AGILENT TECHNOLOGIES
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ARE YOUR DISSOLUTION SAMPLES READY FOR USP <857>?

On May 1st, 2016 the USP General Chapter <851> Spectrophotometry and Light Scattering was discontinued. As a result, several new chapters covering Atomic Absorption, Fluorescence, Mid-Infrared, Nephelometry and UV-Vis Spectroscopy became official. The new General Chapter <857> Ultraviolet-Visible Spectroscopy* has outlined new requirements for control of wavelength and absorbances, stray light, and resolution, which also brings the USP requirements more in line with international pharmacopeial requirements. Being an official USP chapter below the number 1000, laboratories involved in testing for the US market are required to implement these new changes as of the date the new chapters became official.

Besides HPLC methods of analysis, spectroscopy is one of the primary analytical finishes for dissolution samples. It is vital for the GMP laboratory to maintain compliance with current verification of instruments and analytical methods. The primary focus of the new chapter deals with the qualification (OQ and PQ) of the UV-Vis spectrophotometer and demonstration of its suitability for use by conducting specific tests and passing associated acceptance criteria. In some cases, there are slightly different procedures for diode array and non-diode array instruments in terms of precision, yet overall, the general acceptance criteria are the same between the two platforms.

In addition to the specific ongoing qualification tests for the spectrophotometer outlined in the table below, validation and verification of methods intended for use on UV-Vis spectrophotometers are outlined in the new chapter. Proper verification of methods is essential to ensure that the measurements obtained and used in quantitative determinations are suitable in terms of accuracy, precision, specificity, linearity, range, detection, and quantitation limits, as well as robustness. Properly qualified or calibrated instruments, combined with properly validated analytical methods, properly trained analysts, and proper performance of system suitability activities at time of use, generally assures the integrity and quality of test results.

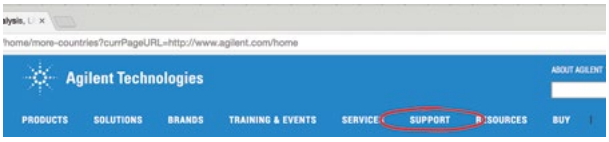
UV-Vis Spectrophotometric Qualification Requirements:

Test	Changes	Tolerances/Limits
Control of Wavelengths: Accuracy – Rare Earth Oxide Solutions	1. Additional test for long wavelengths if part of operational range: Didymium Five wavelengths: 731.6, 740, 794.1, 799, 864.4 nm 2. Mean absorption peak compared to hardcoded value, must be within tolerance	Accuracy: ±1 nm (200–400 nm) ±2 nm (400–900 nm)
Control of Wavelengths: Reproducibility – "Precision"	1. Perform this test for all wavelength accuracy tests performed 2. SD of the mean compared to tolerance	
Control of Absorbance: Accuracy – 935a	1. Determine difference between measured absorbance and CRM value, must be within tolerance 2. 10 replicates performed	Accuracy: ±0.01 Abs (<1 Abs) ±1% Abs (>1 Abs)
Control of Absorbance: Reproducibility "Precision" – 935a	1. Data taken from accuracy test 2. SD must not exceed tolerance	Precision: ±0.005 Abs (<1 Abs) ±0.5% Abs (>1 Abs)
Control of Absorbance: Accuracy – Neutral Density Filters	1. Up to three filters can now be used 2. Determine difference between measured absorbance and CRM value, must be within tolerance 3. 10 replicates to be performed (not specifically requested, but data required for precision)	Accuracy: ±0.008 Abs (<1 Abs) ±0.8% Abs (>1 Abs)
Control of Absorbance: Reproducibility "Precision" – Neutral Density Filters	1. 10 replicates to be performed 2. SD must not exceed tolerance	Precision: ±0.005 Abs (<1 Abs) ±0.5% Abs (>1 Abs)
Stray Light – Acetone	1. Same parameters and tolerances as per NaI test (this is the alternative method described) 2. Measure %T at 320 nm and must be less than tolerance	<1% T

For additional information, Agilent has produced a white paper on the subject entitled: **Spectroscopy Solution for Pharmaceuticals: Confidence in Compliance to USP <857> Using the Agilent Cary 60 UV-Vis Spectrophotometer**. Please visit Agilent Technologies website at www.agilent.com and search for publication 5991-7269EN

How does this impact your dissolution tests?

