Fiberoptic UV Dissolution Method Development

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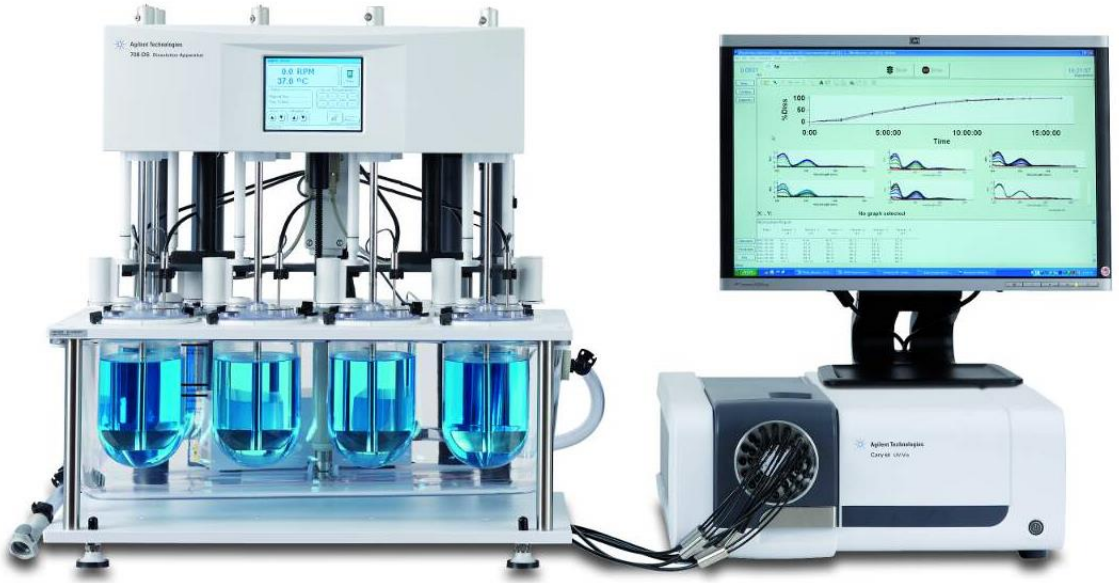
Agenda

- Background of Fiber Optic Dissolution (FOD) testing.
- What are the benefits of Fiberoptic testing?
- What factors need to be considered with FOD testing?
- Agilent Cary60 Fiberoptic Dissolution System
- Developing a Fiberoptic Method

Background of Fiber Optic Dissolution testing

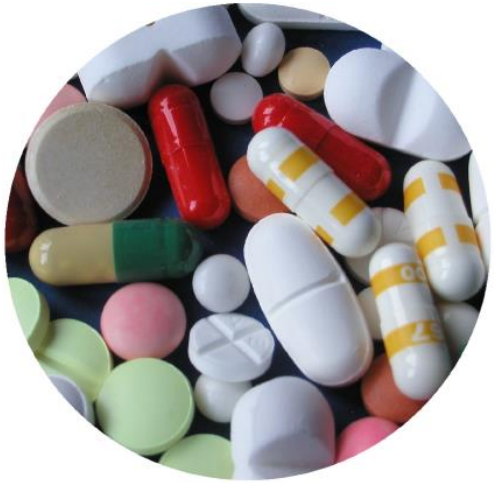


Fiber Optic Background.

- Dissolution testing can be a labor intensive and time consuming process.

- Traditionally we have looked to automate with off line fraction collector systems, or on line UV & LC systems.

- These systems have proved to be extremely popular, but have limitations.

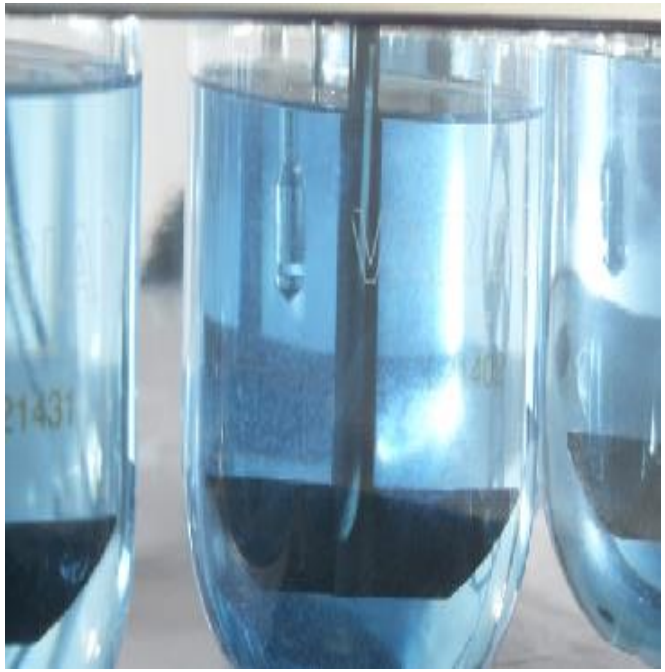


Fiber Optic Background – Traditional Sample Method Limitations

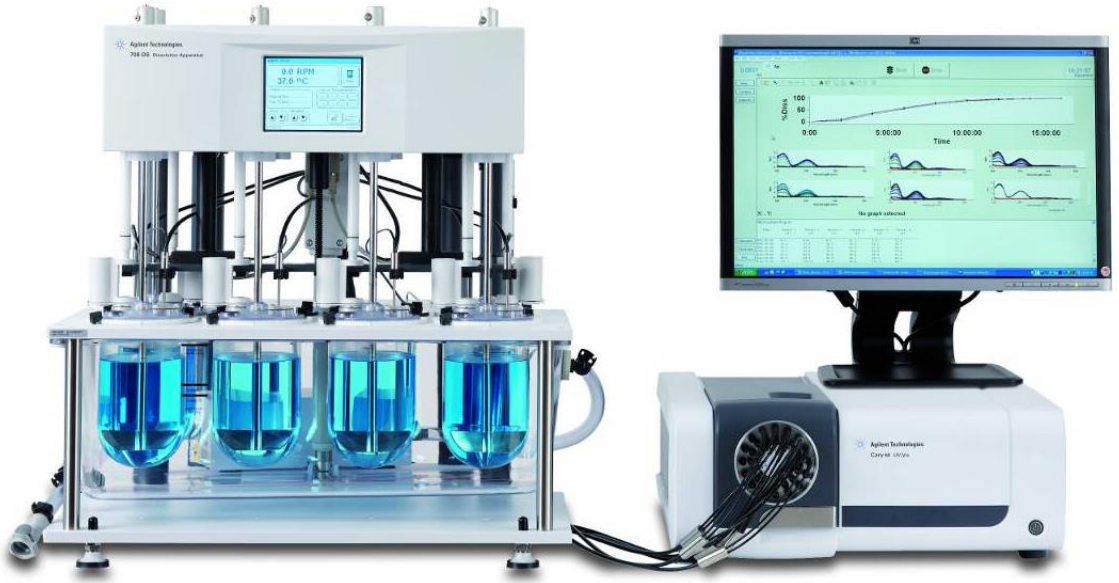
- Sampling speed
- Pumping systems
- Micro/Nano Particles
- Aggressive, organic & high viscosity media's
- Small volumes
- Analysis cost

