AGILENT TECHNOLOGIES
PRACTICAL SOLUTIONS NEWSLETTER

The Measure of Confidence

VOLUME 16
ISSUE 1

BRYAN CRIST, SCIENTIFIC AFFAIRS MANAGER, AGILENT TECHNOLOGIES INC.

TRENDING DISSOLUTION MECHANICAL PERFORMANCE

What if you could service a dissolution apparatus before it fails enhanced Mechanical Qualification (eMQ)? The Agilent 280-DS Mechanical Qualification System (MQS) measures critical physical parameters with unmatched, unprecedented precision.

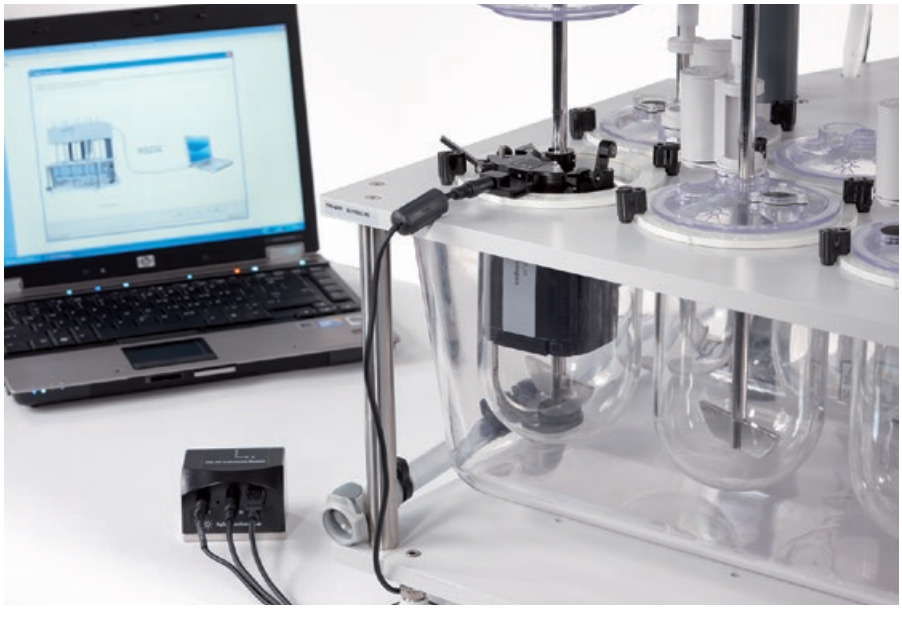


Figure 1. Agilent 280-DS Mechanical Qualification System.

Agilent Technologies

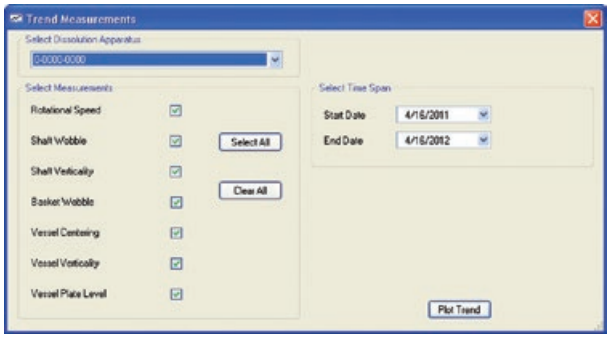


Figure 2. Trend Analysis.

Consider a routine dissolution apparatus qualification that unfortunately resulted in an out-of-tolerance measurement, which was confirmed to be due to a mechanical issue that affected apparatus alignment. According to GMP stated in 21 CFR Part 211.160(b)(4) "...Instruments, apparatus, gauges and recording devices not meeting established specifications shall not be used." This presents several problems, beginning with downtime for the apparatus that requires service or mechanical adjustment, which would be followed by a full eMQ to measure and document that the apparatus again conforms to specification. In due diligence, a comprehensive review of dissolution test results from all drug products tested and released with the apparatus should be conducted since the last time that the apparatus was found in conformance. These retrospective reviews and possible retests often result in significant costs and time and are damaging to laboratory productivity.

The 280-DS Mechanical Qualification System has been developed exclusively to measure and report all physical parameters required by the FDA and ASTM standards for enhanced mechanical qualification of USP Apparatus 1 and 2. The instrument has two devices – Vessel Module (VM) and Instrument Module (IM) – which are capable of taking each of the physical parameter measurements at each location within the dissolution apparatus in less than 25 minutes. The high-precision construction of the device allows it to take reproducible and accurate measurements at the exact positions required by the MQ standards. The reporting of results documents that the apparatus is within the rigorous tolerances defined in the eMQ standards.

