American Pharmaceutical Review™

Dissolution Developments

Advanced tools and techniques for efficient and accurate dissolution testing

Contents

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Distek, Inc.

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COMPANY DESCRIPTION

Distek, Inc. is a leading manufacturer of laboratory testing instruments for the pharmaceutical and biotechnology industry for over 40 years, as well as an experienced provider of validation and qualification services.

Our mission is to design, manufacture, sell and support state-of-the-art laboratory testing equipment that performs flawlessly and meets our customer's needs and expectations. It is our belief that a strong focus on quality, innovation and support are essential to our current and future growth and continual improvement is crucial to ongoing success.

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Gerald Brinker started Distek from his garage in 1976 as a modest business that manufactured dissolution equipment. Over the next four decades, Distek's business has expanded to provide instruments for tests performed in pharmaceutical and bioprocessing laboratories offering innovation and support to companies on a global scale. Distek's sales and staff have grown dramatically. Today, Distek employs staff from 11 different countries, covering five continents.

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In Situ UV Fiber Optics for Dissolution Testing

What, Why, and Where We Are After 30 Years

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Abstract

Ultraviolet (UV) fiber optic spectroscopy has been applied to dissolution testing for more than 30 years. Multiple types of instrumentation schemes have been designed and implemented over that time, all aimed to introduce UV light into the dissolution apparatus to perform in situ measurement of the percent dissolved of the active pharmaceutical ingredient (API). In situ UV fiber optic systems provide many advantages over conventional dissolution testing. It generates realtime dissolution profiles with more frequent data points, providing rich information useful not only for regulated quality control tests, but also for formulation development, troubleshooting, and analysis of novel formulations, such as nanoparticles that are hard to filter. In situ UV measurement without filtration is challenging due to the effects of particulates and scattering. Mathematical "filters" including baseline correction and derivative spectroscopy can overcome these challenges and remove the contribution of non-API components. Innovative applications such as multicomponent dissolution, small volume bio-predictive dissolution, and biphasic dissolution are also being advanced by using in situ UV testing. More benefits are expected as the in situ UV methodology for dissolution is more broadly accepted and implemented in pharmaceutical arena.

Keywords: UV fiber optics, dissolution, in situ measurement, multicomponent analysis

Introduction

Ultraviolet absorbance spectroscopy (UV) was one of the earliest ways to measure active pharmaceutical ingredient (API) percent dissolved values in dissolution testing, and it is still one of the most common methods. The traditional method involved removing an aliquot from the dissolution apparatus at time points of interest and bringing it for analysis to the UV spectrophotometer, either manually or using some form of automation. It has been more than 30 years since researchers have started to develop ways

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to perform the measurement in situ in the dissolution test apparatus using fiber optics and probes.[1] Over that time, multiple schemes have been implemented, and all have been predicated on the idea that moving photons is much more convenient than moving liquid, making it possible for dissolution test users to perform measurements they always wanted to do but could not.[2-6]

Over the years, conventional dissolution testing has been optimized to meet the requirements established by the various regulatory bodies. Yet it was well understood that the test itself had greater potential and could provide additional useful information beyond that required by the regulations for formulators, quality control (QC), and analytical services. In particular, if one could get a complete dissolution profile with adequate temporal resolution and number of data points, then one can use dissolution in ways beyond simple manufacturing validation and QC. Formulators could use this information to better understand ratelimiting steps of fast dissolving products. They can also consider implementing predictive dissolution testing, using the high data density of early times to accurately forecast the ultimate long-term dissolution results for development (and perhaps someday QC) of extended release formulations, reducing the duration and cost of such testing.

Similarly, QC can benefit from a technique that yields complete profiles and real-time results. Manufacturing and analytical services can use the information contained in a complete profile to better diagnose an Out of Specification (OOS) test. They can use the immediate results to alert operators of problems with a run sooner and avoid the time and cost of completing and analyzing samples from an obviously failed test. QC would also greatly benefit from dissolution automation that was less labor intensive and prone to error.

These were the motivations for developing in situ UV testing. UV light could be introduced into the apparatus as often as desired and measured in real-time and without any disturbance of the hydrodynamics that would result from such frequent sampling. This enables immediate recording of percent dissolved values measured with extremely short intervals between time points and a very large number of readings. Eliminating sampling obviously removes sampling errors, such as incorrect sampling times, positions, filters, and handling. Additionally, it also prevents issues with carryover, cross contamination of filters and lines associated with automated liquid sampling, and the need for volume corrections due to media loss. Immediate in situ analysis also eliminates the possibility of partially filtered samples continuing to dissolve until the actual measurement can be made. And, because there is no filtering, there are fewer issues with analyzing hard-to-filter samples like nanoparticles.[7] Other innovative applications being advanced by using in situ UV testing include USP apparatus 4, small volume bio-predictive dissolution, and biphasic dissolution.[8-11]

Design of In-Situ UV Systems

In situ UV testing is not a new idea. The first publication describing such a system was by researchers at AstraZeneca (then Astra Hässle) in Mölndal, Sweden in 1988.[1] The first system to be later commercialized was conceived by Walker at GlaxoSmithKline (then Burroughs Wellcome Co.) and developed into a working system in conjunction with Gemperline and Cho at East Carolina University in the early 1990s. The system was described by Walker et al in 1995.[12,13] This was shortly followed by Bynum et al at Purdue Pharma, where a system was developed for in-house use.[14] A company to commercialize the system was spun out of Purdue Pharma and eventually

sold. These and other systems became commercially available in the late 1990s and early 2000s.[15–17]

In situ UV systems share the majority of the elements of conventional spectrophotometers. There is a light source which supplies the UV and a detector (or detectors in some implementations) that measures the light transmitted through the sample volume. The difference from conventional UV spectrophotometry is that rather than a cuvette to hold the sample, there are fiber optics that transmit the light to and from the apparatus and in situ probes that define the sampling volume (path length). Multiple variations of the scheme have been utilized in designing these systems.[18] These have mostly varied in the choice of detector and probe design. Some systems are simple single-channel designs only capable of measuring one vessel at a time. The majority, however, measure all the vessels at or near the same time. The simplest of these use a conventional scanning or diode-array–based spectrophotometer with a multiplexer to sequentially switch amongst the vessels (Fig. 1). This means that the dissolution is not measured truly simultaneously in each vessel, and the reproducibility of the multiplexer needs to be validated. To eliminate these problems, some systems opt to use multiple diode array detectors, one per vessel. This approach permits simultaneous measurement from all vessels but introduces the need to validate and crosscorrelate the multiple detectors, because it essentially the same as using multiple spectrophotometers to measure each vessel. To simultaneously measure all vessels with one detector, some systems use a multichannel charged couple device (CCD) detector and imaging spectrograph. In this design, the spectrum from each probe is created on a separate part of the two-dimensional detector, allowing one detector to act as multiple ones. Because the light from all vessels are collected in one optical system, care needs to be taken in the design of such systems to avoid crosstalk amongst the various vessels.

