be considered and adequate validation performed to ensure that the probes are not introducing a significant change in the dissolution rate.[1]

A typical acceptance criterion is that the difference in the mean value between the dissolution results at any two conditions using the same strength does not exceed an absolute 10% at timepoints with less than 85% dissolved, and does not exceed 5% for timepoints above 85%. Acceptance criteria may be product-specific, and other statistical tests and limits may be used.[1]

Regarding the dissolution environment, validation of the resident probe effect is a primary concern. When performing manual sampling, the sampling probe is only in the vessel for a short time and has minimal impact on the hydrodynamics of the vessel. Fiber-optic systems may use resident probes — probes immersed in the dissolution media at all times — or nonresident probes. This is the most significant area of validation. Increased dissolution rates due to hydrodynamic interference have been shown, and are proportional to the size of the probe and length of time a probe is in the media.[2]

USP <1092> states that the validation be done in a manner consistent with requirements for intermediate precision if the automated and manual methods are considered to be interchangeable. In addition, f1 and f2 calculations may be used to show similarity between profiles generated from automated and manual methods. Regarding the analytical portion of the validation, several other aspects must be validated. These include range, linearity, precision, accuracy, and robustness.

Additionally, a fiber-optic system validation needs to ensure that undissolved drug and excipient particles do not create a bias in the data, and that results are equivalent to filtered results since a fiber-optic system is not capable of filtration. Corrections for undissolved materials are typically completed through a baseline correction, which is valid in most cases.[3]

A cleaning validation of the fiber-optic system is also required to ensure proper cleaning between dissolution runs and elimination of cross contamination. This proves to be one key advantage of the system – since moving light from the spectrophotometer is much "cleaner" than movement of sample from the vessel. As with any automated system, the accuracy of timing intervals for fiber-optic readings and assurance that readings are performed at the correct USP sampling position should also be validated.

Conclusion

Fiber optics is an extremely useful tool in the laboratory after a proper validation, which would be required for any automated dissolution method. Fiber optics provides for a greater level of information for formulation and method development, as well as routine analysis. Fiber-optic systems also greatly reduce analyst time by performing calculations and managing reporting functions. Real-time data is also an advantage in comparing observations and analysis simultaneously, giving better clues into the behavior of a dosage form.

Validation of such a system is needed to ensure the analytical method is accurate and precise in its measurements. Proper validation of an automated system should be completed for each formulation, as each formulation can behave differently to the same perturbations. With proper validation, fiber optics can provide higher quality data than traditional methods.

In addition to the scientific and time-saving options discussed, there are a number of other advantages to a fiber-optic system. There is a long-term cost savings with fiber optics as there is no fluid movement or filtration. This eliminates the need to purchase regular consumable products associated with a pumping system such as filters, tubing, syringes, cannulas, etc. There is also a reduction in cleaning time and contamination issues with a fiber-optic system. The only parts of a UV fiber-optic dissolution system that need to be routinely cleaned are the fiber-optic tips and the dissolution apparatus itself.

For more information about the validation of dissolution methods using fiber-optic technology, read the Technical Overview describing these individual steps in greater detail at https://www.agilent.com/cs/library/technicaloverviews/public/5991-8787EN_Dissolution_TechnicalOverview.pdf.

References
1. US Pharmacopeia 36, NF 31, <1092> The Dissolution Procedure: Development and Validation, US Pharmacopeia, Rockville, MD, USA.
2. Wells, Clyde. Effect of Sampling Probe Size on Dissolution of Tableted Drug Samples. Journal of Pharmaceutical Sciences, 1981, 70, 232.
3. Xujin Lu, Ruben Lozano, Pankaj Shah. In Situ Dissolution Testing Using Different UV Fiber-optic Probes and Instruments. Dissolution Technologies, [Online], 2003, 10, 3-15.

Compendial Update

Bryan Crist, Scientific Affairs Manager, Dissolution Systems

General Chapter Prospectus: <1711> Oral Solid Dosage Forms – Dissolution Testing

USP has made a general announcement concerning this new chapter. The information in the chapter is intended to guide the development of the dissolution methodology of various solid dosage forms intended for human and veterinary use. This is an extension to provide additional information covering sample preparation and introduction as well as case differentiation when disintegration tests could be used as a surrogate for dissolution testing.

The proposed chapter deals primarily with the dissolution of various tablets: effervescent, chewable, sublingual, buccal, osmotic pumps, orally disintegrating, extended- and delayed-release forms, and tablets for oral suspension. Other dosage forms covered are capsules, granules, pellets, buccal film, suspensions, powders and granules, lozenges, oral paste and gels, chewable gel, and medicated animal feed.

The estimated proposed date for appearance in the Pharmaceutical Forum is in PF 44(4) [July-August 2018].

General Chapter Prospectus: Tablet Breaking Force <1711>

Few chapters, other than those on dissolution and drug release, have more bearing on the performance of solid oral dosage than the Tablet Breaking Force chapter. This well-established chapter is undergoing revision to incorporate numerous editorial changes and to focus on the interrelationship of tablet breaking force with thickness, weight, and friability. In the age of continuous manufacturing models and formulating dosage forms through Quality by Design (QbD) principles, physical testing will be important for at-line monitoring of tablet production. Such testing is needed to ensure that the performance characteristics of tablets are consistently met. The revision of this chapter focuses on tablet placement and orientation as well as size and position to obtain the most precise measurement.

