Application of Fiber-Optic Dissolution Testing for Actual Products

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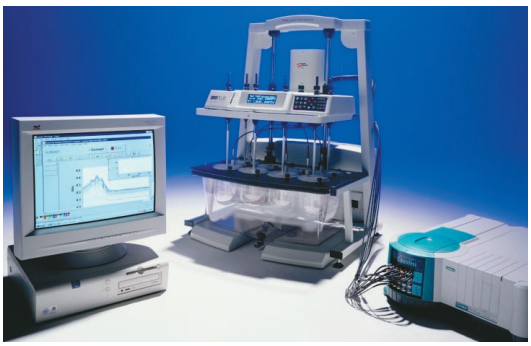

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Fiber-optic dissolution analysis has evolved from a novel technique to a validated test method that can be used routinely in both research and development and quality control. To demonstrate the applicability of the technique, the authors have performed fiber-optic dissolution measurements on three new products currently under development.

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Fiber optic–based UV absorption analysis for dissolution testing is a technique that has been under investigation for many years (1–4). The concept is to use a fiber-optic probe inserted directly into each vessel to perform measurements in situ. The obvious advantage of this system is the simplification of dissolution analysis. Because no sample extraction is required, all sippers, filters, pumps, and attendant plumbing are eliminated. Additional benefits of fiber-optic dissolution include speed of acquisition, real-time analysis, and automated unattended measurements. Together, these advantages permit the acquisition of complete dissolution profiles for both the fastest release products and the longest extended-release products.

Recently, interest in fiber-optic dissolution has increased greatly with the introduction of several commercial systems that offer turn-key solutions (5,6). Initially these new systems, as with most new technology, were shown to work with USP calibrators or a limited number of specific drugs. However, because these systems have come into broader testing and use, they now have been successfully used with a growing range of real-world products. This article describes several examples of the adaptation of fiber-optic dissolution to methods for actual products.

Principles of operation

To understand the challenges of developing a method for dissolution analysis using a fiber optic–based UV system, it is useful to first examine the operation of such a system. The photo on this page and Figure 1 show one fiber-optic dissolution system (the IO from C Technologies, Cedar Knolls, NJ). The schematic diagram in Figure 1 shows the four major parts of the analysis system: the spectrophotometer (Cary 50, Varian, Walnut Creek, CA), the fiber multiplexer and probes (C Technologies), and a computer. The system is connected to one or two standard Apparatus 1 or Apparatus 2 dissolution testers. Light from the flashed xenon source in the spectrophotometer is coupled to optical fibers via the multiplexer. The fibers transfer the light from the source to the probes, which are immersed in the bath vessels. The fibers are made with a silica core and silica cladding specifically selected for transmission in the UV range. The probes are specifically designed for dissolution measurements. They comprise the illumination fiber from the source,

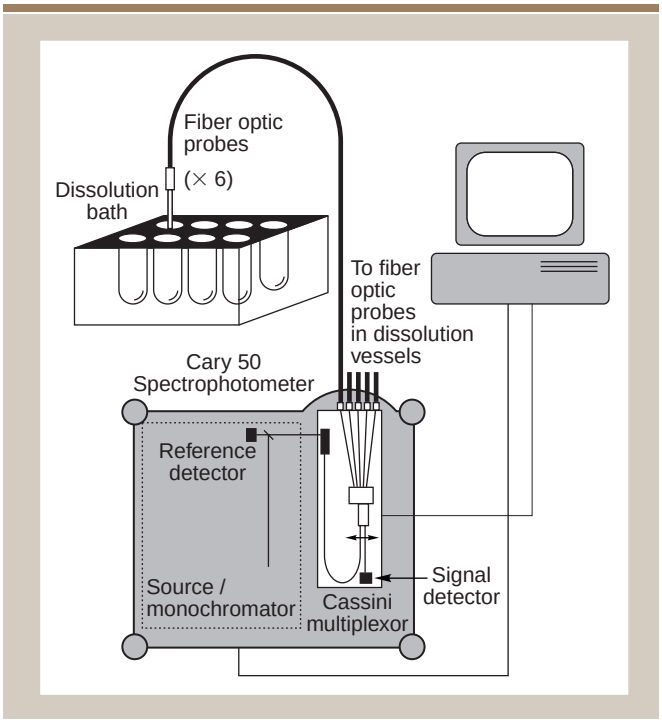

Figure 1: Schematic of a fiber-optic dissolution system.

