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ALLAN LITTLE, DIRECTOR OF MARKETING, DISSOLUTION SYSTEMS

THE 400-DS JUST GOT EVEN BETTER

Based on the USP Apparatus 7 reciprocating design, the Agilent 400-DS instrument utilizes sample cells of either 5 or 10 mL volumes to allow dissolution in as little as 3 mL. The unique design incorporates a 13-position apparatus with a built-in autosampler. Many of the products tested on this instrument have very long test cycles (days, weeks, or even months). For that reason, the unit is a sealed system to minimize evaporative loss – even with the use of solvents. A multi-port valve allows the use of up to five different media in a single test. At designated intervals either a full or partial media change can be performed – thereby allowing the total volume of media used to be greater than the cell size. The release profile is based on the cumulative amount released in each interval.

Agilent 400-DS Dissolution Apparatus 7

Agilent Technologies

We recently added several enhancements to the 400-DS, including additional safety features that allow up to 100% of select solvents to be used as media. We've also updated the hardware and software to ensure your safety.

We recommend any existing 400-DS customers using solvents have their equipment updated. Please contact your Agilent representative for more details.

Learn more about the 400-DS at: www.agilent.com/chem/400-ds

DAN SPISAK, PRODUCT MANAGER, DISSOLUTION SYSTEMS

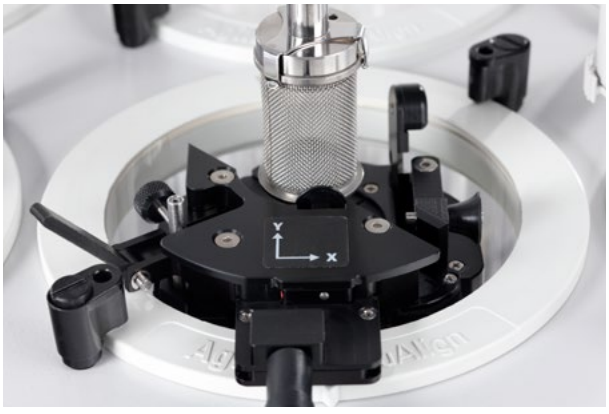
ACCEPT THE CHALLENGE: FIND TRUE EFFICIENCY WITH THE 280-DS MQS

ef·fi·cient /a'fiSHant/ adj. - (especially of a system or machine) achieving maximum productivity with minimum wasted effort or expense.

Breaking down the above definition provides a glimpse of the full potential of how the Agilent 280-DS Mechanical Qualification System (MQS) can move dissolution labs forward, while keeping costs to a minimum.

System or machine?

Technically, the 280-DS MQS qualifies as both. The "machine" portion includes only two modules that measure each physical parameter in a hands-free manner, eliminating the guesswork. When paired with the compliance-friendly software, this "system" works to capture data that is organized in such a way that each dissolution apparatus has its own chapter in the database. This takes data retrieval (for investigations or audits) and trending to unprecedented levels.



Agilent 280-DS Vessel Module

Achieving maximum productivity ...

How is your productivity measured? It's most likely a determination of how much can be accomplished in a given period of time. The 280-DS MQS gives you a way to complete the qualification of your dissolution apparatus in significantly less time than any other device available (conservatively, 15 minutes for either paddles or baskets). And, because it's software-based, the documentation is easier to produce and review. In fact, when the measurements are done, so is the fully quantitative final report.

The 280-DS MQS improves daily investigations as well. This device can identify or eliminate a physical issue in a minute or two (per vessel position). Making the 280-DS MQS part of your toolkit allows you to focus on the dissolution of your dosage form, not the instrumentation.

... with minimum wasted effort or expense

The 280-DS MQS is designed to simplify measurements and remove analyst variability. This concept provides a consistent technique, allowing for performance monitoring over time. Each qualification requires minimal preparation and time to complete. How much time and energy are you spending on your qualifications today? To really determine the 280-DS MQS

benefits for your lab, enter your own parameters in the Agilent 280-DS MQS Cost Savings Calculator on agilent.com. This tool gives you a glimpse of the actual savings that can be achieved and lets you reexamine your qualification schedule – an opportunity to truly redefine dissolution qualification.