Fiber Optic Background – A New Approach

- Fiber optic dissolution systems started to appear in the mid 1990's.
- They eliminate the need to remove the sample from the vessel.
- Light is "pumped" into the vessel from the spectrophotometer for "*in situ*" analysis, then back to the spectrophotometer where the absorbance is measured.
- They offer significant advantages for many dissolution tests.

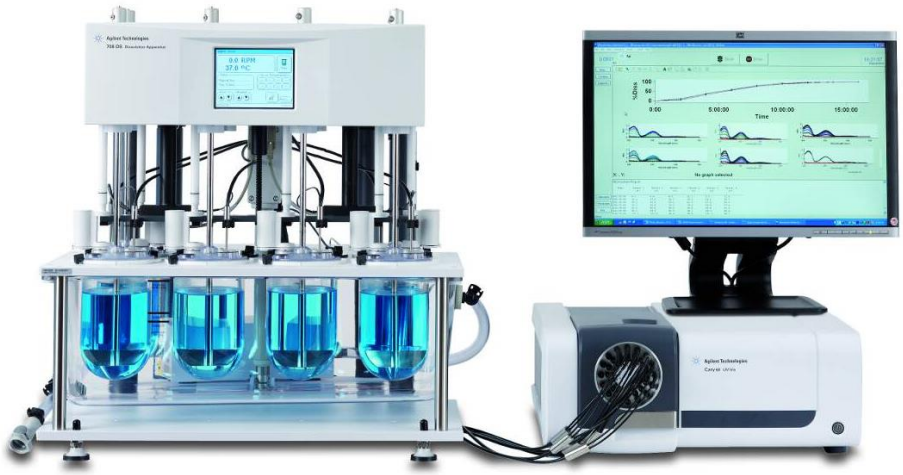


What are the benefits of Fiber Optic Dissolution testing?



Fiber Optic Benefits

- Rapid Sampling Time
- Immediate Results
- Poor Stability Compounds
- Few Consummables/Low Upkeep/Easy Cleaning
- Handles high surfactant media, viscous media
- Can be converted to small and large volume



Samples Suited for Fiberoptics

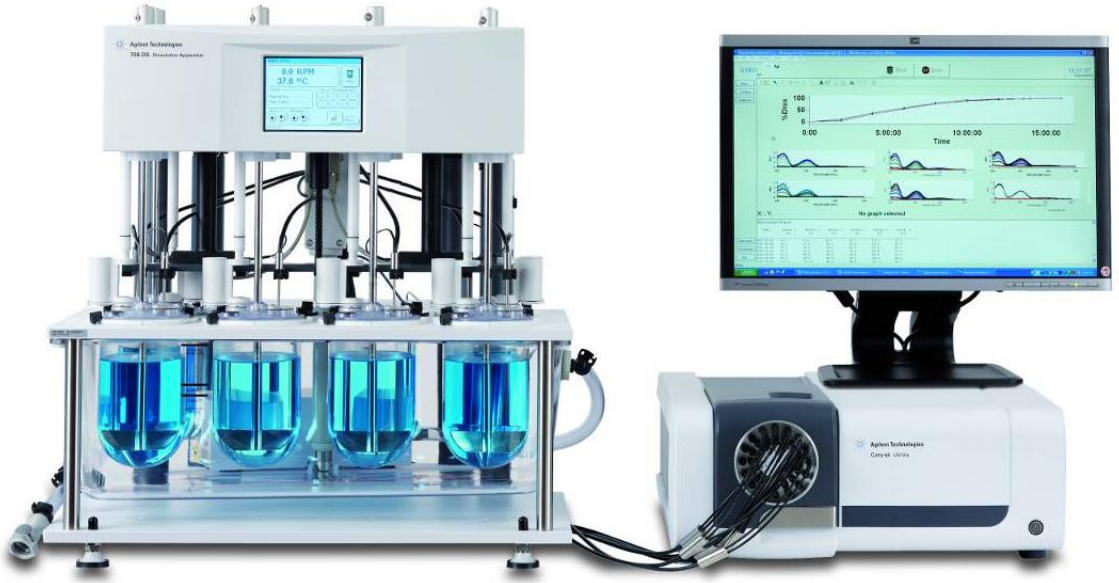
- Multiple timepoints needed for Immediate-Release Drugs
- Profile mapping of new formulations
- Nano and Microparticle API in Formulation (can’t be handled w/ conventional filters)
- Poor Stability Samples
- Challenging Medias for Pumps

Samples Not Suitable for Fiberoptics

- HPLC Required for Separation
- Samples requiring pathlengths <1mm or with large dilutions
- Colloidal Media (milk)
- Excipients with Refractive Properties (rare)

Typically, UV FO will work in about 85-90% of samples where UV is currently used

What factors need to be considered with Fiber Optic dissolution testing?