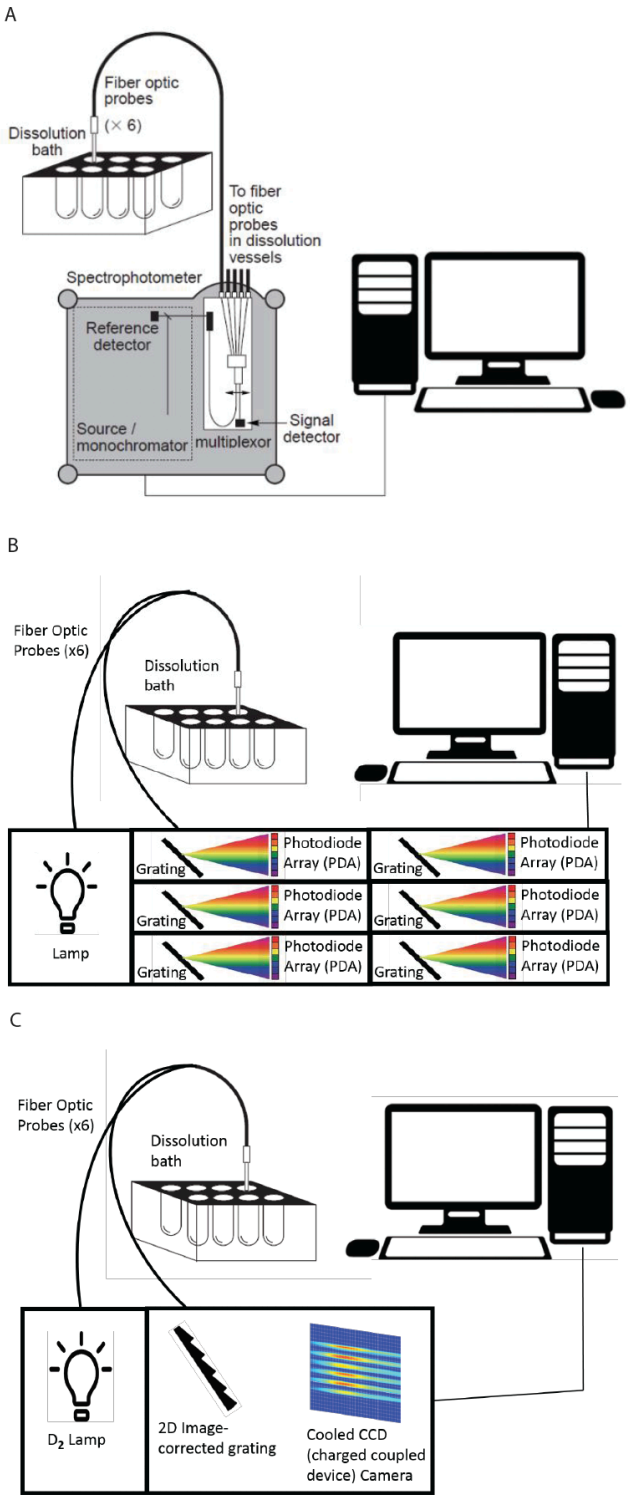

Figure 1. Different configurations of in situ UV systems. (A) Multiplexor and scanning monochromator. (B) Multiple photodiode array spectrographs. (C) Imaging spectrograph and CCD.

As is the case with detection schemes, there is also variation in design of the fiber optic probes (Fig. 2). Early systems used standard transmission dip probes designed for general purpose liquid measurement. Some of these probes had the nice feature of having interchangeable tips, which allow changing the pathlength, like selecting different cuvettes in a conventional UV system. Unfortunately, these also had several issues when applied to dissolution testing. In their normal use, there is no concern about hydrodynamics, so these probes tended to be thick (typically ~6 mm). Such large probes being resident during a dissolution test could affect the results, so implementation required either validation of the lack of such effects or the addition of a raising and lowering manifold to remove the probes from the media when not sampling.[19–21] Another issue was that the vertical design meant that the probes were prone to trapping air bubbles and particulates. Also, the original designs, when used with pathlengths below 2 mm (which translates to a 1-mm opening because the light traverses the opening twice in these probes), would sometimes result in inadequate liquid flow through the probe, especially with viscous media or use of surfactants. Later generations of transmission probes addressed some of these concerns. Models became available with a diameter less than 3 mm, much closer to that of cannulas conventionally used in dissolution testing. Also, the sampling cavity flow was improved by changing the design from having supports on two sides of the opening to one. This also reduced the bubble and particulate trapping.[18]

Another recent design also bends the probe 90 degrees to create a horizontal sampling volume, which further reduce the chance of trapping bubbles and particles. One drawback of this design is that because the probe is no longer rotationally symmetric, it is not possible to align the opening of the probe the same way in all vessels and for all pathlength

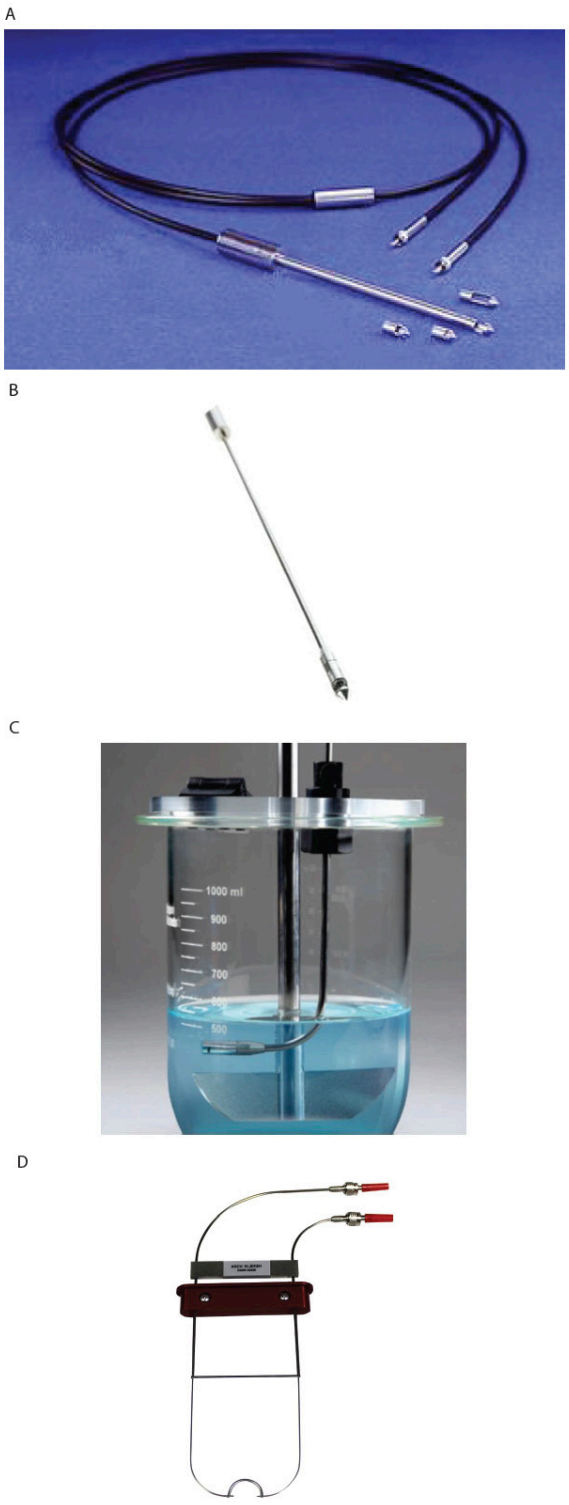

Figure 2. Different probes utilized in in situ UV systems. (A) Conventional transflectance probe. (B) Optimized transflectance probe. (C) J-Probe. (D) Arch probes.

