Agilent Practical Solutions Newsletter

Agilent
Trusted Answers

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Product News: 280-DS MQS Software Updated to Meet Latest MQ Regulations

Dan Spisak, Product Manager, Dissolution Systems

Updated software is now available for the Agilent 280-DS Mechanical Qualification System (MQS), which continues to be the leading choice for qualification of USP Apparatus 1 and 2 instrumentation in the pharmaceutical industry. Using only two modules and user-friendly software designed for compliance, the 280-DS provides a way for dissolution laboratories to qualify and monitor instrument performance with superior efficiency.

Agilent 280-DS MQS

In keeping with the latest industry requirements as well as current operating system and database management platforms, this latest update (version A.01.05) provides the following improvements:

- Validated for use with Windows 10 operating systems (Windows 7 remains supported)
- Updated version of Microsoft SQL (2014 Express)
- Increased list of preloaded qualification methods
- Added graphs of wobble, RPM, and measurements for upper and lower limit detection
- Expanded custom vessel orientation options for dissolution apparatus
- Modified measurements of certain parameters based on Chinese Pharmacopeia mechanical qualification requirements

Whether your laboratory adheres to the USP performance verification test (PVT) or an alternative mechanical calibration/qualification procedure, the 280-DS MQS can help you ensure that your dissolution apparatus—from Agilent or another supplier—is running properly.

Register with the Dissolution Discussion Group (DDG) at www.dissolution.com to stay up to date with the latest dissolution qualification requirements. Current 280-DS MQS users should contact their Agilent representative for software upgrade details.

Check Your Mobile

Allan Little, Director of Marketing, Dissolution Systems

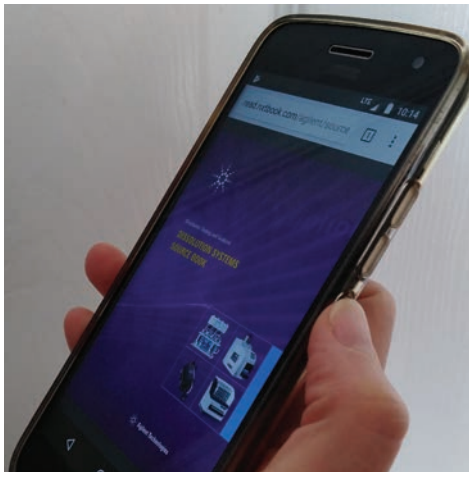
For several years, we have provided a Dissolution Systems Source Book. What makes this version unique is that it incorporates the detailed catalog information from our printed catalog along with embedded videos, as well as hyperlinks to posters, videos, brochures, and white papers.

This easy-to-navigate version is now available in a new, mobile-friendly format. The table of contents outlines the information in convenient thumbnails to help you find exactly what you are looking for. Simply swipe or scroll to view the information.

Whether you are looking for accessories, instruments, qualification tools, or application information, it is all here. In addition, there are numerous links to other dissolution sites like the Dissolution Exchange and the Dissolution Discussion Group (DDG).

2017-2018 Dissolution Systems Digital Source Book

For a short video of a specific feature or for an instructional video, you can click one of the camera icons in the Digital Source Book.



Dissolution Systems Source Book is optimized for mobile devices

You can access this new version on your PC, phone, or tablet at the following link: www.agilent/source_book/dissolution_systems_2017_2018/index.html

Qualification of Noncompendial Dissolution Apparatus

Bryan Crist, Scientific Affairs Manager, Dissolution Systems

USP <1058> Analytical Instrument Qualification

Noncompendial peak vessel

The informational chapter in USP <1058> suggests that users of analytical equipment validate their procedures, calibrate their instruments, and perform additional instrument checks. These may include system suitability tests or evaluation of control samples. The requirements to fulfill cGMP for ensuring that an instrument is suitable for its intended purpose include an installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). The focus of this topic relates to the ongoing PQ of modified dissolution apparatus.[1]

While compendial dissolution apparatus have PQ methods outlined in USP <711> dissolution, and enhanced mechanical qualification (eMQ) procedures outlined in FDA and ASTM methodology, noncompendial dissolution apparatus must be similarly qualified. However, direct procedures to do so may not exist for the many modifications of the apparatus. Noncompendial dissolution apparatus may include: small volume vessels and agitating shafts; suspended basket methods; immersion cells for testing ointments and creams; and dialysis chambers for testing micro- and nanoparticles, to name a few.