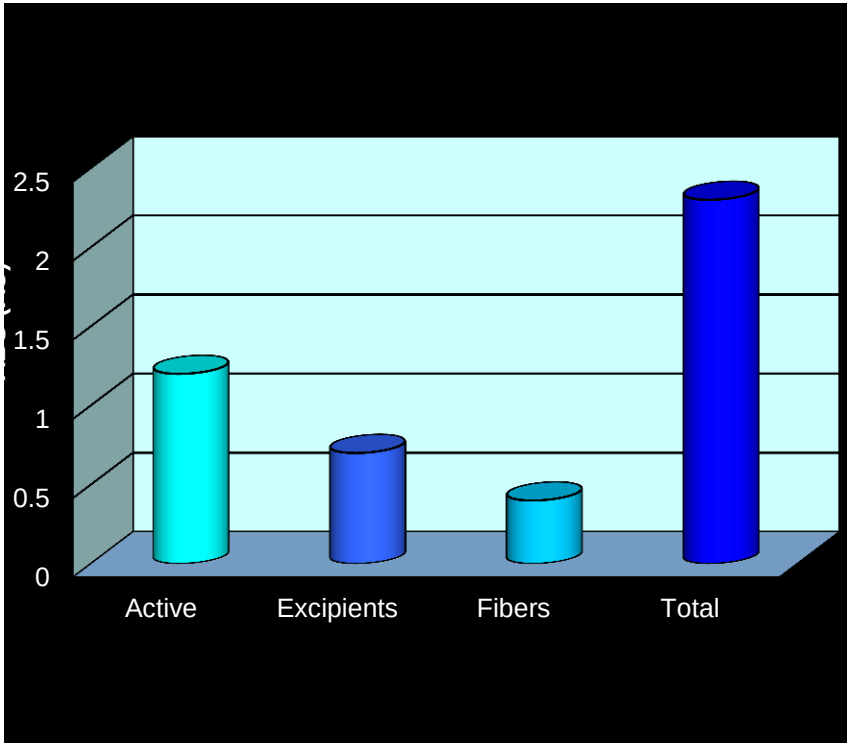
Fiber Optic System Considerations

- Spectrophotometer Linear Range and Wavelength Range
- Fiberoptic Probe Type
- Flexibility for Different Methods (hardware + software)
- Ease of setup and changeover of system

Spectrophotometer Linear Range

Linear Range Reflects the Total Absorbance, in Fiberoptics it is made up of:

- API Absorbance
- Absorbance of Excipients and Undissolved Materials (no filter)
- Absorbance of Probes themselves

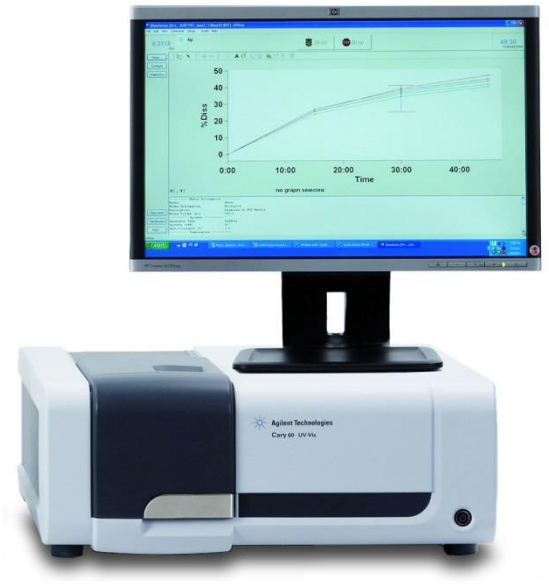


Need to choose UV which allows high linear range after reductions from probes and excipients

Spectrophotometer Wavelength Range

The Spectrophotometer chosen should work within the desired range, in particular be able to read:

- Max absorbance (<210nm can be difficult with some systems/methods)
- Area where no API absorbance exists for baseline correction



UV Spectrophotometer Type

Diode Array

- Quicker – constant readings
- Lower Wavelength Range, but full scans
- Lower Linear Range
- High Solarization Damage to Fiberoptic Probes

Scanning Spectrophotometer

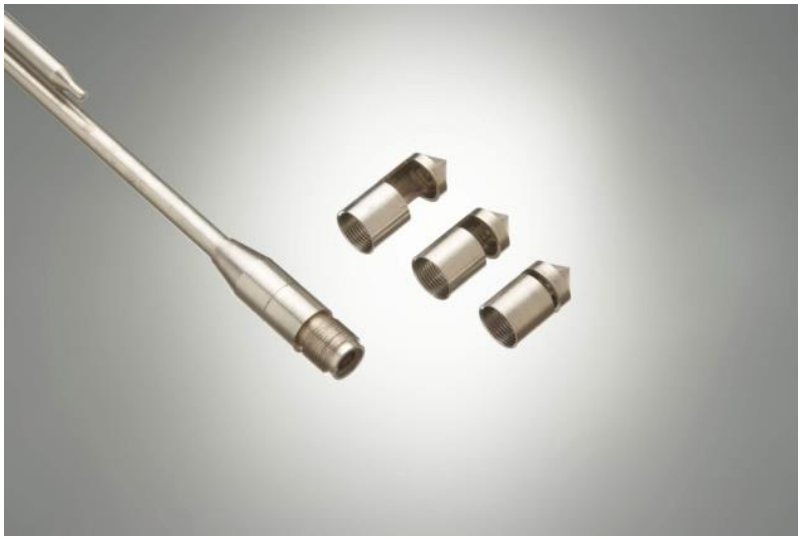
- Quick – Every 30 seconds
- Wide Wavelength Range
- High Linear Range – up to 3.5AU
- Low Solarization Damage – longer life probes

Fiberoptic Probe Types

There are 2 Styles of Probes Typically Available:

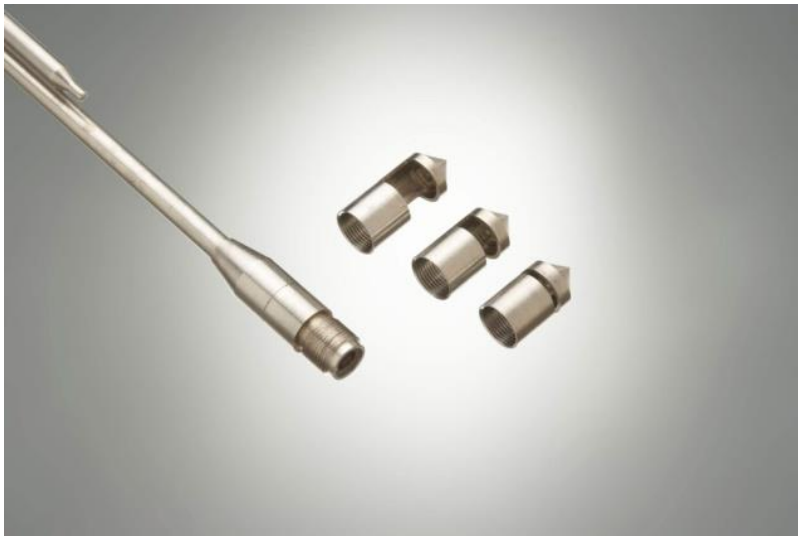
- Dip Probe
- Arch-shaped Probe

Dip Probes are usually ideal because they are adaptable to multiple volumes, and pathlengths are easily changed



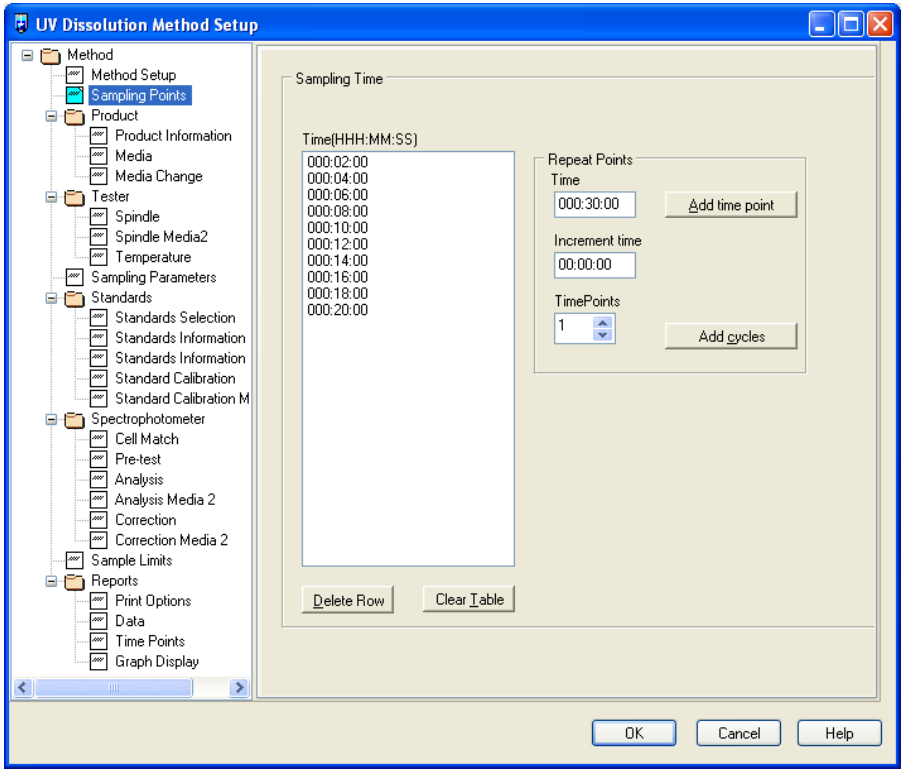
Other Probe Considerations

- Is the Probe Resident?
- What is the absorbance of the fiber itself?
- What Pathlengths available?
- UV cutoff with probe?
- Expected Life of Probe (solarization)

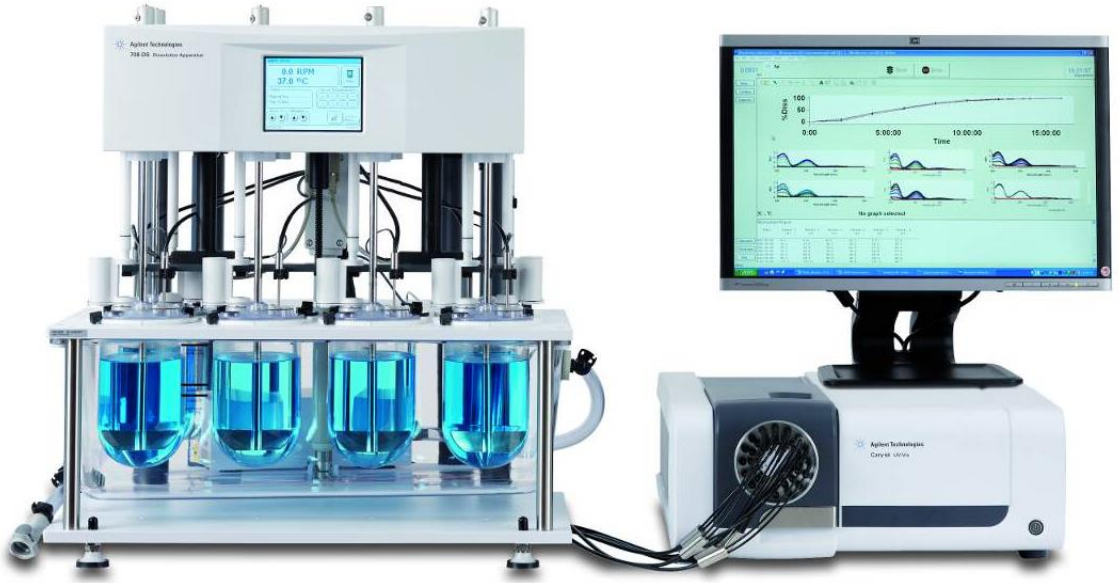


Flexibility of System

- Hardware
  - Small/Large Volume?
  - Pathlengths Available?
  - Non-resident Probes?
- Software
  - Dissolution Specific Software?
  - App 1/2/5/6?
  - Media changeover?