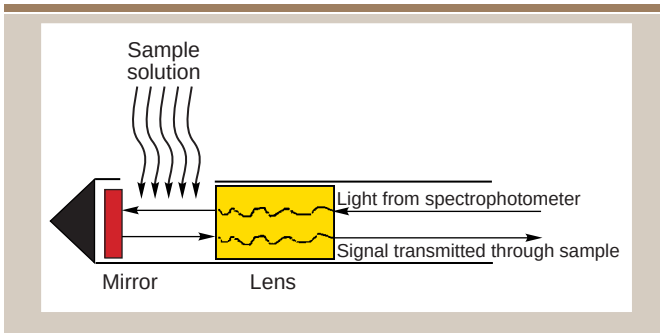

Figure 2: Schematic of a fiber-optic probe.

the signal fiber to the detection system, a quartz focusing lens, and a back-surface mirror. The body is constructed of stainless steel. Figure 2 shows the geometry of a probe.

Light from the source is focused by the lens through the liquid that occupies the gap and then reflects back from the mirror at the other end. The light again traverses through the liquid in the gap and is then refocused by the lens into a signal fiber in the probe. The signal channel carries the light transmitted through the sample back to the detection system. In a fiber-optic dissolution system, the sample is simply the liquid present in the probe gap at the time of the measurement. The pathlength of the cell is determined by this gap, which can be changed by choosing a replaceable tip with the appropriate spacing.

Challenges of adaptation

In situ measurement offers obvious advantages but also presents two major potential issues that must be accounted for in successfully implementing the system. The first issue is the effect of the presence of a probe on the hydrodynamics of the vessel and, therefore, on the dissolution rate being measured. The second concern is the possible interference in the measurement caused by the presence of excipients and other components of the product (e.g., the capsule).

The issue of hydrodynamic effects caused by the probe altering the dissolution rate can be tackled in three different ways. In most cases, with the exception of the longest time extended-release drugs, the presence of the probes does not create a significant change in the dissolution rate. The lack of effect for a particular formulation just needs to be demonstrated, and the method can then be validated with the probes remaining in the vessel throughout the entire run. An example of such a validation study is discussed later.

In the minority of cases in which a statistically significant change in the dissolution rate does occur, two options exist. The first is to use an automated manifold to raise and lower the probes so that they are present in the vessel only at the time of measurement. It turns out that in practice total withdrawal of the probe is not desired because it can lead to the drying of any residue on the mirror and also possibly lead to the creation of air bubbles in the gap when the probe is reinserted. Instead, the probe is withdrawn so that all but the mirror and half the gap are submerged in the vessel. The second option is to use in-shaft sampling, such that the probe is resident in the paddle/basket shaft and therefore does not disturb the hydrodynamics of the vessel (7).

In conventional UV dissolution studies, one normally addresses the issue of excipients by suitably filtering the sample withdrawn from the vessel. In fiber-optic dissolution testing, however, excipients remain present and therefore are in the volume sampled by the probe. The problem with excipients in the measurement pathlength is that they absorb or scatter the UV light, creating a false increase in the absorption measured. The simplest solution one could imagine for eliminating the problem would be to surround the opening in the probe with a mesh. This turns out to be unacceptable for two reasons: First, such a probe would change the hydrodynamics of the vessel to an even greater degree. Second, excipients would collect on the mesh, eventually preventing proper circulation of vessel solution through the probe and distorting the drug concentration measured.

Because elimination of the excipients is not an option, solving the problem instead requires sophisticated data correction methods. Two prevalent correction algorithms are in use: The first is a second derivative method that eliminates the contribution of excipients by analyzing the rate of change of the absorption curve rather than its actual value (5). The second method corrects the data collected from the spectral absorption band of the active by subtracting the measured absorption value of a reference wavelength outside the drug's absorption band.