Agilent Service can perform the qualification of your UV instruments in order to meet the new requirements. Simply go to www.agilent.com and click on Services for Analytical Instruments and select Compliance. Choose your country and submit a service request.



Agilent offers a choice of UV systems suitable for use in dissolution methods. Both the Cary 60 and Cary 8454 are designed for use in GMP environments. The software enables 21 CFR Part 11 compliance. The dissolution modules make calculations simple, and reports are easily customized.

Agilent UV-Dissolution Offerings

- Stand-alone UV
- On line real-time analysis
- On line real-time analysis with archival capability
- Automated systems with 1, 2, 3, or 4 dissolution apparatus
- In situ fiber optic measurement

*United States Pharmacopeial Convention; <857> Ultraviolet-Visible Spectroscopy, Twinbrook Parkway, Rockville, MD, USA, USP 39 NF 34 2016

Cary 8454 UV-Vis

Cary 60 UV-Vis

Contact your Agilent representative for more information or go to the following link to learn more about our online solutions. http://www.nxtbook.com/nxtbooks/agilent/dissolution_sourcebook/#/26

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MEETING SUMMARY FOR THE JOINT ASTM E55/FDA WORKSHOP

Based on current and future standards activities, the ASTM E55 Technical Committees develop voluntary consensus standards focused on the manufacture of pharmaceutical and biopharmaceutical products. The committee comprises three major sub-committees: E55.01 (Process Analytical Technology – PAT), E55.03 (Pharmaceutical Standards) and the most recent committee, E55.04 (Biopharmaceutical Standards).

The relationship that ASTM has with the development of pharmaceutical standards begins with dissolution. One of the first standards that the E55.03 Technical Committee officially released was E2503-07 "Standard Practice for Qualification of Basket and Paddle Dissolution Apparatus" in 2007. Since that time the committee has developed and officially released 22 standards primarily focused on pharmaceutical manufacturing. This particular standard has gained widespread attention as pharmaceutical laboratories around the globe have been implementing Enhanced Mechanical Qualification of dissolution apparatus as an alternative to the USP Performance Verification Test.

Other than citing the E2503-07 (now listed as E2503-13) standard in "FDA Guidance for Industry on the Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 CGMP" in 2010, no E55 standards have been cited in regulations and adoption of standards has been relatively slow. Although USP standards have been relied upon by industry for many years, the White House Office of Management and Budget issued OMB Circular A119 instructing US federal agencies to consider using more private sector voluntary consensus standards whenever possible. The FDA announced during the workshop that although they don't plan to endorse consensus standards, they will consider opening up the process by recognizing such standards. FDA recognition of the ASTM standards will most likely increase adoption of the standards, especially for Pharmaceutical and Biopharmaceutical manufacture which require rapid development and adoption of standards to keep pace with current and future technology.

Joint ASTM E55/ FDA Workshop took place on October 11, 2016

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MEETING SUMMARY – DDG LUNCHEON AT AAPS ANNUAL MEETING AND EXHIBITION

The Dissolution Discussion Group (DDG) held its fourth 1-hour Face-to-Face meeting during the AAPS Annual Meeting in Denver, Colorado on November 15th, 2016. The main difference between the meeting last year and previous meetings was moving the time slot to the lunch hour, which greatly improved attendance over our breakfast meetings held at 7 a.m. The result: standing room only, with around 75 participants who offered great reviews of the event.

As in previous years, the format was multiple soapbox-style presentations from multiple dissolution experts from across the globe. The meeting was moderated by Bryan Crist of Agilent Technologies; each panelist presented a 5-minute topic or update from current activities within the international dissolution community of scientists. The actual presentations, along with updates for our quarterly DDG online meetings, are available at www.dissolution.com.

