Technical Overview

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

Introduction

Online fiber-optic and multicell UV-dissolution systems have become increasingly used in the pharmaceutical industry. Fiber optics offer many advantages over traditional manual sampling and autosampling methods. 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. The *in situ* analysis eliminates the need for sample filtration, allowing for analysis of select microparticle and nanoparticle formulations.

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 assists 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.

The 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. The determination of parameters for a successful validation requires:

- Surveying the dissolution process
- Establishing the steps that differ between a manual and automated method
- Ensuring that each step 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 that encompass both the dissolution process and analytical finish[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. It has been documented that resident probes can impact the dissolution rate of many drugs. If a resident probe is used, its effect on the results, if any, must be determined. In the case of a nonresident dip probe, such validation may not be required if the cross-section of the probe is similar to that of a manual sampling probe, and the duration of time the probe is inside the vessel is minimal.

According to 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]." 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 must be done in a manner consistent with requirements for intermediate precision if the automated and manual methods are considered to be interchangeable. Specifically, the chapter states, "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]."

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
- 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].

To ensure proper cleaning between dissolution runs and elimination of cross-contamination, a cleaning validation of the fiber-optic system is also required. This proves to be a 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.

Validating the Differences

Hydrodynamics

Hydrodynamic interference should be determined based on the type of fiber-optic probe being used, and the duration of time the probe is in the dissolution media. There are three basic classes of fiber-optic probes. See Table 1.

Table 1. Probe descriptions[4].

Probe	Resident or nonresident	Characteristics and attributes
Dip-style	Either	A stainless steel probe with a cross-section approximately the size of a cannula contains the fiber-optics, and the probe is equipped with a filter tip.
Arch-shaped probe	Resident	A thin metal tubing houses the fiber-optic component
In-shaft probe	Resident	The fiber-optic probe is located in the center of a metal paddle or basket shaft.

Validation should be completed to ensure that the hydrodynamic integrity is preserved, and any readings taken at a non-USP location do not bias results. Sampling at non-USP positions may not be homogeneous, as higher % dissolved values have been found near the vessel wall at early timepoints. Methods would need to validate that there are not corresponding lower values at the center of rotation near the shaft. Systems able to raise the fiber-optic probes provide an advantage by reducing hydrodynamic changes in the dissolution vessel.

When comparing fiber-optic sampling to manual sampling, dissolution runs will determine any impact on the test caused by fiber-optic probes, especially at early time points. Testing should be completed (n = 12) for both sampling approaches, and the data compared. The manual sampling and fiber optics should not be performed from the same test, as this does not challenge the hydrodynamic interference, but only the analytical finish. However, sampling manually while fiber-optic measurements are made will be useful to verify baseline correction, described in the next section.

Once the data are collected for a minimum of n = 12, the results should be compared either through comparison of the two means at multiple timepoints or through an f1 or f2 statistical analysis. The most commonly used comparisons are f2 with a result greater than 50 or comparison of means at each timepoint with a maximum of 10 % difference at <85 % dissolved, and a maximum of 5 % at >85 % dissolved[5]. Additionally, the % relative standard deviation (RSD) should be equivalent between the two approaches, and the fiber optics should not be a source for additional variability.

Filter Versus Baseline Correction

The impact of the presence of undissolved drug and excipients in the dissolution vessel needs to be validated. Since filtration is not used, fiber-optic systems must have a way of dealing with the absorption and light scattering from particles. The most common of these is a baseline correction. The theory of the baseline correction is based on the principle that undissolved particles will absorb light equally along all wavelengths. As a result, one could subtract the absorbance at an area of the baseline where the drug is not absorbing, then subtract this from the peak at the wavelength of interest. The absorbance result is equivalent to that of a filtered sample. See Figure 1.

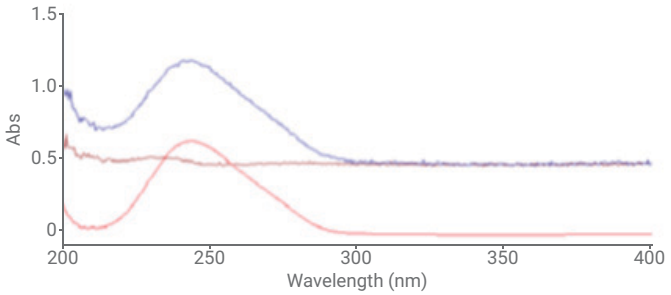

Figure 1. Scans include a prednisone standard, an excipient mixture, and prednisone with an excipient mixture. The excipient mixture's absorbance is relatively unchanged across the wavelength range as particles block light evenly across wavelengths. As a result, the absorbance value of the excipient at a wavelength where prednisone does not absorb, such as 350 nm, can be subtracted from the standard at the maxima of the compound to give a corrected reading.