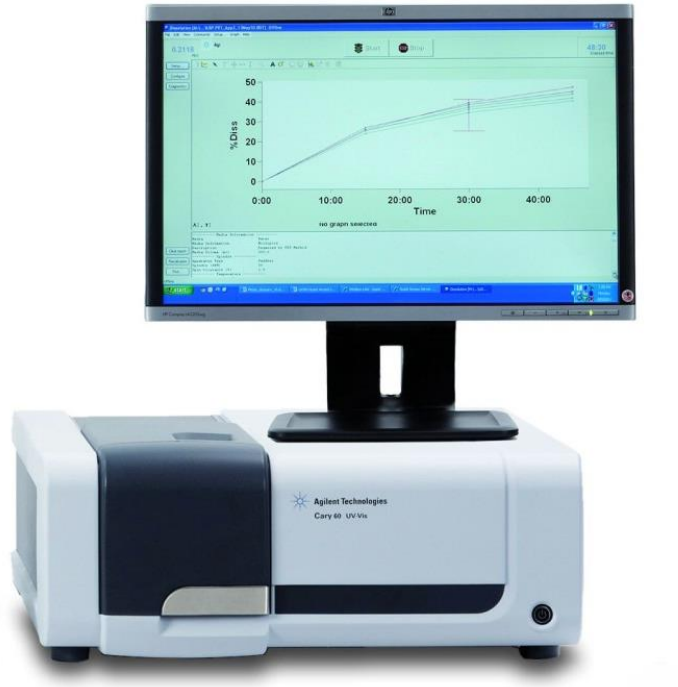


Agilent Cary60 UV-Fiberoptics



Agilent Cary60

- Linear over 3.5 absorbance units
- High intensity Xenon flash lamp
- No warm-up time
- Scanning Spectrophotometer
  - 80 readings a second
  - Scanning speed up to 24,000 nm/min



Agilent Cary60

- Very large dynamic working range, 0.0001 – 3.5 AU
- Lamp only flashes when taking a reading – very long lamp life 8+ years
- Very low baseline noise
- Long-lived FO probes – limited solarization due to UV design

Agilent Cary60

- 12 channel system for dual bath capability
- 30 sec timepoints for single system
- Purpose built for dissolution testing & Cary 60
- Each Fiber is individually connected to the multiplexer
- Highest Optical Transmission on the market

Agilent Fiberoptic Probe Design

- Specially designed for dissolution testing
- 600 micron silica/silica Fibers for optimised transmission down to 190 nm
- 1, 2, 5, 10, 20mm tips available
- Streamlined to minimize hydrodynamic influence
- Non-resident when used with Agilent dissolution units

Agilent Fiber Optic Probe Design

- Different pathlengths can be quickly swapped at low cost.
- Mirrors raised to avoid particle build up.
- Fibers encased in 316 stainless steel making them incredibly robust, and “QC friendly”.
- Simple and easy to clean and exchange.

Developing a Fiberoptic Method

Same Validation Requirements as Traditional UV

- Linearity
- Range
- Limit of Detection
- Limit of Quantitation
- Specificity

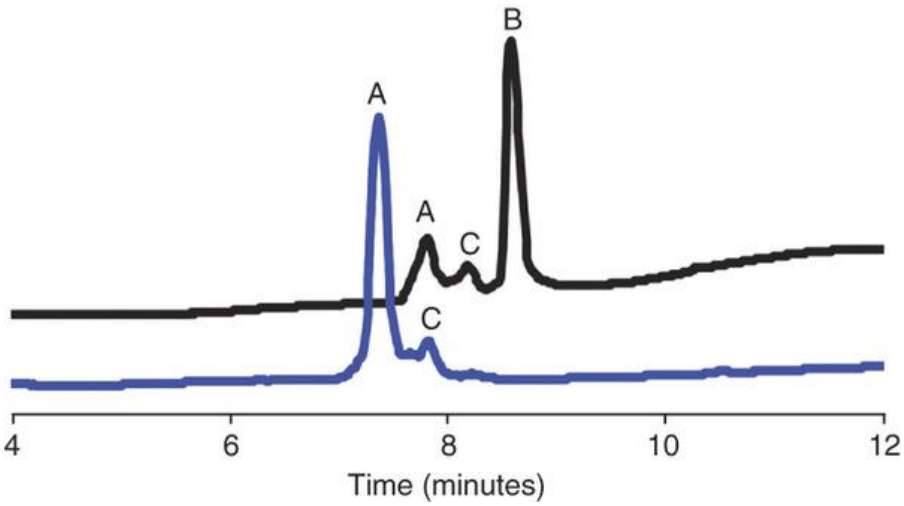
Main Differences Between Fiberoptic and Traditional UV Measurement

- Apparent Dissolution vs. Filtered Dissolution
- Pathlength chosen may differ
- Deaeration Requirements
- Resident Probe Impact (if applicable)
- Standards and Blanks run only before and after run

Specificity

Specificity is the ability to determine the amount of API in the presence of other components that may be expected to be present such as:

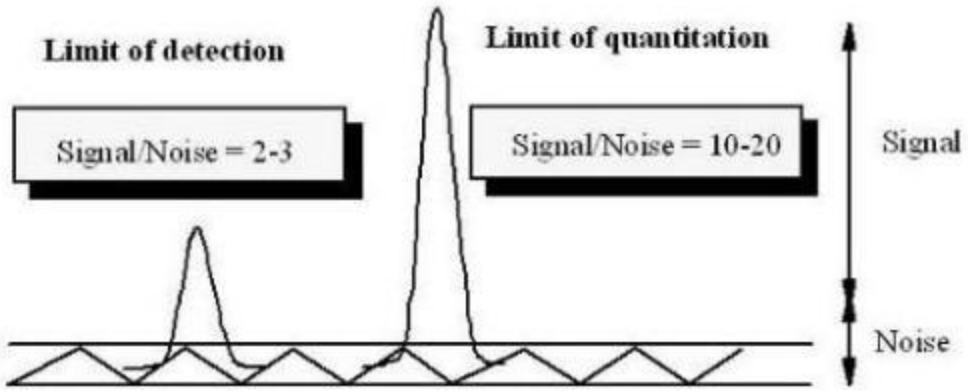
- Impurities
- Degradation products
- Excipients



Detection and Quantitation Limit

Detection Limit (LOD) is the lowest amount of your compound which can be detected, but not necessarily measured. Typically set at 3:1 signal to noise ratio.