tips. This can be an issue since the literature contains examples of dependence of dissolution rates on probe orientation. A very interesting design was also developed that featured two simultaneous pathlengths to expand the range of concentrations that can be measured in one dissolution test.[22]

Another probe design was developed specifically for dissolution testing. The probe uses curved input and output legs facing each other and separated by a fixed gap that becomes the pathlength.[16] This design yields the thinnest probe with a horizontal gap that is the least likely to capture bubbles or particles. Because the gap is equal to the pathlength in this design, and because of the small size that the liquid has to transverse through, this design supports pathlengths as short as 0.25 mm, allowing measurement of solutions four times as concentrated as other probes. Drawbacks of this design include limits on the maximum pathlength to 10 mm (versus 20 mm for dip probes) because there are no focusing optics, and the fact that the pathlength is fixed, meaning a different probe must be used for each pathlength. Also, as is the case with in-vessel temperature probes, the thin portion of the probe inserted into the dissolution medium requires more careful handling.

Challenge of Unfiltered Measurement

One of the biggest differences between other UV and liquid chromatography (LC) measurements and fiber optic UV measurements is the need to address the challenges of measuring directly in the vessel, where other components such as excipients, undissolved capsules, microspheres, etc. are present and can interfere with the measurement by either absorbing or scattering light. In standard measurements, these challenges are eliminated by first filtering the sample before analyzing it; however, this is not an option for in situ fiber optic systems. Although it would be possible to place a filter over the opening of the fiber optic probe, any blockage of the filter will result in a stagnant volume inside the probe that will not accurately represent the concentration of API dissolved in the rest of the vessel at a given time. This is because unlike or automatic liquid sampling with cannulas, there is no suction applied to continuously supply fresh media past the filter.

Instead, one has to use so-called "mathematical filters" to remove the contribution of non-API components. These filters normally take one of two forms (Fig. 3). The first is baseline correction. The concept here is that the contribution of other components to the absorbance measured at the analytical

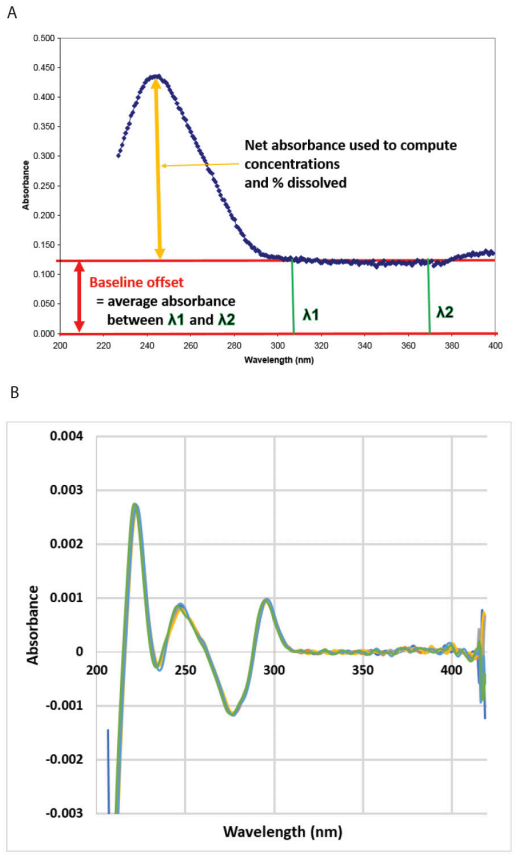

Figure 3. Different "mathematical filters" utilized in in situ UV systems. (A) Baseline correction. (B) Second derivative.

wavelength is modelled by measuring their contribution at a wavelength(s) where the API exhibits no absorbance. These corrections can range from a simple one-point baseline offset correction to more complicated multipoint schemes, including ones that use an exponential baseline to model the wavelength dependences of light scattering from particles.

The second category of correction algorithms is based on derivative spectroscopy. The idea here is essentially that the slope of the API absorbance peak is different from the slope of the interference, and one can exploit this difference to discriminate the contribution of the API from scattering or absorbance from other components. The percent dissolved is computed by comparing the computational derivative value of the absorbance spectra at the analytical wavelength of the sample versus the standard.

A first derivative is enough to eliminate the contribution from a constant baseline shift but suffers from the unfortunate fact of having an amplitude of zero at the analytical peak, so the second derivative is typically used instead. The second derivative goes back to having a peak at the analytical wavelength and can also discriminate between the API spectrum and a complex contribution, such as exponential light scattering from another component. Derivative filtering is particularly useful when there is no convenient wavelength where the API does not absorb but the other components still contribute, or in cases where the contribution from other components is spectrally complex. The drawback to derivative filtering is that since the derivative spectra are produced computationally rather than in closed form, they have reduced the signal-to-noise ratio. This reduction is even greater for the second derivative. A consequence of this reduced signal-to-noise ratio is that the measurement is less sensitive, i.e., the minimum concentration and label claim that can be correctly quantified is increased. This limitation can be somewhat overcome by applying spectral smoothing. This comes at the expense of effective resolution, but given the broad width of pharmaceutical API peaks, this is normally not an issue.

Multicomponent Analysis

Traditionally, analysis of multicomponent (multiple API, multiple interfering components, matrix effects, etc.) samples in dissolution have been relegated to LC analysis. However, work predating LC and subsequent methods have been developed to apply UV to these samples. In situ UV testing is particularly suitable for these methods because what they typically require is complete spectra at each time point collected as close to simultaneously as possible. Many chemometric methods such as PLS and PCR have been applied to this problem. Most tend to be limited in utility, especially when the multiple components exhibit a "matrix effect", where the total spectrum is not a simple superimposition of the API spectrum and the other components spectra. Instead, the constituents' spectra themselves are altered by the concentration of the other components.

Again, two computational methods are employed to extract the dissolution profiles of multiple components in in situ UV. The first is the derivative zero crossing method.[23] The idea of this method is that the derivatives of the spectra of the different components have a zero value (zero crossing) at different wavelengths, so, at that wavelength, they do not contribute to the derivative spectrum of the mixture. Using a two-component mixture as an example, one measures the concentration of component "A" by analyzing the value of the mixture at a wavelength where component "B" has a zero crossing, and vice versa. The drawback of this technique is that if the two components have similar spectra, the signal of

the other component at the zero crossing of the first tends to be low, making accurate quantitation difficult. This is further acerbated by the fact that data from only one or a few wavelengths are used in the calculation (Fig. 4).