This chapter also references a new general information chapter, <1062> Tablet Compression Characterization, as another valuable source for information.

The In-Process Revision of <1217> is presently available in the USP Pharmacopeial Forum 43(6) [Nov-Dec 2017] and its comment deadline is January 31, 2018.

DDG Lunch Meeting at AAPS, San Diego, California, USA

Bryan Crist, Scientific Affairs Manager, Dissolution Systemsn

At the Dissolution Discussion Group's annual luncheon, presenters from across the globe provided updates on a range of topics that included compendial and regulatory trends in the pharmaceutical industry.

With nearly 100 individuals in attendance, the luncheon employed a unique soap-box style in which each presenter provided a five-minute recap of their affiliate activities throughout 2017.

The moderator, Bryan Crist of Agilent, began the meeting with an overview of the DDG, its bulletin board activity, and quarterly DDG online meetings. The luncheon continued with an impressive list of topics by the following speakers:

- **"Update on the USP Dosage Forms Expert Committee," by Vivian Gray of V.A. Gray Consulting and Dissolution Technologies**. Information provided on USP chapters under review; <1092, <701>, <1087> and proposed Monographs for Hard Gelatin and Hypromellose Capsule Shells as well as a new in-process chapter <1711> Dissolution Procedures for Oral Solid Dosage Forms.
- **"Dissolution Technologies Update," by Vivian Gray.** Provided information on special editions from 2017 on veterinary products and IVIVC and future review articles for 2018.
- **"Dissolution Methodologies from Biorelevant to Quality Control – Bridging the Gap," by Xujin Lu of Bristol-Myers Squibb**. A review of IVRDT Focus Group article appearing in AAPS Journal, which outlined the relationship between biorelevant dissolution methodology and quality control dissolution practices.
- **"Updates for AAPS In-Vitro Release and Dissolution Testing Focus Group," by Nikoletta Fotaki of the University of Bath, UK.** A review of 2017 accomplishments, including a Predictive Dissolution Modeling Workshop and the AAPS Symposium on Spectroscopic Imaging for In-Vitro Dissolution and Formulation Characterization.
- **"USP Chapter <1236> Solubility" overview, by Margareth Marques of USP, Rockville, Maryland, USA.** Reviewed the new chapter's highlights, including thermodynamic equilibrium and solubility, methods for determining and estimating aqueous solubility and factors that affect solubility and their measurements.
- **"USP Workshop on Drug Release Modeling" (held Oct. 23-25, 2017), reviewed by Margareth Marques.** The workshop focused on in-vivo tools for dissolution pre-assessment in terms of uncertainty, dissolution, supersaturation/precipitation, PBPK, IVIVC, intrinsic dissolution, and the hydrodynamics in dissolution apparatus.
- **"Disintegration or Dissolution: How to Decide?" by Raimar Loebenberg of the University of Alberta, Canada.** The relationships between disintegration apparatus in USP 701 and 2040 compared to rupture and dissolution testing for various formulations was discussed.
- **"Update on Activities of the International Pharmaceutical Federation," by Johannes Kraemer of PHAST, Homburg, Germany.** A review of the FIP/USP/AAPS Workshop on Nanomedicines – Technology and Regulatory Perspectives (held March 20-22, 2017) was provided.

- **"USP Dissolution Vibration Collaborative Study Update," by Erika Stippler of USP, Rockville, Maryland, USA.** The update included information on progress towards and participation in a USP collaborative study underway for determining environmental vibration effects on dissolution apparatus.
- **"AAPS In Vitro Predictive Dissolution Workshop," reviewed by Bryan Crist of Agilent.** The workshop provided concepts for dissolution modeling and surrogate testing that could be applied to achieve real time release testing (RTRT) for dissolution to evaluate the performance quality of in-process and/or final product based on process data.

Please look for our DDG Luncheon again next year, when the annual AAPS meeting will be relaunched as the new AAPS PharmSci 360 Meeting, in Washington, D.C., November 4-7, 2018.

Online DDG meetings will be conducted on February 8, May 10, August 9, and November 8, from 10:30 to 11:30 a.m. Eastern Time in the United States. Topics will be announced for each session through the DDG website.

Questions You Asked

Q. I have a specific product that gets stuck to the vessel wall causing delays on the disintegration. Is there any recommendation that we can make to avoid this without causing a big difference on the dissolution assay?

A. I would suggest that you try a sinker on the tablet as this will allow the tablet to slide to the center of the vessel and provide less variability in test results because the sinker should allow media to surround the tablet allowing uniform wetting and disintegration.

Capsule Wire, Weights and Sinker Baskets

Q. I understand that dissolution media containing surfactants cannot be deaerated since it will foam terribly during the process. Is there any way possible to do this?

A. Most attempts to deaerate surfactant containing dissolution medium will result in a significant amount of foam. The secret to successful deaeration of surfactant containing media is to deaerate the media without the surfactant and it doesn't take much more time than traditional deaeration:

1) Prepare media with everything except the surfactant

2) Dissolve the buffers if necessary, bring close to volume, adjust pH

3) Deaerate the media at this point

4) Remove about 150 mL of the deaerated media and set aside

5) Measure out the require surfactant and place in weigh boat

6) If the surfactant is a solid (SLS) add some media to make a slurry

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