Yet for all of its features, the added benefit is realized through the ability of the 280-DS to store the data for comparison with previous data for trend analysis on any dissolution apparatus in your laboratory. Imagine if you could remove an apparatus from service before it actually fails – for instance, if a centering measurement in the lower portion of the vessel increases slowly over time from 0.1 mm to 0.9 mm. Wouldn't it be great to have the ability to take the apparatus offline for service prior to reaching a failing calibration result? This not only meets but exceeds regulatory expectations to maintain apparatus between calibration intervals and its value will be realized in laboratory operating cost and time.

Agilent provides the solution for maintaining your dissolution apparatus in top condition and alignment as required by GMP to ensure high-quality pharmaceutical products. For additional information on the 280-DS and trending dissolution eMQ results, please contact an Agilent sales representative.

DAN SPISAK, PRODUCT MANAGER, DISSOLUTION

UPCOMING AUDIT? GET PREPARED WITH DISSOLUTION WORKSTATION SOFTWARE

If your business is manufacturing pharmaceuticals or medical devices, or importing any product in the United States that falls under current Good Manufacturing Processes (cGMP) regulations, you better be ready – the FDA is coming. Your facility will be inspected by the U.S. Food and Drug Administration (FDA) at regular intervals to ensure proper standards and processes are in place to guarantee safe, high-quality products are being produced and distributed as intended.

A simple way to ease this burden on your dissolution laboratories is to implement Agilent Dissolution Workstation software. This paperless, compliant solution organizes all your dissolution methods and test data while controlling access and preventing unwarranted changes or errors. There's no easier way to satisfy the necessary requirements for data storage and traceable records than this easy-to-implement software solution.

Figure 3. Dissolution Workstation Software.

Better organization

Store each of your dissolution methods as well as your instrument and accessory information in a single, secure database. This database can be maintained locally on a workstation PC in the laboratory, or located on a network server. Each workstation can support up to four individual systems running independent dissolution tests.

The software contains a filtering mechanism that may be used to recall test data from a particular date range, instrument, or the unique report ID number. This makes it simple to find specific data, which is especially useful in an audit situation. No more sifting through hardcopies or random scans of PDFs – let the built-in capabilities of Dissolution Workstation work for you.

Time for compliance

Dissolution Workstation software is designed to facilitate operation in a 21 CFR Part 11 environment. This includes features like:

- Access to electronic records
- Ability to make changes to methods and system information
- Complete test reports including instrument activity logs
- Unique filenames and data integrity verification
- Secure data archival
- Audit trails detailing software modifications and application access
- Ability to prevent modifications to output data
- Electronic signatures and approvals
- System-locking capabilities
- Unique user IDs with specific access levels and privileges

These built-in features limit unwarranted changes or access to files or tests by using exclusive user groups based on integrated Microsoft Windows security. All system activity is traceable, with system and security audit trails that can be recalled, displayed, and printed using the standard reporting structure.

What logbooks?

The trend toward a paperless environment continues to grow and Dissolution Workstation software can get you there in a hurry. By eliminating the redundant task of manual documentation for each dissolution test, the software provides immediate time savings and unmatched traceability.

Once you have your system and method information entered and stored in the database, it's simply a matter of recalling these files each time you run a test. Beginning a test is as easy as two steps – simply choose the instrumentation and then the desired method and you're off and running. Test-specific data, such as lot or batch information, can be entered prior to test initiation and is documented on the final report. You'll wonder why your instrument logbooks weren't replaced sooner.

Data security brings peace of mind

Taking the steps to automate data collection and archival may seem like an arduous task. When the alternative is considered, however, prolonging the switch to a fully electronic environment is becoming riskier by the day. As regulatory agencies push industry in this direction, it's up to you to be prepared with a solution that meets your needs today and in the years to come.

Don't wait for a 483 or Warning Letter to begin the process of migration and compliance. Dissolution Workstation software meets the industry standards for data security, audit trails, electronic records, and signatures – and Agilent can help put you on the path to making your laboratory inspection ready.

Request a personal demonstration by contacting your Agilent representative or dissolution.hotline@agilent.com.