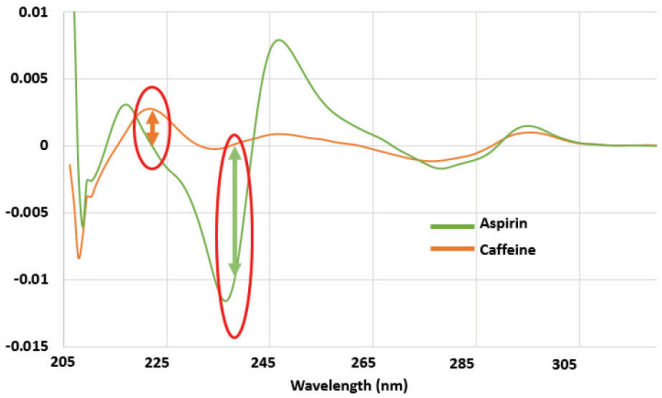

Figure 4. Zero crossing derivative spectra for mathematically resolving multicomponent dissolutions.

The second method, called classical least squares (CLS), addresses this issue. CLS is broadly used to solve problems where some function "C" depends on "A" and "B", but "A" and "B" also depend on each other.[24,25] The way CLS works is that one first measures some known mixtures of "A" and "B", which become a training set for the algorithm. The algorithm is closed form, so always yields a unique answer to a given set of measurements. It is simply based on using matrix math to solve the problem of which mix of "A" and "B" would most closely yield the observed combined spectrum at all wavelengths analyzed. Because it considers as many spectral points as possible, this algorithm works for a wider range of pharmaceutical products. The only added complexity in its use is the fact that one must typically prepare two or three extra standards (Fig. 5).

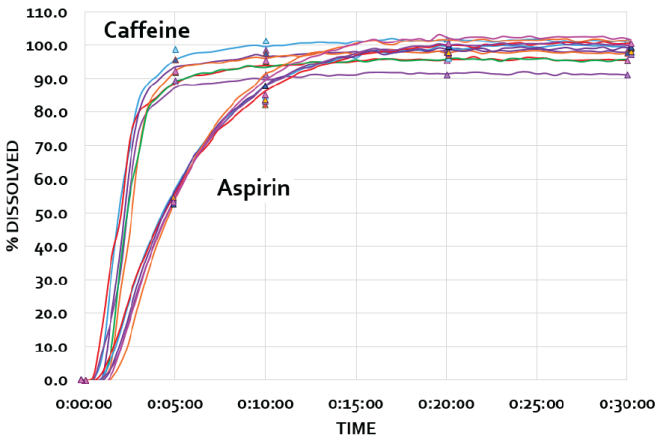

Figure 5. Comparison of multiple APIs mathematically resolved using CLS vs. HPLC. API, active pharmaceutical ingredient; CLS, Classical Least Squares; HPLC, high-performance liquid chromatography.

Present Situation of QC Dissolution

As with any new technique, the industry has shown caution in the acceptance of UV fiber optic dissolution for QC and drug product batch release. From a regulatory perspective, in situ UV dissolution analysis has always been regarded as simply an alternative way of doing conventional UV.[26] USP Chapter <1092> The Dissolution Procedure: Development and Validation Spectrophotometric Analysis Section explicitly states that "fiber optics as a sampling and determinative method, with proper validation, is an option." The FDA has also recognized the technique in its own internal training as early as 2004. Finally, both the FDA and USP have directly purchased and been using in situ UV dissolution systems internally for nearly two decades.

Currently, there are many hundreds of commercial in situ UV systems in use in the pharmaceutical industry. These include units utilized in research and development, formulation, stability, analytical, and QC groups. The use of fiber optic-based in situ UV dissolution testing has been validated in multiple studies comparing results with established techniques such

as conventional UV and LC. Furthermore, suitability has been documented by the implementation of hundreds of systems worldwide, including at regulatory agencies such as the FDA and USP. There are multiple products around the world being released based on dissolution testing performed using in situ UV systems. For some of these products, the in situ method was the primary method documented in the original NDA filing. These include ximelagatran (Exanta) from AstraZeneca and venlafaxine (Effexor) from Pfizer (of course, the description in the monographs simply reads UV, and an analytical wavelength and the UV method like diode array versus scanning, is never specified). Others have been released with in situ UV as a secondary method, such as oxycodone (Oxycontin) from Purdue Pharma. Another application involved the use of in situ UV for a two-step tier-2 dissolution of over-encapsulated erlotinib (Tarceva) tablets.[27]

Applications in Bio-Predictive Dissolution

In situ UV dissolution has found its niche in bio-predictive dissolution, which serves the need for API characterization and drug product formulation development. Alternative techniques are more readily adopted in this area due to its non-GMP status and not being subject to regulatory compliance requirements. The focus is to evaluate the physicochemical properties of the API, assess biopharmaceutics risks, screen formulation prototypes, perform relative comparison and trending analysis, and generate data for decision making in a timely fashion. UV fiber optic systems have become an ideal choice for meeting these needs.

An early application commercialized by Delphian Technologies was monitoring concentrations of API in small volumes (2–20 mL). Their solution, an in situ fiber optic UV monitoring system with real time data display, was suitable for evaluation of various effects on solubility, intrinsic dissolution rate, dissolution profiles, supersaturation, precipitation profiles, etc.[28] The UV fiber optic probes were flexible and durable stainless-steel dip probes with variable pathlengths. Due to the small volume and floating particulates, possible particulate accumulation on the surface of the probe that may affect UV detection needs to be considered during experiments. A further innovation on the small volume apparatus was to combine the dissolution experiment with transmembrane permeation (Fig. 6), which enabled evaluation of the formulation dissolution performance and the drug absorption potential and flux at the same time.[9] For such an apparatus, a donor chamber and a receiver chamber are connected through a membrane. Two fiber optic probes are mounted in these two chambers (one in each) to measure the drug concentration in the chambers over the time.