After successful completion of the IQ and OQ, the PQ documents the activities that demonstrate the instrument consistently performs according to the requirements and specifications of the end user. In addition to the periodic performance checks included in the PQ, the instrument must have specific preventive maintenance (PM) at routine intervals to keep the apparatus in top operating condition.

Brief overview of *in vitro* dissolution apparatus

The dissolution test has evolved to become a definitive tool used to characterize the performance characteristics of solid oral dosage forms.

The dissolution test is remarkably sensitive to the slightest perturbations. As a result, it is critical to isolate the effects of the dissolution tester and the environment from the release characteristics of the dosage form.

Traditionally, "calibrators" have been used to determine the acceptance of an apparatus. With modifications to apparatus, however, a prescribed calibration regimen may not be available.

In vitro dissolution data will be of great importance when assessing changes in production site, manufacturing process, or formulation, and will help with decisions concerning the need for bioavailability studies. The proper qualification of the apparatus is critical to accurate and precise evaluation of dosage form performance.

The dissolution apparatus allows the testing of six dosage forms. Each position has:

- An inert hemispheric **vessel**
- A dissolution **solvent** (medium)
- A **rotating spindle** that provides the hydrodynamic flow of the solvent across the surface of the dosage form

The dissolution apparatus must maintain these three components in terms of alignment, stability, and isolation from the environment.

200 mL vessel and mini paddle

Qualifying noncompendial apparatus without an established compendial PQ

Several methods have been historically used for qualification of noncompendial dissolution apparatus. These include switching components of an otherwise "calibrated" dissolution apparatus or substituting a mechanical approach such as the eMQ of the dissolution apparatus. Either approach should be sufficient for cGMP if appropriate procedural documentation exists along with acceptance criteria.

Switching components on a calibrated dissolution apparatus from 1000 to 200 mL vessels and mini paddles may be performed by removing the dedicated vessels and replacing them with the noncompendial equipment. A gap analysis should indicate which physical parameters should be measured on the components that have been replaced. These would include height, wobble, and centering at minimum. However, it is important that a procedure contains the specifications of the small volume vessel and mini paddle, since a compendial chapter that contains the dimensions may not exist. It is also important to establish and verify the acceptance criteria for the measurements on the small volume equipment. Although height, wobble, and centering could remain at dimensions for the compendial vessel and paddle, the tolerance may be more critical at small volume. Consideration should be given to reducing the tolerance to ±1 mm from the height instead of ±2 mm, for example.

The second technique that may be used stems from the adoption of eMQ procedures currently in use. These eMQ procedures are more modular in nature, utilizing measuring devices and tools, rather than the holistic approach to qualification with the USP Performance Verification Test (PVT), which utilizes actual tablets with known performance criteria. Unfortunately, the performance criteria in alternative vessels and agitating elements has not been determined, so reliance on mechanical qualification makes good sense.

Standard paddle (bottom) with noncompendial mini paddle

Proposed eMQ procedure for 200 mL dissolution apparatus

Similar to requirements for eMQ, the absence of PVT should require additional steps to ensure the apparatus is suitable for its intended use.

Mechanical qualification:

- Certification of components
- Documentation of preventive maintenance
- Mechanical qualification parameters
- Operational checks

Certification of components: Individual measurements for each dimension of each component should be documented. Certificates of conformance (CoC) with actual measurements may be obtainable from dissolution apparatus manufacturers. Otherwise, measurements should be documented by the end user.

Preventive maintenance: An apparatus used for 1000 mL will have a periodic evaluation and receive care to keep it in top mechanical condition, maintaining a qualified state. For changing components, procedures may need to be added to ensure that adjustments of alternative configurations are correct and maintained from test to test.

Mechanical qualification parameters: All critical parameters that may be affected by changing equipment should be re-evaluated and documented with measuring devices and tools that are capable of accurately and precisely producing reliable measurements. All measuring devices and tools must be maintained in a calibration program and used within their period of calibration.