The idea behind the second correction method is that excipient particles present in the probe gap during the measurement obscure both the reference and peak wavelengths. The key assumption is that the contribution to the in-band absorption measurement as a result of these particles is the same as the additional absorption recorded in the out-of-band reference wavelength. Subtracting this offset value from the measured in-band

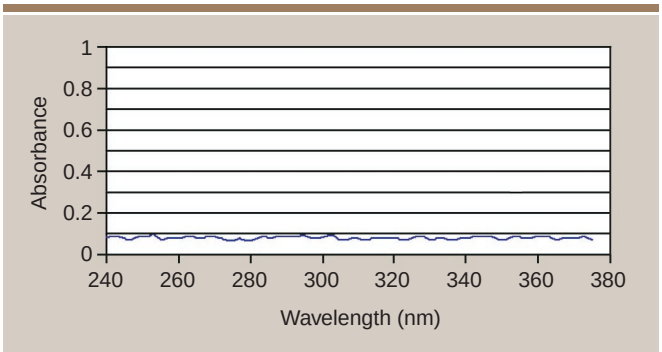

Figure 3: Spectrum of a typical excipient. Note the equal absorption at typical drug absorption values and wavelengths further into the visible range, which can be used for correction values.

absorption therefore corrects that value for the effects of the particles. Figure 3 shows the spectrum of a typical excipient and the validity of the previous assumption. Obviously, however, this is an assumption that must be verified on a product-by-product basis.

Although both excipient correction algorithms work well for most products, the second baseline correction method seems to enjoy better acceptance by the dissolution community (8). This is based on several reasons. Method developers feel more comfortable trying to justify a data manipulation to regulatory agencies such as FDA when the manipulation is based on a physically understandable principle and can be verified directly. Unlike the case of the second derivative algorithm, the baseline correction method still relies directly on absorption values to determine the dissolution rate. In addition, the validity of the subtracted values can be verified during method development by taking a spectrum of the placebo and showing that the assumption regarding the contribution of excipients on and off peak holds.

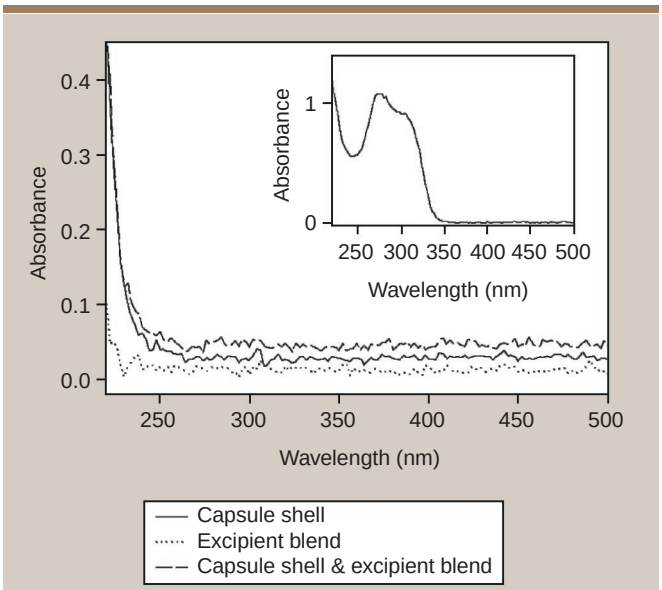

Figure 4: UV–vis spectra of matrix interferences collected by fiber-optic probe in vessel with paddles in motion. Insert: UV–vis spectra of active ingredient of drug P.

Application to real-world products

One example of the evaluation of the baseline correction method involved a developmental immediate-release pharmaceutical drug, "P" (Pfizer, Morris Plains, New Jersey). This product comprised commonly used excipients and an active ingredient delivered in a capsule shell. Initial spectral experiments were carried out to determine the contributions of the excipients and capsule shell to the overall UV spectra. Figure 4 shows that a simple linear baseline offset correction is applicable as a result of the uniform nature of the spectral contributions of the capsule shell and excipients. In the optimal case, the correction wavelength should be far removed from the spectra of the active ingredient, and the quantitation wavelength should be a maxima of the active ingredient. Therefore, the correction wavelength of 450 nm and the quantitation wavelength of 276 nm (inset) were selected. In addition, linearity was demonstrated for the fiber-optic dissolution system at 276 nm in the desired working range (data not shown).