UV fiber optics systems have also been applied to biphasic dissolution, an alternative testing

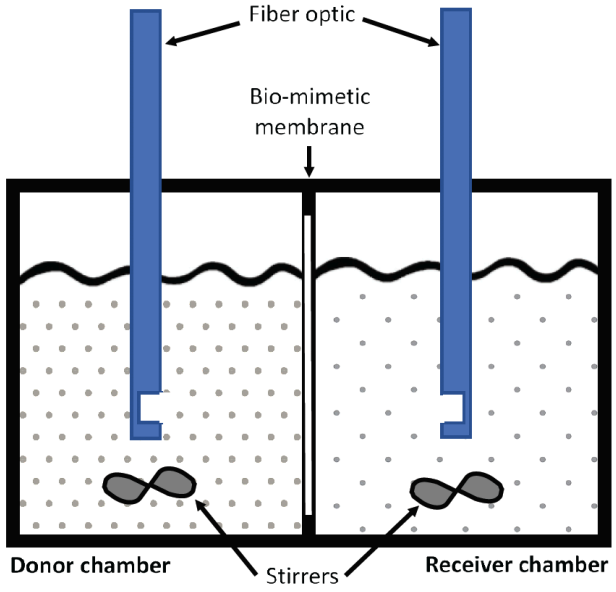

Figure 6. Schematic drawing of pION, Inc. µFlux apparatus, with two UV fib er optic probes added to each the donor and receiver chambers.

methodology that integrates the in vitro dissolution of a drug in an aqueous phase and its subsequent partitioning into an organic phase to simulate the in vivo drug absorption. A biphasic dissolution system consists of two immiscible phases: an aqueous phase and an upper organic phase. In an early application, a UV fiber optic probe was placed in the organic phase, while the detection of drug release in the aqueous phase was performed by withdrawing aliquots for offline measurement.[10] A recent application was demonstrated where two sets of fiber optic probes were used, each controlled by a separate UV spectrometer.[29] The set of the probes placed in the aqueous phases of the multiple vessels were Arch probes, and the other set of probes placed in the organic phases of the vessels were dip probes (Fig. 7). The in situ UV measurements provide detailed drug release profiles for both phases, helping to improve the understanding of the formulation's performance and make better decisions regarding these choices.

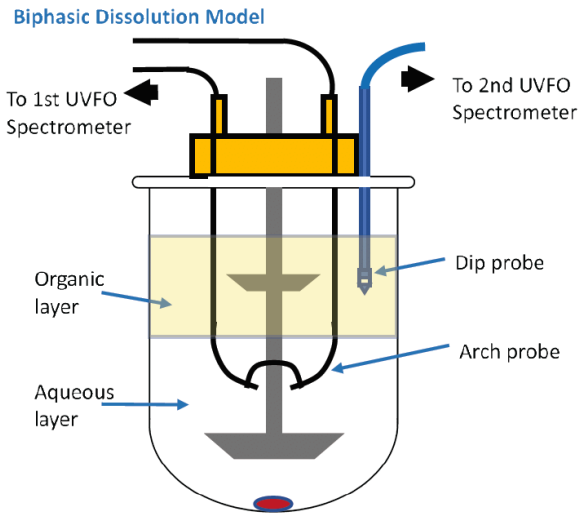

Figure 7. Schematic drawing of biphasic dissolution in USP apparatus 2, with use of two UV fiber optic probes (one Arch probe, and one dip probe) controlled by two UV spectrometers for detection of the drug concentrations in the two phases (29). UVFO, UV fiber optic.

Conclusion

Early adopters of in situ UV fiber optic dissolution testing were drawn to these systems because of the unique capabilities – the ability to produce complete profiles with hundreds of time points, the ability to characterize extremely fast dissolution such as orally dissolving products with several second temporal resolution, or the ability to measure data unattended for multiday or even weeks-long tests. Next came users who needed a solution for samples that could not be addressed by conventional dissolution methods. These included samples that could not be readily filtered, such as nanosuspensions or coated microspheres, where the only option was real-time measurement because it is almost impossible to avoid erroneous results due to continuing release between sample collection and analysis more recently, samples with two APIs or a matrix effect that would otherwise only be possible to analyze by LC.

These non-conventional samples that defy normal dissolution testing will continue to attract first-time users. Far more exciting, however, is the adoption of in situ UV for conventional dosage forms that could be done using other methods. Instead, these dosage forms are validated and manufactured using in situ UV systems because these systems offer the cost and time savings associated with UV analysis, amplified by the lack of need for sampling consumables, such as filters, syringes, lines, and cleaning solvents. In addition, in situ UV systems finally realize the promise of automation where user errors are eliminated and labor is actually reduced by true unattended operation.

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Conflict of Interest

The authors disclosed the following conflict of interest: I. Nir is employed by Distek, Inc., a manufacturer of a commercial fiber optic dissolution system.

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2. Brown, C. W.; Lin, J. Interfacing a fiber-optic probe to a diode array UV-visible spectrophotometer for drug dissolution tests. Applied Spectroscopy. 1993, 47, 614–618. DOI: Figure 6. Schematic drawing of pION, Inc. µFlux apparatus, with two UV fiber optic probes added to each the donor and receiver chambers. Figure 7. Schematic drawing of biphasic dissolution in USP apparatus 2, with use of two UV fiber optic probes (one Arch probe, and one dip probe) controlled by two UV spectrometers for detection of the drug concentrations in the two phases (29). UVFO, UV fiber optic. AUGUST 2018 77 www.dissolutiontech.com 10.1366/0003702934067261.

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A Green Solution for the Dissolution Laboratory

by Ishai Nir, Jeff Seely, and Sean Gilmore
Distek, Inc., North Brunswick, NJ

A Green Solution for the Dissolution Laboratory

Going "Green" in today's business climate where maximizing shareholder equity and conserving capital is a top priority can be difficult, especially if the project increases the overall cost of doing business. Unfortunately, when business conditions are difficult many environmentally friendly initiatives and other peripheral programs not deemed critical to the performance of the business are some of the first to be put on hold or abandoned altogether. Fortunately, there are several solutions from analytical instrument suppliers which offer cost and time savings as well as being environmentally friendly. Distek, Inc. offers one such solution for the dissolution lab.

One method of saving money and reducing a company's carbon footprint is by decreasing the amount of electricity that is consumed by a lab in its day-to-day operations. When an instrument with equal or superior performance capabilities requires less electricity than other instruments that perform the same function, serious consideration should be given to using the more energy efficient instrument. With USP 1 and USP 2 dissolution testing, a "traditional" water bath based system is used to heat the vessels and the medium contained within them. Now consider if there was a bathless dissolution unit which eliminates the water bath and consumes less than half of the electricity while still offering similar or superior performance to that of a water bath system. The amount of money that can be saved on electricity in a dissolution lab by simply changing the type of dissolution tester used would be substantial.

Does such a system currently exist? The answer is yes. The Distek Model 2500 Select Bathless Dissolution Test System (2500 SELECT), which is the fourth generation of the patented bathless system. In energy consumption tests, the water bath based dissolution systems typically used at least twice the amount of energy of the 2500 SELECT. In the studies conducted for this article, two typical operating scenarios were considered: the time and power consumed when performing a 24 hour dissolution run, and the power consumed by the equipment between runs.

When a water bath based dissolution tester is not being used to execute a run, the thermocirculator is typically left running to maintain the heat of the water bath, continuing to consume energy. Even if the bath is turned off between tests, it uses comparatively large amounts of electricity to re-heat several gallons of water to 37°C, whereas the 2500

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SELECT has no such requirement, making it more energy efficient.

Below are the results from two power consumption studies involving typical operating scenarios. The studies were conducted using an Energy Consumption Monitor/Logger, Model ECM-1220 by Brutech. The baths used in the study were manufactured by various suppliers including Distek, Inc., Agilent, Inc., and Hanson Research.