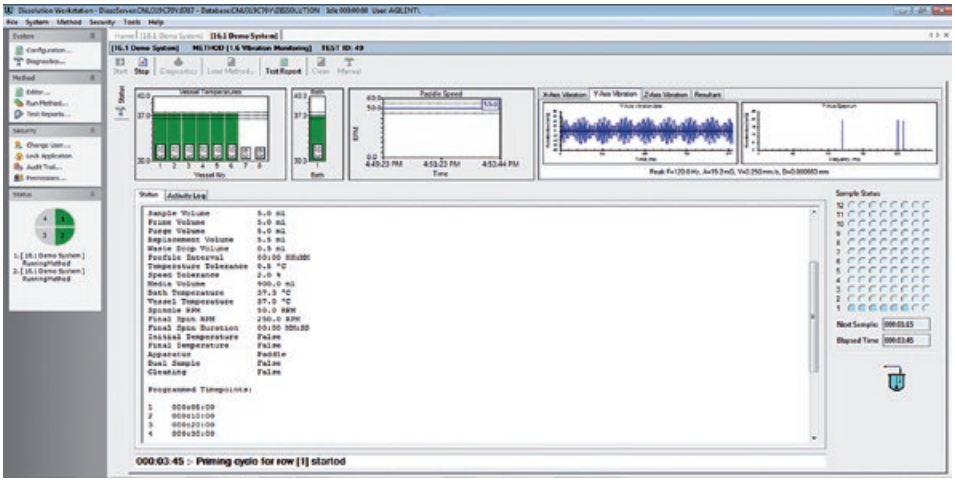


Figure 4. The Agilent Dissolution Workstation software sends real-time notifications to keep you informed of system status, wherever you may be.

EWA HARTWELL, PRODUCT MANAGER, CAMBTEK LIMITED

VERSATILE SAMPLE PREPARATION FROM THE CAMBTEK RAPID EXTRACTION SYSTEM

The CambTEK Rapid Extraction System (RES) prepares analytical samples of pharmaceutical dosage forms ahead of testing. It dissolves, extracts, filters, and dilutes the solid, semi-solid, or liquid product before dispensing an aliquot into a sealed sample vial.

The system automatically returns to a clean and dry state ready for the next sample, allowing continuous unattended operation.

Modern pharmaceutical formulations can incorporate complex matrices, often presenting significant sample preparation challenges. Poor solubility of the matrix often results in lengthy assays, regardless of the solubility of the active pharmaceutical ingredient (API). Lengthy preparation time may reduce product integrity, which can lead to further testing burden.

To speed up the sample preparation of dosage forms, manual cutting, crushing, or grinding is traditionally employed, which can easily result in sample loss. In contrast, using CampTEK's proprietary sample preparation technology, the dosage form to be prepared by the RES is in a closed system, allowing a representative sample to be produced for testing with no loss of sample. Additionally, the system is fully auditable, giving both a controlled and transparent workflow.

Figure 6 shows four challenging sample types being processed: a hard capsule, a high-content HPMC tablet, a crystalline-coated lozenge, and a formulation containing PEO.

The RES greatly reduces the sample preparation process time of these challenging matrices, whilst producing extensive data for each extraction.

To arrange an interactive video demo of CambTEK's proprietary technology, including live sample preparation, please email videolab@cambtek.com.

Figure 5. CambTEK Rapid Extraction System.

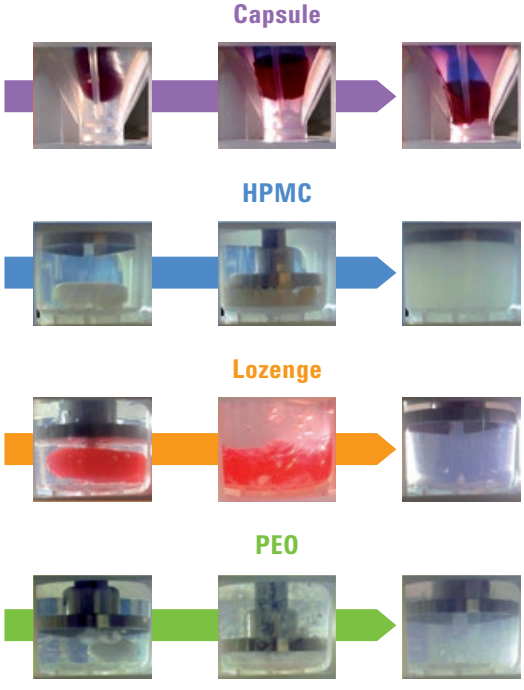
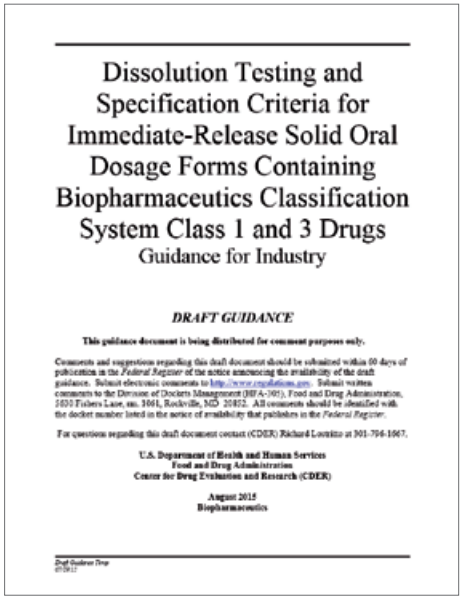


Figure 6. CambTEK Rapid Extraction System.