The fiber-optic dissolution system was tested in a USP Apparatus 2 dissolution tester (AT7 Smart, Sotax AG, Allschwil, Switzerland). UV spectra were acquired every 2 min for the first 20 min and every 5 min subsequently until the end of the experiment. After product insertion, the system obtained dissolution data with no further intervention by the scientist. The UV probe data were compared with a previously validated off-line UV method in accordance with the authors' protocol. Samples were withdrawn and tested at the 6-, 12-, 30- and 45-min time points.

Figure 5 shows the results of the fiber-optic dissolution experiment in comparison with the results of the off-line UV analysis. The off-line UV data points are nearly superimposed with the values from the fiber optic system at those time points where data were acquired. Clearly, the baseline correction completely accounts for any effects on the data caused by the presence of excipients or the remains of the capsule shell. Also, note the initial lag time between 0 and 2 min and the variability of the percent active ingredient dissolved on the plateau region of

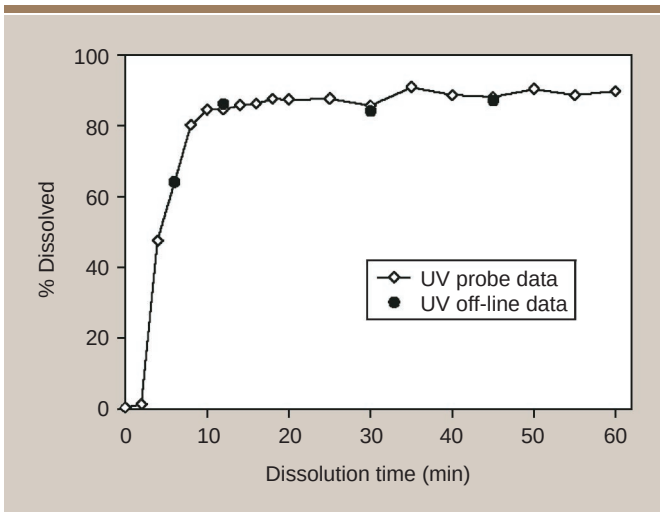

Figure 5: Results of dissolution testing of drug P using the fiber-optic dissolution system and an off-line UV method.

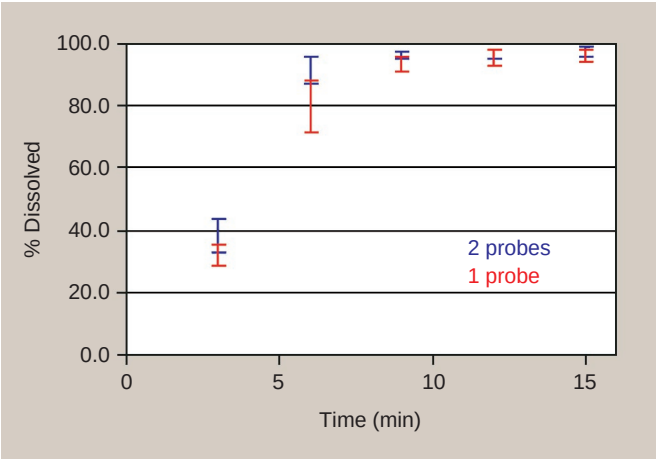

Figure 6: The effect of probes on dissolution rates of product AZ.

the dissolution curve. The data acquisition rate provided by this technology yields unique information not readily obtained using current dissolution technology. For example, data could have been acquired as rapidly as once every 30 s if one wished to study in detail the rate of the capsule shell disintegration and the solution dynamics of the bulk dissolution media.

