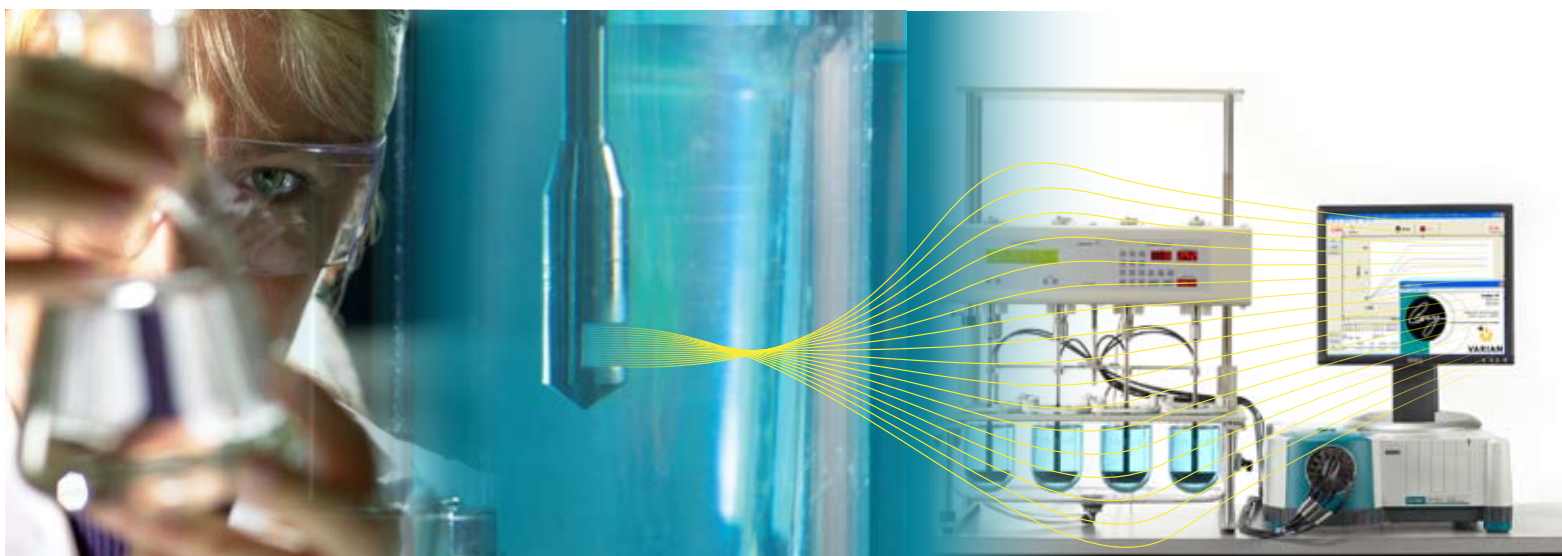


# Practical Solutions

A PUBLICATION OF VARIAN, INC. • VOLUME NINE, # 2



## Method Development and Validation for Online UV and Fiber-optic Dissolution Methods

Fiber-optic UV and other online dissolution methods 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.

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, as well as other automated methods, 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, online fiber optics greatly reduces analyst time by performing calculations in 21 CFR Part 11 environments and writing reports for the dissolution analysis.

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 what validation can be accomplished requires:

- » 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 the changes have not created bias. USP <1092> advises several areas for validation which will encompass both the dissolution process and the analytical finish.<sup>1</sup>

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 located in the vessel at all times — or non-resident probes. It has been documented that resident probes can impact the

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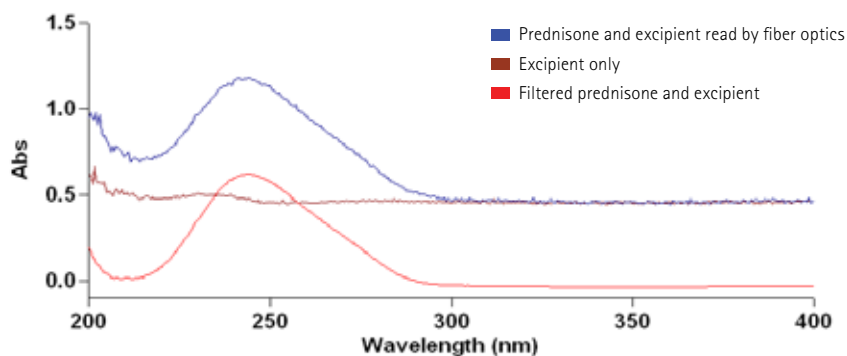
*Fiber-optic probe in sampling and raised positions (top and bottom, respectively) to minimize hydrodynamics during the test.*

dissolution rate of many drugs. If a resident probe is utilized, its effect on the results, if any, must be determined. In the case of a non-resident 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."<sup>1</sup> This is the most significant area of validation. Increased dissolution rates due to hydrodynamic interference have been shown, and are proportional

*Table 1. Probe Descriptions<sup>4</sup>*

Probe	Resident or Non-Resident	Characteristics and Attributes
Dip-style	Either	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	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.



*Figure 1. UV-Vis Scans*

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 active at the maxima of the compound to give a corrected reading.

to the size of the probe and length of time a probe is in the media.<sup>2</sup>

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. Specifically, it says, "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."<sup>1</sup> In addition,  $f_1$  and  $f_2$  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.<sup>3</sup>

A cleaning validation of the fiber-optic system is also required to ensure proper cleaning between dissolution runs and elimination of cross contamination. Chemometric software, if used, must be validated to ensure the results are accurate. 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.