Quanititation Limit (LOQ) is the lowest amount of your compound which can be measured with acceptable prevision and accuracy. Typically 10:1 signal to noise ratio.

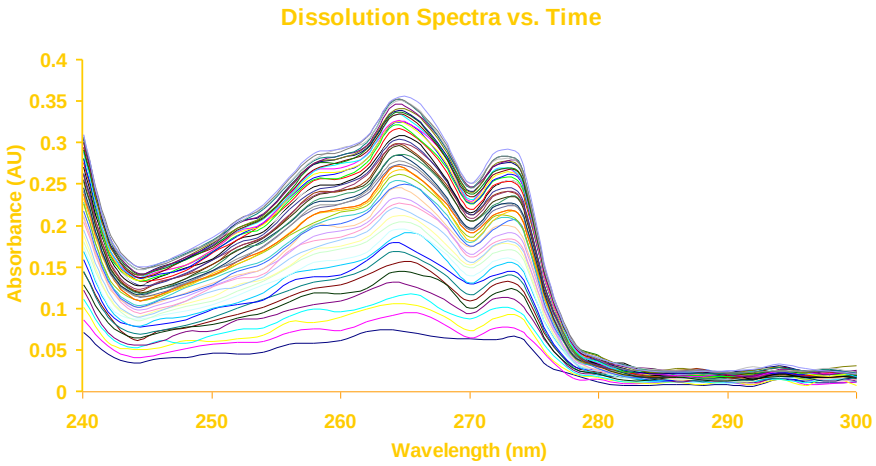


Linearity and Range

Linearity is the ability to elicit test results which are directly (or by a well-defined mathematical transformation) proportional to the concentration of analyte within a given range

Range is the interval between the highest and lowest levels on analyte to be determined with appropriate accuracy, precision, and linearity

Fiberoptic Validation – Apparent Dissolution

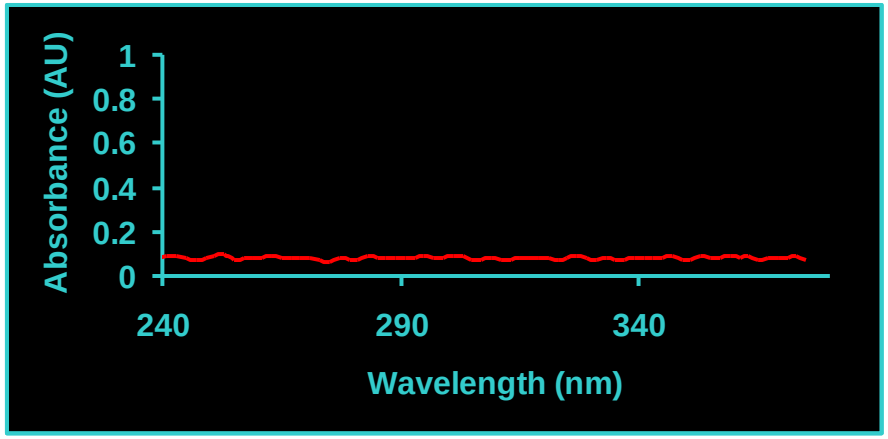


Fiberoptics contains no filters, so your total absorbance is made up of:

- Dissolved Drug Absorbance
- Undissolved Particles
- Excipients
- Media
- Fiberoptic Probes

We can adjust the data to get a corrected reading for the API only through a baseline correction