The lack of a significant effect on measured dissolution rates caused by the presence of the fiber-optic probes is illustrated by measurements on another immediate-release product, drug "AZ"(Astra-Zeneca, Mölndal, Sweden). To maximize the sensitivity of the dissolution measurement to the presence of the probes, two deviations were made from the standard protocol: First, an additional probe was introduced to each vessel. Second, both probes were immersed as deeply as possible, beyond the USP recommended position to a point just above the paddles.

Figure 6 shows such dissolution rate data. These data are compared with conventional fiber optic measurements performed on the same drug. Note that even in this extreme case, the effect of the presence of a second probe is statistically insignificant compared with the variance in measurements from vessel to vessel.

As a final example, the authors present method validation data for applying fiber-optic dissolution monitoring to an immediate-release product, drug "HLR" (Hoffmann–La Roche Ltd., Basel, Switzerland), a soft gelatin capsule containing 200 mg of active substance dissolved in a mono- and diglyceride filling. Validation studies were performed in accordance with standard protocols (9,10). Dissolution testing was performed in a USP Apparatus 2 dissolution tester (AT7 Smart) stirred at 100 rpm and 37.0 ± 0.5 °C in 900 mL of media comprising aqueous citrate buffer solution, pH 3.0, with 12% Cremophor EL (BASF, Ludwigshafen, Germany). Although no excipient particles exist in this case, turbidity is still generated because of the metal oxide pigments from the capsule shell. Table I summarizes the validation experiments conducted, and Table II shows the acceptance criteria for the results of these measurements.

Table III provides the results of the validation experiments. These results meet all the acceptance criteria for linearity (coefficient of correlation and *y*-intercept), precision, and accuracy. In addition, a

Table I: Performed validation experiments for the fiber-optic method.

Parameter	Fiber-optic method
Linearity, precision, and internal recovery	5–120% of dissolved active substance (0.011–0.267 mg/mL) in triplicate
External recovery	80, 100, and 120% of dissolved active substance (0.178, 0.222, and 0.267 mg/mL) in triplicate
Method comparison	Four placebo-spiked model solutions

Table II: Applied acceptance limits according to References 10 and 11 in the program VoAM 3.0 (12).

Criterion	Acceptance limit
Coefficient of correlation (ρ)	>0.99
y-intercept	Within the 95% confidence interval of 5.00% of the reference x-value corresponding to 100% sample concentration
Relative repeatability standard deviation (σ_{rel})	≤2.00%
Recovery	98.00–102.00%.
Method equivalence	The 95% confidence interval of the mean of the fiber-optic method is entirely within the acceptance interval of ±2.00% about the mean of the reference method.

Table III: Validation results of the fiber-optic method.

	Fiber-optic method						
Parameter	Probe 1	Probe 2	Probe 3	Probe 4	Probe 5	Probe 6	Probe 7
ρ	0.99976	0.99975	0.99973	0.99984	0.99983	0.99982	0.99972
y-intercept	0.03569	0.03562	0.03678	0.03452	0.03327	0.03502	0.03690
σ_{rel} (%)	0.94	0.97	1.00	0.77	0.80	0.82	1.03
Internal recovery (%)	100.41	100.41	100.44	100.33	100.31	100.32	100.43
External recovery (%)	98.86	99.41	99.06	98.93	98.92	99.12	98.96

comparison was performed with the existing reference method based on manual sampling and filtration with a 0.45-μm pore filter (GyroDisc-PES 25, Orange Scientific, Waterloo, Belgium). No significant differences ($p = 95\%$) were observed in the fiber-optic data versus the reference method.

Conclusion

Given its advantages in terms of ease of use and suitability for automation, fiber-optic dissolution has been heralded as an important emerging technology. Commercial fiber-optic dissolution systems have become viable tools for analytical and formulations method developers as well as in actual production quality control environments. The technology has been validated at each stage and has been accepted by regulatory agencies.

Further, as better algorithms and computational methods such as chemometrics come into greater use in conjunction with fiber optics, the technique may become applicable to a broader range of products, including multicomponent and other formulations that currently require HPLC methods. Fiber-optic dissolution analysis promises to make dissolution testing no longer one of the more time-consuming and labor-intensive steps of pharmaceutical manufacturing.

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