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.

When comparing fiber-optic sampling to manual sampling, dissolution runs will determine any impact on the test caused by fiber-optic probes. 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.

Once the data is 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  $f_1$  or  $f_2$  statistical analysis. The most commonly used comparisons are  $f_2$  with a result greater than 50 or comparison of means at each timepoint with no greater than 10% difference at <85% dissolved, and no greater than 5% at >85% dissolved.<sup>5</sup> 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 employed, fiber-optic systems must have a way of dealing with the



Increase in turbidity as a tablet dissolves.

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 on previous page.

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.<sup>6</sup>

#### Chemometric Software

Spiked placebo samples of known concentrations of various APIs are used and the comparison of actual concentration to calculated concentration for each API is determined. The calculated and actual concentrations should agree within 2% for all drug components in the formulation.<sup>7,8</sup>

#### 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.<sup>6</sup>

#### Timing

The sample timepoints need to be verified within 2% of the sampling time set point per USP <711>.<sup>9</sup> 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 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 Varian Cary™ 50 spectrophotometer, the Varian Fiber-optic System has an extended linear photometric range ( $\pm 3.3$  Abs), which allows the measurement of highly concentrated samples. The Varian system benefits from the use of multiple tip sizes, including 1 to 10 mm, which allow path lengths of 2 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 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.

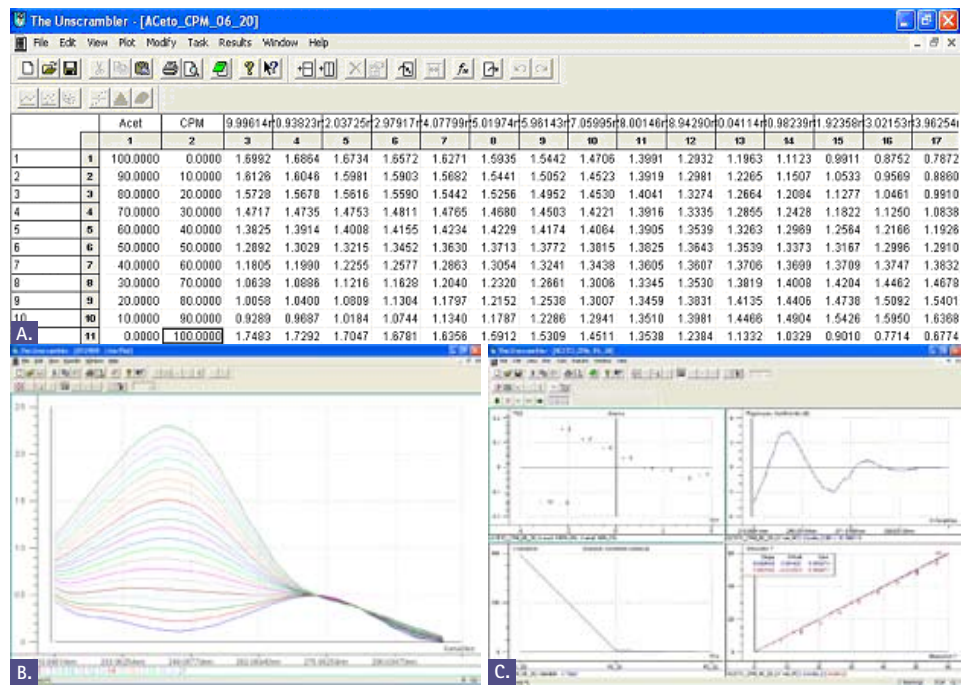
In addition to the scientific and time-saving options discussed, there are a number of other advantages to a fiber-optic system. There is a long-term cost savings with fiber optics as there is no fluid movement or filtration. This eliminates the need to purchase regular consumable products associated 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.

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# Multicomponent Analysis with UV-Vis

Traditionally, pharmaceutical products with more than one active component have been relegated to analysis using HPLC. An alternative solution, however, is available through the partnership created by Varian and CAMO Software, Inc. The Unscrambler® software package works in conjunction with Varian's UV Dissolution Software to provide a multicomponent analysis (MCA) solution for products with multiple active drugs. The procedure to create a model file using Unscrambler is simple and cost-effective – see the basic steps below:

- » Prepare stock standard solutions of the active components of the drug product.
- » From the stock solutions, prepare varying concentration combinations (minimum of 20).
- » Analyze these solutions using the Scan application of Varian's UV Dissolution Software.
- » Import the Scan data into CAMO's Unscrambler Software.
- » Enter the concentrations in the data table.
- » Using Unscrambler, perform a PLS2 regression to create the model file.
- » Setup a dissolution method from the Varian UV Dissolution Software and select the model file created in Unscrambler.
- » Execute the dissolution test. Results of each component's rate of release are based on the model file and displayed in a separate report.



A variety of applications within the Unscrambler Software allow the user to identify, define and quantitate the amount of multiple active pharmaceutical ingredients (APIs) within a single formulation. The figures show: (a) varying percentages of each API, (b) scans with various concentrations of the API, and (c) PLS2 regressions that are used to quantitate the amounts of API in unknown concentrations.

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The Dissolution Discussion Group (DDG) Web site is an invaluable resource for you to research best practices and get direct, timely feedback from industry peers. Although sponsored by Varian, DDG is a vendor-neutral forum for open scientific discussion in an environment that is free from regulatory oversight.

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