Scenario #1

Performing a Dissolution Run

In this scenario, four common brands of bath based dissolution systems were heated up with their vessels in place but without being filled with medium. The thermocirculator temperature was set to 37°C and once the temperature of the bath water reached its set point, 900 ml of room temperature medium was added to the vessels. The time required for the various water bath based systems to reach the set point temperature ranged from 30 to 55 minutes. The temperature of the medium in the vessels was allowed to heat up with the assistance from the paddles stirring at 100 RPM. Once all of the vessel temperatures were at 37°C ± 0.2°C, a 24-hour dissolution run was executed. For the duration of the test, the vessels were kept covered and maintained a temperature of 37°C.

The 2500 SELECT was also programmed to run a 24-hour test at 37°C with paddles stirring at 100 RPMs. Because there is no water bath to heat up, the vessels were filled with 900 ml of room temperature medium, covered, and the method program was initiated. For the 2500 SELECT there was approximately 10 to 12 minutes of preheat and equilibration time. Upon equilibration, the 24-hour program was started.

Table I below shows the power consumed by four typical baths and the Distek 2500 SELECT.

Scenario #2

Between Dissolution Runs

When water bath based systems are not performing a dissolution run, they are typically left on with the thermocirculator heating and circulating the water in the bath. They can also be turned off when not in use but would have to go through the process of re-heating the bath when turned on again. The amount of energy required to reheat the water in the bath is shown in the first row of Table I below. Table II shows the amount of power used to maintain the heat in the bath without any run in progress for a 24 hour period with empty vessels secured into the vessel plate, and a second 24 hour period without any vessels in place.

Some of the variances in power consumption in the different brands of dissolution baths are due to the size of the water bath and the volume of water it holds. The higher the volume of water the greater amount of energy required. Another factor that can have an effect on energy consumption is how well the water is circulated within the water bath. A higher flow rate generally results in a more consistent temperature throughout the bath but may consume more power for the pumping of the water. Lastly, the temperature in the lab itself will make a difference in the efficiency of the water bath based system. When water bath systems are in a cooler environment, they require more power to maintain the proper temperature.

Table 1. Power Consumed by Four Typical Baths and the Distek 2500 SELECT							
	Bath 1	Bath 2	Bath 3	Bath 4	Avg. Bath Energy Used	2500 SELECT	% of Bath Energy Used 2500 SELECT
Energy used heating bath	0.440 KWh	0.353 KWh	0.277 KWh	0.677 KWh		0 KWh with	
Energy used heating media in vessels	0.198 KWh	0.162 KWh	0.228 KWh	0.171 KWh		0.281 KWh	
Energy used running 24 hours test	2.907 KWh	3.507 KWh	2.377 KWh	3.428 KWh		1.505 KWh	
Total Energy Consumed for Scenario	**3.545 KWh**	**4.022 KWh**	**2.882 KWh**	**4.276 KWh**	**3.681 KWh**	**1.786 KWh**	**48.5**

Table 2. Power Consumed to Maintain Bath Heat Without Any Run in Progress							
	Bath 1	Bath 2	Bath 3	Bath 4	Avg. Bath Energy Used	2500 SELECT	% of Bath Energy Used 2500 SELECT
Energy consumed maintaining heat in bath with empty vessels in place	2.707 KWh	3.220 KWh	2.056 KWh	2.263 KWh	2.562 KWh	0.171 KWh*	6.7
Energy consumed maintaining heat in bath without vessels in place	5.110 KW	4.630 KW	3.480 KWh	4.442 KWh	4.416 KWh	0.171 KWh*	3.9

*The 2500 SELECT does not require the heaters to remain active since it has no water bath to maintain at a constant temperature.When the 2500 SELECT is placed in "Sleep" or standby mode, it continues to use a minimal amount of power as shown in Table 2above. Since it requires no water bath re-heat time the unit can be completely turned off between runs consuming zero power with aminimal dissolution medium pre-heat start-up time of 10-12 minutes.

Conclusion

It is clear that, on average, it requires twice the power to operate a water bath based dissolution system than it does a bathless one. Now that the industry and the global community are more cognizant of the need to conserve resources and be more "green", the Distek 2500 Select bathless dissolution unit is an obvious choice for the planet and for the bottom line.

Content Uniformity Measurement of an OTC Product Using a Dedicated Sample Preparation Station and a Fiber Optic UV Analysis System

by Andrew Kielt, Ishai Nir, and Jeff Seely
Distek, Inc., North Brunswick, NJ

Introduction

Content uniformity (CU) is performed using a wide range of techniques for sample preparation and analysis. Most have some obstacles preventing them from being consistent and robust. They result in challenges in batch-to-batch reproducibility due to factors such as operator variability and dilution and other user errors.

What is needed is a solution specifically designed for content uniformity sample preparation. Such a CU sample prep station (PrepEngine, Distek, Inc.) is now available. It offers many advantages over other common sample preparation methods. With its stirring blade, dedicated polypropylene sample processing vessels and adjustable speed ranging from 100 to 6000 RPM, this unit can reduce sample preparation time by up to 90% compared with conventional methods. The system also provides 10 individual stirring stations to match the USP Chapter <905> Uniformity of Dosage Units 10-unit assay requirement.

The CU sample prep station addresses the issue of reproducibility and length of time required for content uniformity sample preparation. The reduced sample preparation time makes an equally rapid sample analysis technique highly desirable. A fiber-optic UV spectrophotometer is ideal for this task. The fiber optic UV removes the need for dilution and filtration, both reducing total analysis time and avoiding the key sources of user errors. Fiber optic UV permits analyzing directly in the sample prep container, allowing instant results.

Apparatus and Materials

Content uniformity testing was conducted using the CU sample prep station and disposable 500 mL

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sample prep vessels (PrepTubes, Distek, Inc). The samples were prepared with deionized water and Tylenol Regular Strength (325 mg) tablets (Johnson & Johnson). The samples were analyzed with a fiber optic UV (Opt-Diss 410, Distek, Inc.) equipped with 0.25 mm pathlength probes (Arch Probe, Distek, Inc.). A reference standard for the fiber optic UV was prepared with Acetaminophen reference standard material (Spectrum Chemical MFG. Corp.).

Method Development

The two parameters to be defined in establishing a content uniformity sample preparation method are agitation speed and duration. To optimize these, CU testing was conducted using different speeds. The goal is to find the lowest agitation speed that will still yield guaranteed complete release in an acceptable test time.

Tylenol Regular Strength tablets were added to 500 mL sample prep vessels containing 500 mL deionized water before connecting to the CU sample prep station. The runs were stopped at different time points and the product absorbance inside the sample prep vessels was measured with the fiber optic UV to determine percent extracted. Acetaminophen standard solution of 0.651 mg/mL concentration was prepared in deionized water to represent fully released product in 500 mL. The UV spectrum of the Acetaminophen standard was measured with the fiber optic UV. The percent extracted values were then calculated using the fiber optic UV software by comparing the sample absorbance to the standard absorbance.