BRYAN CRIST, SCIENTIFIC AFFAIRS MANAGER, AGILENT TECHNOLOGIES INC.

RECENT FDA DRAFT GUIDANCE FOR IMMEDIATE-RELEASE BCS CLASS 1 AND 3 DRUGS

In August of 2015 the US FDA introduced Draft Guidance on Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs.[1] This guidance was intended to describe an alternative approach to dissolution method development, testing, and specification, setting criteria for highly soluble immediate-release products.



Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Richard Lostritto at 301-796-1967.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2015
Biopharmaceutics

Figure 7. FDA Draft Guidance for Industry: Dissolution Testing and Specification Criteria.

The draft guidance targets highly-soluble drug substances that meet BCS solubility requirements; the highest dosage strength is soluble in 250 mL or less of aqueous media over the pH range of 1 to 6.8.[2] Although this fits the description of most immediate-release dosage forms, this guidance does not apply to chewable dosage forms, orally disintegrating tablets, or products with a narrow therapeutic index (NTI). Drugs with narrow therapeutic index have narrow plasma concentration levels and are defined as "drugs where small differences in dose or blood concentration may lead to serious therapeutic failures or adverse drug reactions resulting from inadequate or excessive drug availability." Examples of these drugs include carbamazepine, digoxin, levothyroxine, phenytoin, and warfarin.[3]

When official, this guidance will replace the existing guidance on Dissolution Testing of Immediate Release Solid Oral Dosage Forms issued in August 1997 only for Class 1 and 3 drugs. For Class 2 and 4 drugs and the exceptions stated previously, the original guidance from 1997 is still in effect. The official guidance will also supersede methods contained in the FDA Dissolution Methods Database (for Class 1 and 3 drugs), which will be updated with the standard dissolution methods described in this draft guidance.

The proposed standard dissolution tests are to be conducted with 500 mL of 0.01M HCl aqueous media at 37 ± 0.5°C and without the use of surfactants. The conditions are:

- **Basket Method (USP Apparatus 1):**
  Stirring rate: 100 rpm
- **Paddle Method (USP Apparatus 2):**
  Stirring rate: 75 rpm

The rationale for the method standardization as described in the guidance is based on the fact that the basket and paddle apparatus cannot reproduce the complex hydrodynamics found in the GI tract. Regarding agitation: the basket method at 100 rpm and the paddle method at 75 rpm are felt to be discriminatory for high-solubility drugs. The proposed acidity and volume represent the acidic conditions in the stomach when an oral drug is taken with a glass of water (250 mL). Regarding volume, 500 mL of media will be used since 250 mL is insufficient operational volume for the standard 1 liter dissolution apparatus.

The proposed specifications are based on the drug's respective BCS classification:

A) For BCS Class 1 products, a single point dissolution specification of Q = 80% in 30 min.
B) For BCS Class 3 products, a single point dissolution specification of Q = 80% in 15 min.

The rationale for tighter Class 3 specification is to ensure that the drug is bioavailable and not limited by dissolution, since gastric emptying often occurs around 15 minutes.

Lastly, the draft guidance contains a provision where rapidly dissolving drugs with dissolution specification of Q = 80% in 15 minutes or less may be alternatively tested by the USP disintegration test instead of dissolution. The acceptance criteria will require that the disintegration test is conducted in 0.01M HCl and complete disintegration is observed within 5 minutes.

In summary, this draft guidance could greatly reduce the time and expense of dissolution method development, especially for generic products. Although the 60-day comment period for the draft guidance has expired by the time of this publication, please refer to the FDA website for updated information on this guidance.

References

1. FDA Draft Guidance for Industry, Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs, August 2015
2. FDA Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, 2015
3. Quality and Bioequivalence Standards for Narrow Therapeutic Index Drugs; Lawrence Yu, GPhA 2011 Fall Technical Workshop presentation

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Printed in the USA, February 1, 2016
5991-6545EN

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