The content and presenter for each of the sessions is listed below:

- Opening remarks, activities and DDG Online Meetings – Bryan Crist, Agilent Technologies
- Update on Activities of the USP Dosage Forms Expert Committee – Dr. James DeMuth, Univ. of Wisconsin, USA
- Update on USP Dissolution-Related General Chapters – Vivian Gray, Dissolution Technologies and V.A. Gray Consulting
- Update on AAPS In Vitro Release-Dissolution Testing (IVRDT) Focus Group Committee Activities – Dr. Nikoletta Fotaki, University of Bath, UK
- Disintegration and Dissolution – Dr. Raimer Lobenberg, University of Alberta, Canada
- Dissolution Technologies Update – Vivian Gray
- Preview of new publication: "Poorly Soluble Drugs: Dissolution and Drug Release" – Dr. Gregory Webster, Abbvie
- International Pharmaceutical Federation (FIP) Update – Dr. Johannes Kraemer, PHAST, Homburg, Germany
- USP Update on Dissolution Vibration Collaborative Studies – Dr. Erika Stippler, U.S. Pharmacopeia

We hope to see you at the **2017 Annual AAPS Meeting** in San Diego, California, USA — but don't wait until then — please visit the DDG online for continuous activity on the Bulletin Board for dissolution related discussion. The quarterly DDG Online meeting dates are also provided, as well as recordings of each of our past 24 meetings!

DDG DISSOLUTION DISCUSSION GROUP

QUESTIONS YOU ASKED

Filter adsorption problems

Question: We are having some difficulties with filter retention using pH 1.2 N HCL as the dissolution media. It seems the retention may be coming from both the filter and the tubing. Do you have any suggestion for how best to address the retention issue?

Answer: You may condition a filter sufficiently if your automated sampler is programmed to prime sufficient sample through the filter, sampling lines, and the autosampler. The media returns directly to the vessel through the return cannula.

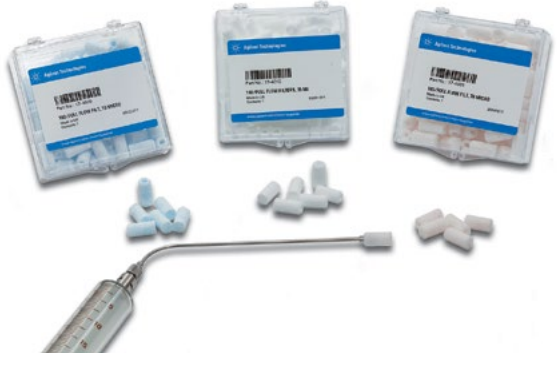
The priming step does two things to avoid suppression of sample results:

i. It conditions the filter at the first timepoint by flushing sufficient volume of sample through the filter so it no longer binds drug substance; and then...

ii. For subsequent timepoints, the priming step flushes away remaining sample from the previous timepoint from the filter, sampling lines, and valves, helping ensure the integrity of the sample by avoiding carry-under.

The autosampler may additionally be programmed to provide a drop volume, which flushes a small volume of sample through the needles to ensure there is no carry-under from the previous sample.

If this does not sufficiently improve the problem, the next thing to try is to switch to PVDF Full Flow Filters. This solves many problems with binding active drug and may alone be the solution to your issues.



PVDF Full Flow Filters

Sinker Basket for Pellets in Apparatus 2 Paddle

Question: Could you please recommend which is the best sinker for pellets and paddles? We are currently using 40-mesh for the same product in an Apparatus 3.

Answer: Yes, if you wish to develop a separate method with Apparatus 2 paddle, a 40-mesh sinker basket would probably be best. This is not a USP sinker but it should work to contain the beads. A further problem with beads and pellets is that they tend to pile up on each other, which restricts the movement of media around them and could produce lower rates. This is why USP 3 does a good job keeping fresh media around each. Alternatively, the Peak Vessel may also be useful for this issue.

Sinker basket, with cover, 40-mesh, 381 µm

Agilent Sites and Services for Your Dissolution Workflow

Agilent Dissolution Systems Digital Source Book
www.nxtbook.com/nxtbooks/agilent/dissolution_sourcebook/index.php

Dissolution Exchange
www.dissolution.chem.agilent.com

Dissolution 1-on-1 Training
www.dissolution.chem.agilent.com/learndissolution-1-on-1

Dissolution Hotline (Email Address)
dissolution.hotline@agilent.com

Dissolution Discussion Group (DDG)
www.dissolution.com

Learn more

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