Baseline Correction

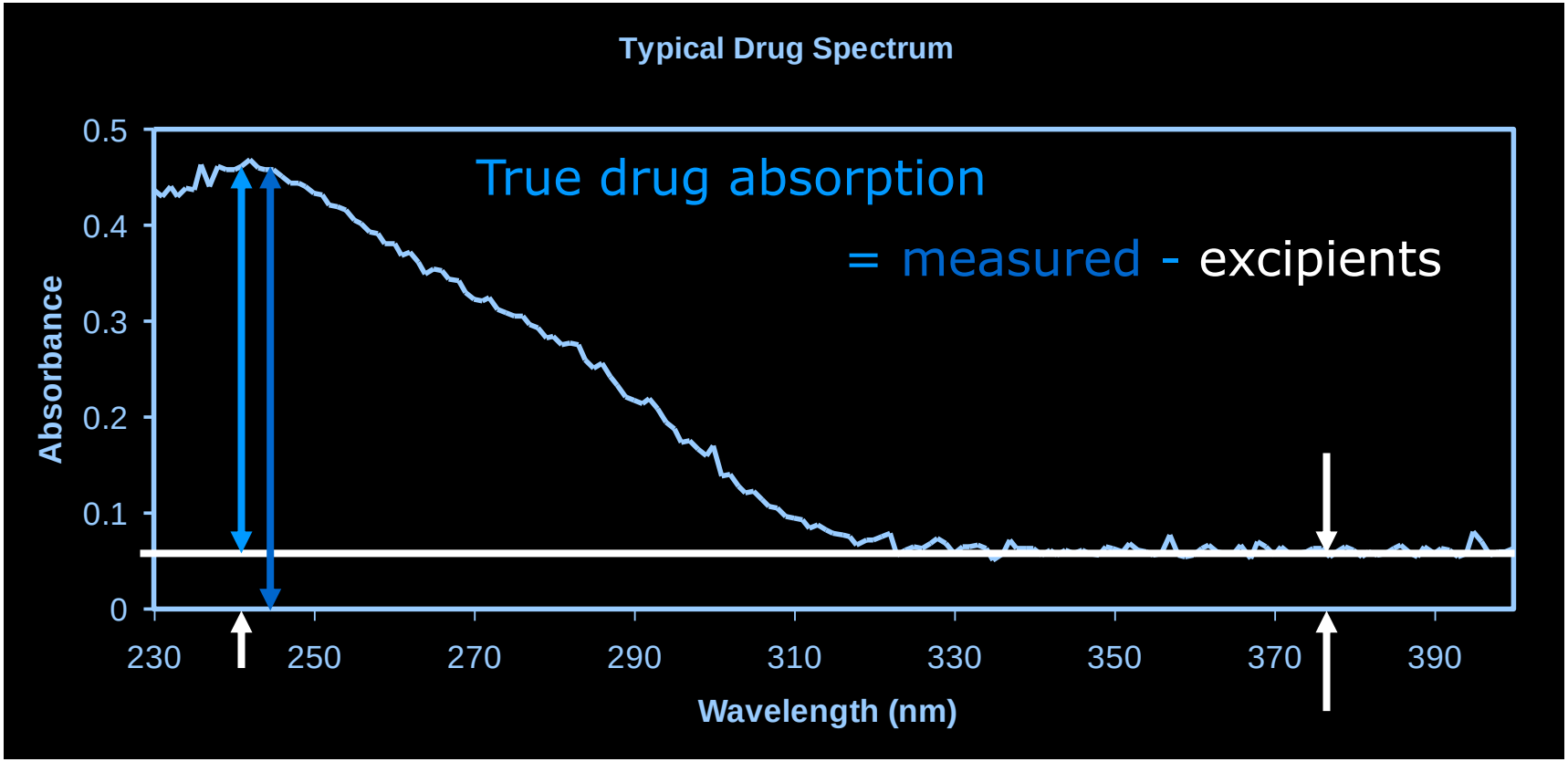


Undissolved particles generally will absorb equally across all wavelengths

A solid particle blocks all wavelengths equally – and does not have a specific chromophore

If a baseline is flat, we can correct based on it

Baseline Correction



Baseline Correction

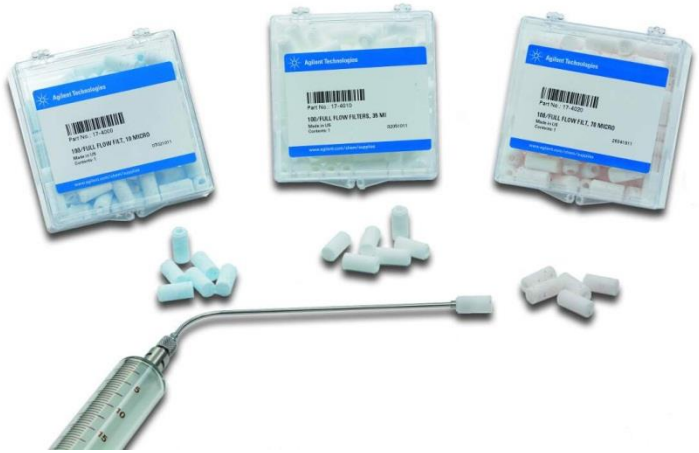
Baseline correction can account for most undissolved particles and other interferences, but does not work in all situations.

- Colloidal particles
- Reflecting/Diffracting Particles
- Total absorbance needs to be in Linear range

Validation should be done to show that filtered samples give them same result as baseline corrected fiberoptic data

Comparison to Filtered Results

Results can be compared between filtered and FO results in a number of ways, concurrent sampling tends to be the most popular.



You can also do:

- Spiked Placebo
- F2 Analysis (intermediate precision)

Pathlength Selection

- 1, 2, 5, 10, and 20mm sizes available
- Choose tip size which will give appropriate linearity 1 – 125%
  - Cary60 typically aim 100% dissolved to be b/w 0.5 – 2 AU
  - Other systems may only work up to 1AU
- The larger the opening, the less susceptable they are to air bubble formation (5mm and above unlikely to form bubbles)

Fiberoptic Validation - Deaeration

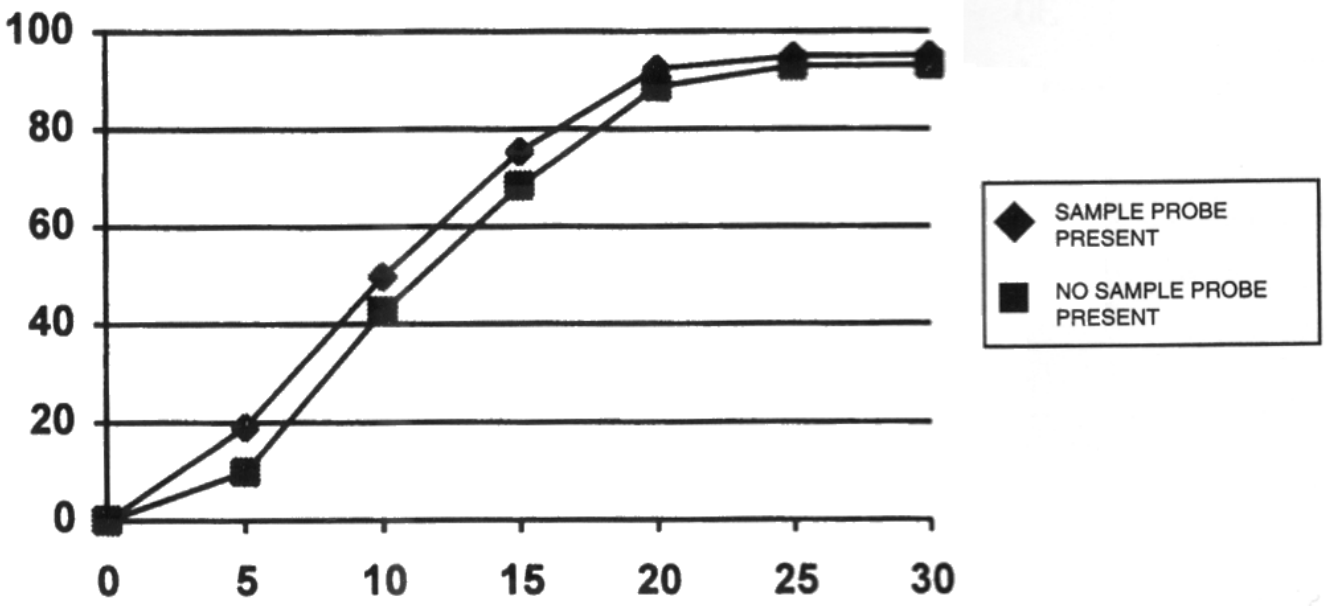
Bubbles cannot be optically corrected for

All Fiberoptics are susceptable to air bubbles to varying degrees

Minimize air bubble impact:

- Deaerate so there is no significant formation
- Choose larger tip size if practical
- Face probes towards or away from shaft – maximize current ACROSS probe to sweep anything which may have settled

The Resident Probe Effect



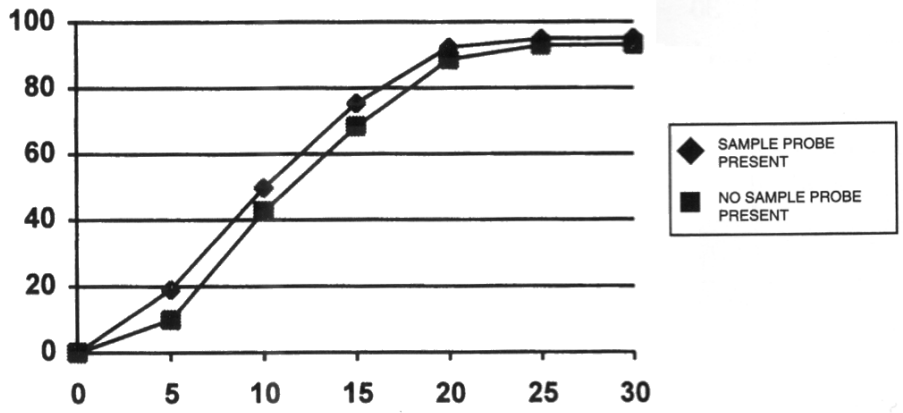
Resident Probes can greatly alter hydrodynamics and alter results vs. manual methods

Higher % Dissolved and more variability

Validation Resident Probe Effect

For each method:

- Perform n=12 dissolution manually
- Perform n=12 dissolution w/ automation
- Compare mean of n=12 data and obtain f2 value
- f2 must be greater than 50, perhaps higher



Standards and Blanks

Standards and Blanks are used to calibrate each probe prior to the run, and can be checked at the end of the run

To run FO with a method you should:

- Demonstrate stability of reading over time
- Ensure SOP allows for “non-bracketed” samples

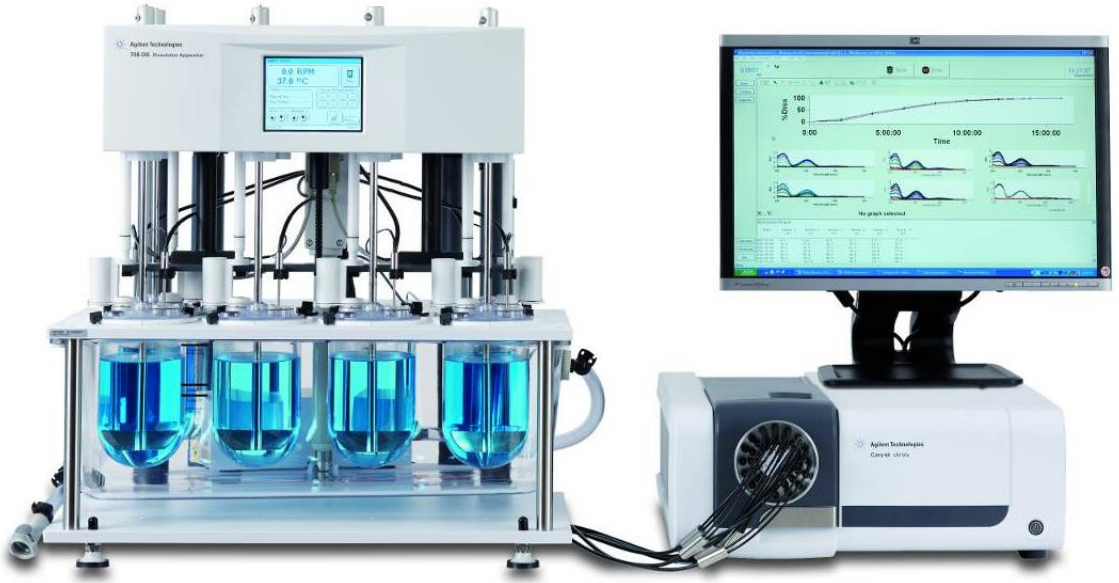
Fiberoptic Cleaning

Easy!

Squirt down with Water, Ethanol, or other solvent

Wipe mirror w/ kimwipe gently

Summary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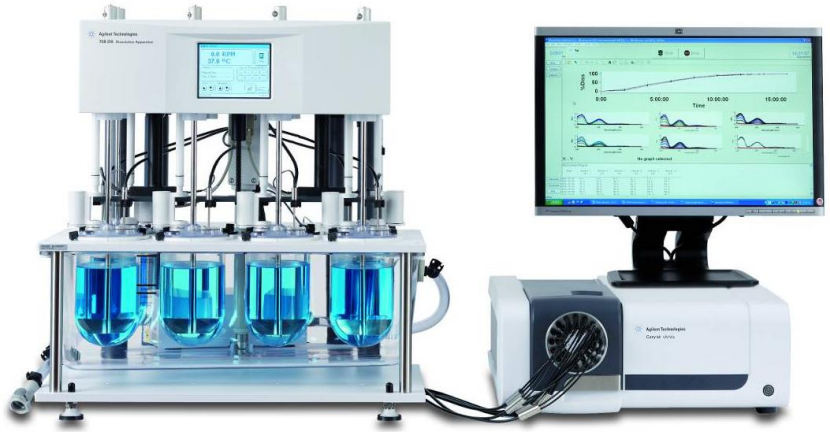
Summary

- Fiberoptics offers many advantages to traditional approaches
  - Timepoint frequency reduced
  - Ability to work w/ unfilterable samples
  - Poor stability samples



Summary

As with other automation and analysis components:

- Needs to be accurate and precise
- Minimize or eliminate bias
- Appropriate selection of pathlength, wavelengths, etc. is chosen for best test performance

Agilent vs. Other FO systems

The Agilent FO solution offers cost advantages vs. other vendors:

- Fewer pathlengths needed
- Lower cost when needing more pathlengths
- Longer life fiberoptic probes
- No lamp replacements
- Solution incorporates standard Cary 60 UV-Vis – not a customized spectrophotometer that could be difficult to service
- Single vendor solution

Thank you for your attention!

Any Questions?

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