Operational checks: Similar to the eMQ procedures, analysts must be trained to know when a component or vessel is defective and needs replacement. Observational checks must be performed at the beginning of each test to evaluate the condition of components and verify that they are clean, properly aligned, and not damaged in any way. The beauty of this system is that when a defective component is found: (1) it is to be removed from service; (2) it is replaced with another component that has had each critical physical parameter measured and verified; (3) the mechanical parameters critical to the performance of that component are measured and found to be within tolerance; and (4) full documentation of the replacement and all measurements for verification must be performed and maintained.

Summary:

Whether you have a compendial or noncompendial instrument or apparatus, you still need the same documentation. While many specifications and tolerances may be available in compendial procedures, noncompendial apparatus will need extra documentation to ensure that proper specifications, tolerances, and procedures are developed that mirror the compendial ones. This documentation should address:

- Environmental assessment to ensure there is no vibration
- Proper installation and installation verification (IQ)
- Functionality verification after installation or major repair (OQ)
- Component dimensional verification or CoC (OQ)
- Fixed parameter verification (OQ & PQ)
- Secure data storage, backup, and archive (OQ)
- Periodic performance checks (PQ)

Established practices should also be developed to address operation, calibration, maintenance, and change control. These may involve SOPs and systems to manage calibration and maintenance, including the frequency at which these are performed.

Reference:

[1]USP General Chapter <1058> Drug Release, USP 41, 2018, United States Pharmacopeial Convention, 12601 Twinbrook Parkway, Rockville, MD

Questions You Asked

Q. I frequently find variability in using the immersion cell listed in USP <1724> to test ointments and creams. Sometimes results appear high, which may be due to a ruptured membrane, and sometimes they are low.

A. I agree that the membrane is suspect and needs to be evaluated post-test to check for a tear or wrinkle that could have caused the variability. Initially, the cell must be completely clean and no traces of drug should be present on your hands or benchtop as you are prepping the product into the immersion cell. Any product on the exterior of the cell will adversely affect the apparent release of the product under test. Here are a few common steps in prepping the immersion cell.

Preparation tips for the immersion cell to help eliminate variability:

1. First, waste at least a couple of mL of the cream from the tube. Then, squeeze the ointment, cream, or gel into the diffusion cell reservoir by swirling it in as you rotate the cell. Tap to ensure that you have eliminated air bubbles, depending on the viscosity of the product.

2. Pre-soak the membranes in the media for at least 10 minutes.

3. With a straight edge spatula, level the product by pushing down and away as the spatula moves across the surface.

4. Roll the pre-soaked membrane onto the surface, taking care not to entrap any air bubbles.

5. Position the PTFE spacer that defines the surface area and holds the membrane in place.

6. Place the retaining ring and gently tighten about a ¼ turn after feeling slight resistance.

7. The adjusting plate in the immersion cells should also be adjusted with a screwdriver-type tool that ensures the drug is pressed up against the membrane. Simultaneously, an alignment tool should center the spacer and prevent the membrane from rupturing or deforming during this process. Do not overtighten; this requires only about a ¼ to ½ turn. The immersion cell is now ready for testing.

A video of the preparation may be found on the Agilent website: www.agilent.com/en/products/dissolution/accessories/enhancer-cell-(immersion-cell)/enhancercelltechnique

Q. I am using a method from the FDA Dissolution Methods database and the API does not appear stable in the dissolution medium. I am seeing several degradants from HPLC analysis. Why would this occur?

A. In developing any method, it is important to understand the degradation pathway for the API from sources like light, oxidation, heat, etc. For instance, if your product is light sensitive, then it is possible that you will require low actinic vessels, evaporation covers, and HPLC vials, or need to provide a location that is conducive to testing light-sensitive products.

Unfortunately, the Dissolution Methods database as well as USP monographs are not truly "methods" because they only provide run conditions: apparatus, speed, media, time points, and acceptance criteria; few other details are usually offered. Critical details of the test such as the influence of dissolved gases, sample introduction technique if required, alternative sinkers, filter type, conditioning volume, light protection, and many others need to be "developed" and documented to truly provide a viable method that is proven through proper method validation. USP <1092> provides some good direction here.

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