Measurement results are presented in the Table 1 and 2, and Chart 1.

Based on the above, an agitation speed of 3000 RPM and a run time of 1.5 minute were selected as the final method parameters.

Table 1. Percent extracted results at different time points and RPM speeds

	% Extracted		
Total Time (s)	500 RPM	1000 RPM	2500 RPM
0	0	0	0
30	53.3	60.5	86.5
60	80.2	90.8	101
90	89.7	98.6	100.8
120	95.3	100.4	101.1
150	98.5		
180	98.6		
210	99.4		
240	99.5		
300	100.2		

Table 2. Percent extracted results at different time points and 5000 RPM

	% Extracted
Total Time (s)	5000 RPM
0	0
10	51.8
20	88.5
30	97.5
60	101.4
90	101.6
120	101.4

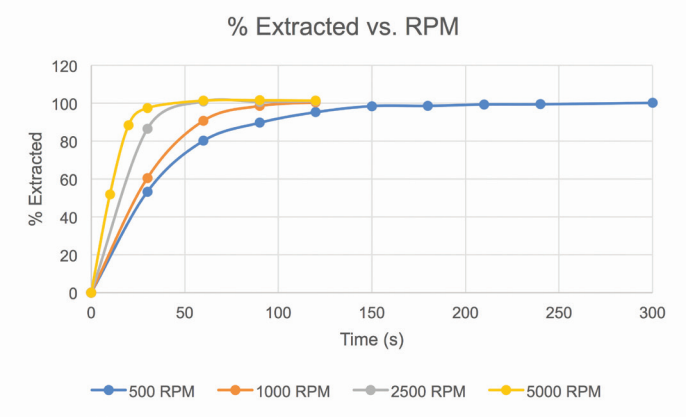

Figure 1. Percent extracted results as a function of agitation speed

Results

Ten 500 mL sample prep vessels were prepared by adding 500 mL deionized water and one Tylenol

Regular Strength tablet before connecting to the CU sample prep station. At the end of the run, the fiber optic UV was again used to measure the final percent extracted in each sample prep vessel. Table 3 provides the measured percent extracted of the 10 tablets. The results shown were weight corrected to eliminate the variation from tablet to tablet and highlight the measurement variability instead. The weight corrected results have a mean of 99.5% and %RSD of 0.12%. (For the uncorrected results, the mean is 99.5% and %RSD is 0.66%).

Table 3. Final CU results at 3000 RPM

Tablet	Weight Corrected % Extracted
1	99.4
2	99.4
3	99.6
4	99.5
5	99.3
6	99.6
7	99.7
8	99.4
9	99.7
10	99.5

The limit of the acceptance value (AV) set in USP Chapter <905> is less than 15.0 for 10 units. For the data presented in Table 3, the corresponding AV value is 0.29 for weight corrected values and 1.59 for uncorrected results, both well below the allowed value.

Conclusion

Dedicated CU sample preparation instrumentation provides a significant increase in efficiency and reliability. Paired with a fiber optic UV, the combination creates a fully robust measurement process spanning sample preparation to analysis with the important additional benefit of significantly shorter total test times and instant results. The simplicity of method development, robustness of measurement and time savings were demonstrated in actual measurements using a representative OTC product.

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Analysis of Two Active Pharmaceutical Ingredients (API) Products Using UV Spectrophotometry with Multi-Component Analysis and a Fiber Optic Dissolution Analyzer

by Andrew Kielt, Ishai Nir, and Jeff Seely
Distek, Inc., North Brunswick, NJ

Introduction

UV Spectrophotometry has traditionally been a simpler and less time and labor consuming method for analyzing dissolution testing samples. However, as soon as a product contained more than one active pharmaceutical ingredient (API), analysis with UV was no longer considered an option. This is because both species often absorb over the same spectral region, causing deviations from Beer-Lambert Law. This linear relation between absorbance and the absorbing species is the basis for calculating concentration values based on the measured absorbance at a specific wavelength. In these cases, separation techniques such as HPLC become the de facto analysis methods.

While it has been long shown that using Multicomponent Analysis (MCA) software and complete spectral and temporal profiles make it possible to analyze such products using UV, the drawback has always been the difficulty in acquiring all the required data. However, with a modern fiber optic UV dissolution analyzer, these obstacles have been removed. Analysis of the two spectrally overlapping components is accomplished by applying the Classical Least Squares form of Multiple Linear Regression to the complete spectral and temporal profiles obtained using these new analyzers. The algorithm uses a calibration matrix of extinction coefficients to calculate component concentrations in an unknown mixture. These are derived from a training set comprised of the spectra of multiple standard solutions.

This white paper explains the theory behind the MCA algorithm methodology. Then, used in tandem with in-situ fiber optics, the accuracy of the technique is demonstrated by recovering the concentration of two APIs in known mixed solutions. Finally, an example is given of accurately monitoring and quantifying the dissolution profile of an actual commercial product containing two APIs, demonstrating the elimination of the need to draw samples or to perform HPLC analysis for many of these type of products.

In the case of dissolution, Classical Least Squares analysis involves the application of Multiple Linear Regression to the classical expression of the Beer's law. Since complete UV spectra are measured, Beer's law can be expanded to incorporate absorbance of multiple components at different wavelengths, λ:

$$A_\lambda = \sum_{j=1}^{p} E_{\lambda j} \cdot c_j \qquad (1)$$

Where:

A_λ = Absorbance of the mixture of ***p*** components at wavelength **λ**

$E_{\lambda j}$ = Response sensitivity factor (molar absorptivity × probe path length) of component ***j*** at wavelength λ

Cj = Concentration of component ***j*** in the mixture

However, interactions between components including excipient materials also need to adequately represented. This leads to the need to expand the simple equation above into a more complex matrix:

$$A = K \cdot C \qquad (2)$$

Where:

A = Matrix of absorbance values for the calibration solutions

K = Matrix of sensitivity factors determined from measured spectra of mixtures with known component concentrations.

C = Matrix of known standard concentration values

K is calculated using the concentration matrix ***C***, its transpose C^T, and the calibration set absorbance matrix A_{std}.

$$K = A_{std} \cdot C^T \cdot [C \cdot C^T]^{-1} \qquad (3)$$

From ***K*** and its transpose K^T, K_{cal} (referred to as the calibration or regression matrix) can then be generated:

$$K_{cal} = [K^T \cdot K]^{-1} \cdot K^T \qquad (4)$$

The least-squares solution to determining analyte concentrations in an unknown mixture is then determined by the applying K_{cal} to the measured absorbance values of the unknown mixture A_{unk}.

$$C_{unk} = A_{unk} \cdot K_{cal} \qquad (5)$$

C_{unk} is the vector containing predicted concentration values (C_1, C_2, …, C_n) for each analyte in the unknown mixture.

As an example of the ability of this technique to measure the concentrations of components in a mixed solution, known mixtures of two ingredients found in common OTC products, Acetaminophen and Caffeine were measured.

The spectra of pure standards of Acetaminophen and Caffeine are shown in Figure 1.