To challenge the baseline correction, samples should be read both by UV and a filtered manual sample to show comparability. The samples should be taken at the highest and lowest concentrations of active pharmaceutical ingredient (API) expected in the dissolution. These samples could either be actual dissolution samples where concurrent sampling would be taken at the initial and final timepoints, or spiked placebo samples. A minimum of three replicates should be used for this experiment, and the results should agree between the filtered and fiber-optic read samples within 2 % absolute[6].

Cleaning Validation

Cleaning validation should be completed to ensure that there is no carryover from one run to the next. This is easily accomplished by taking a reading of the blank solution, then taking a reading of a standard or spiked placebo at 100 % dissolved. The cleaning is performed before taking a final blank reading. The blank reading after cleaning should be <1 % of the absorbance of the standard at the wavelength of maximum absorbance. Alternatively, a blank run could be completed after a run of the highest dosage strength is performed to validate the cleaning process in place of a separate test[6].

Timing

The sample timepoints need to be verified within 2 % of the sampling time set point, per USP <711>[7]. In addition, the location of the sample probe should be verified to be within the USP sampling area. In the case of an in-shaft fiber-optic probe, validation would be required to show that the sample is homogeneous enough to allow for sampling at a non-USP position. The most effective way to do this would be to take a manual sample at the USP position concurrently with the fiber-optic analysis; the results should be within 2 %.

Standards

Most dissolution methods require duplicate or bracketing standards to be read every 1–2 timepoints to demonstrate that the UV is giving consistent results and that the readings can be trusted. Fiber-optic analysis requires standards to be read before the start of the *in situ* analysis of samples. Validation should prove the repeatability of absorbance values during the length of the run.

Use of a standard solution in three or more vessels and a sample reading at the timepoint specified in the method could easily show repeatability of the UV system and ensure that absorbance values are consistent. Readings should be within 1–2 % throughout the entire run, and care should be taken to control evaporative loss. Standard agreement should be 98–102 %, per USP <1092>, which can be used for justification.

Fiber-optic measurement is applicable to many dissolution tests. Due to the incorporation of the Agilent Cary 60 spectrophotometer, the Agilent Fiber-optic System has an extended linear photometric range (±3.5 Abs), which allows the measurement of highly concentrated samples. The Agilent system benefits from the use of multiple tip sizes, including 0.5 to 10 mm, that allow path lengths of 1 to 20 mm. These various tip sizes allow a wide concentration range to be read, so the system can be used with a variety of samples and dosage strengths.

Conclusions

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 are also an advantage for comparing observations and analysis simultaneously, giving better clues into the behavior of a dosage form.

To ensure that the analytical method is accurate and precise in its measurements, validation of such a system is required. Proper validation of an automated system should be completed for each formulation, as each formulation can react 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 such as filters, tubing, syringes, cannulas, and so forth, that are associated with a pumping system. 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.

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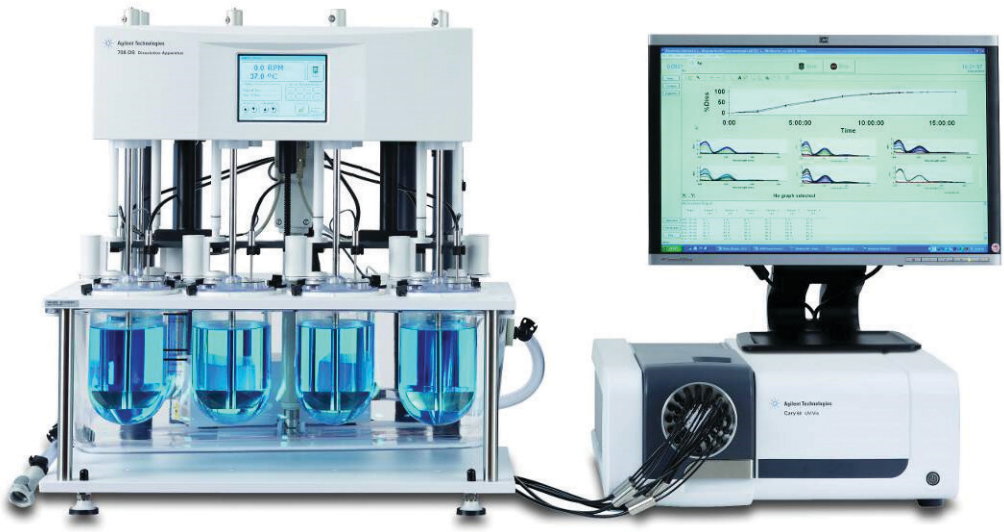

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