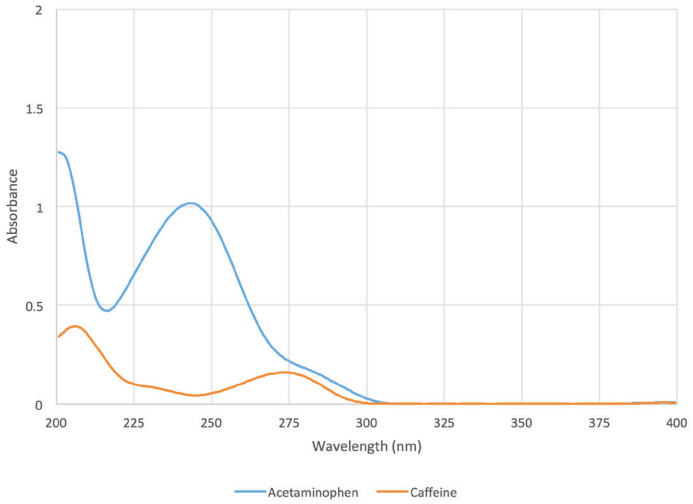

Figure 1. Absorbance spectra of Acetaminophen and Caffeine standards.

The technique was then used to analyze data collected using the Distek Opt-Diss 410 Fiber Optic Dissolution System from five mixtures with varying amounts of Acetaminophen and Caffeine. The computed values produced by the Opt-Diss 410 MCA software are compared to the actual values in the Table 1 and represented graphically in Figure 2.

One can clearly see that the method accurately quantitates the amounts of Acetaminophen and Caffeine in mixtures with an error well less than 2%.

To illustrate the applicability of the technique to real measurements, the dissolution of a tablet containing 400 mg Aspirin and 32 mg Caffeine was analyzed. Absorbance spectra of pure standards of Aspirin and Caffeine at 80% are shown in Figure 3.

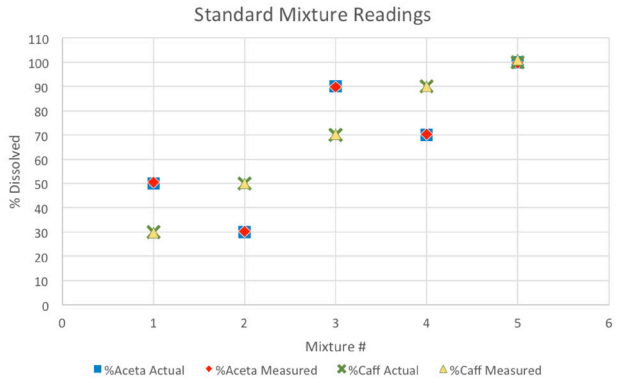

Figure 2. Comparison of measured versus actual results of standard mixtures.

Complete spectra from all six vessels were collected every 10 seconds for 30 minutes, again using the Distek Opt-Diss 410 Fiber Optic Dissolution System. The results were then analyzed using the method described above. In this case, the training set used comprised the measured values of five different mixtures of Aspirin and Caffeine plus the 80% pure standards shown in Figure 3.

As the results in Figure 4 demonstrate, the technique measures the simultaneous dissolution rates of the two components, readily resolving caffeine's very fast release rate as well as aspirin's slower one.

Summary

UV spectrophotometry combined with MCA has been demonstrated to yield accurate analysis of the absolute concentrations of each component in two component mixtures. The technique has been

Table 1. Measured versus actual percentage values of standard mixtures.

	Acetaminophen			Caffeine		
Mixture	% Actual	% Measured	% Error	% Actual	% Measured	% Error
1	50	50.43	0.9%	30	29.60	1.3%
2	30	30.30	1.0%	50	50.08	0.2%
3	90	89.83	0.2%	70	70.40	0.6%
4	70	70.19	0.3%	90	90.16	0.2%
5	100	99.68	0.3%	100	100.96	1.0%

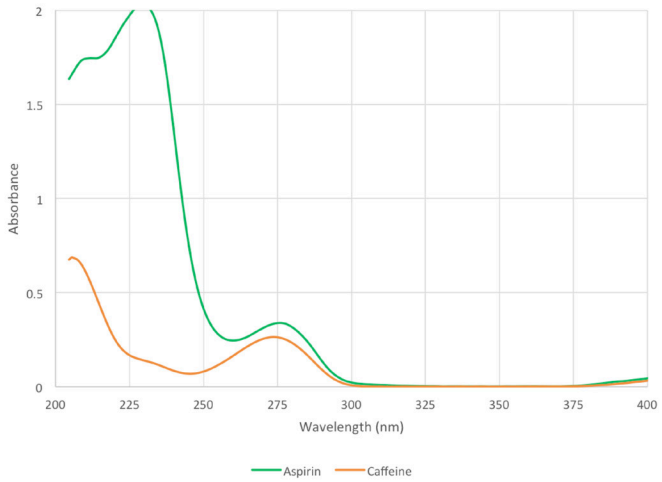

Figure 3. Absorbance spectra of Aspirin and Caffeine standards.

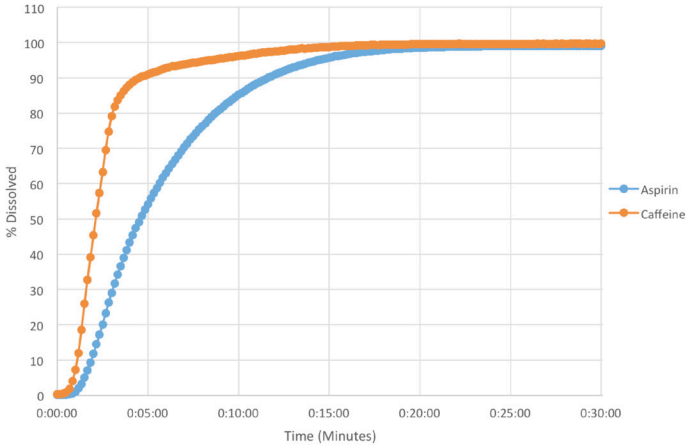

Figure 4. Average dissolution profile of six Aspirin Caffeine tablets.

also successfully applied to measuring the separate dissolution rates of two APIs in a commercially available product. These results demonstrate the method can accurately quantify two components even with highly overlapping spectra without the need for a separation step. The key to this process is using large data sets consisting of large spectral regions instead of individual wavelengths and complete temporal profiles instead of a few points. This rich data set collection is enabled by the use of in-situ sampling utilizing fiber optics probes which analyze the sample within the vessel. This circumvents the limit of the speed of moving the liquid from vessel to the analyzer that encumber traditional methods such as HPLC or conventional UV spectroscopy. An additional benefit of the instantaneous data collection of in-situ probes is that they allow near real-time dissolution analysis.

As these measurements of commercial products under real-world conditions illustrate, the addition of MCA and fiber optic in situ measurements allow formulation and analytical chemists, as well as QC analysts to realize the time and labor savings associate with UV spectrophotometry even when measuring products with two APIs.

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