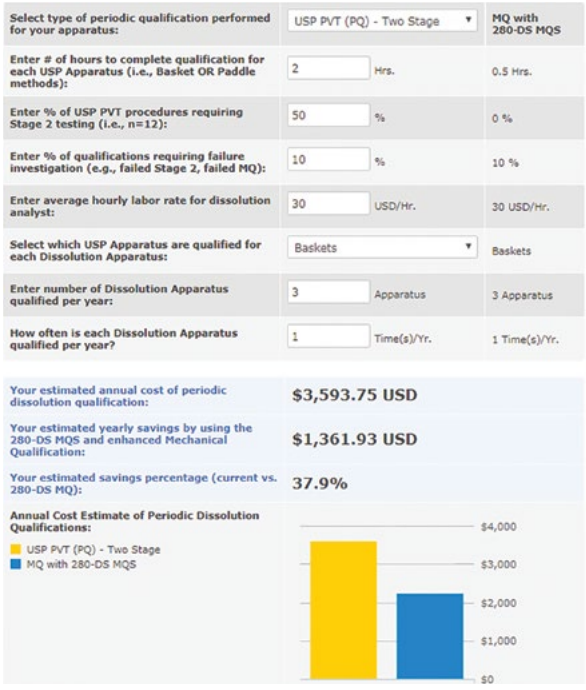
Contact your Agilent representative for more information about the 280-DS MQS. For dissolution qualification assistance, you can always reach out to the Dissolution Hotline at dissolution.hotline@agilent.com

Learn more about the 280-DS MQS

Product Website: www.agilent.com/chem/280-ds

Cost Calculator: www.agilent.com/chem/280-ds-calculator

Brochure: www.agilent.com/chem/280-ds-brochure



280-DS Mechanical Qualification System Cost Saving Calculator

DAN SPISAK, PRODUCT MANAGER, DISSOLUTION SYSTEMS

STAY CURRENT WITH COMPLIANCE REQUIREMENTS: DISSOLUTION WORKSTATION SOFTWARE UPDATE

It's no secret that compliance is important. Recent guidance from regulatory authorities indicates that as technology progresses, it is expected that the data acquisition tools and processes in pharmaceutical laboratories should do the same. Sometimes dissolution data can be overlooked in the overall compliance discussion. After all, it's only sample preparation, right? This laissez-faire attitude can cause problems when conducting failure investigations or, more importantly, in an audit situation.

Agilent's Dissolution Workstation software is under constant scrutiny in the rigorous pharmaceutical laboratory environment. It has been evaluated and challenged internally and externally by quality and compliance departments worldwide. Time and time again, it has revealed its ability to facilitate compliance in such situations. And, because of the ever-changing landscape of electronic data capture, record-keeping, and so on, it has once again been updated for improved performance and ease of use. The latest version:

- Accommodates Microsoft Windows 10 operating systems
- Includes remote support for the 708-DS Dissolution Apparatus
- Links directly to individual accessory Certificates of Conformance
- Automatically calculates time point frequency intervals
- Includes advanced report filtering criteria

While no software is 21 CFR Part 11 compliant on its own, Dissolution Workstation gives you the necessary tools to manage your dissolution systems, methods, and data as encouraged by regulatory authorities worldwide. Be sure to stay current with both your practices and software solutions for all electronic laboratory systems.

Contact Agilent for guidance or to learn more about how Dissolution Workstation software can help you meet these requirements at: www.nxtbook.com/nxtbooks/agilent/dissolution_sourcebook/index.php#/21

Agilent Dissolution Workstation software

BREAKING DOWN 21 CFR PART 11

In addition to the technical controls provided by the software, the user's organization must establish procedural controls–standard operating procedures (SOPs)–to address relevant nontechnical requirements. For example, controls such as internal audit programs must also be established to ensure that system operators follow the SOPs. 21 CFR Part 11 covers three specific elements of a regulated laboratory's operation:

Security of electronic records

Regulated organizations must be able to both verify the identity of system users, and limit system access to trained, authorized individuals.

Attribution of work

Attribution of work refers to documenting the who, what, when, where, and why of work performed. Automated audit trails independently record users' actions, thus connecting laboratory staff to the work they perform. Audit trail entries enable staff and regulatory inspectors to reconstruct the complete history of an electronic record.

Electronic signatures (if used)

While 21 CFR Part 11 does not require the use of e-signatures, it does provide regulations for when they are used. In this case, the system must ensure that e-signatures:

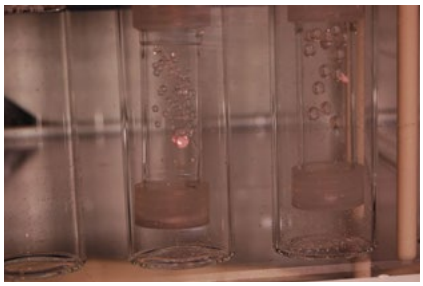
- Are irrevocably linked to their respective records
- Show the full name of the signer, date, and time, as well as the meaning of, or reason for, the signature (such as review, approval, responsibility, or authorship)
- Are present whenever the signed records are displayed or printed

Reference:
Support for Title 21 CFR Part 11 and Annex 11 Compliance: Agilent UV-Visible ChemStation, Agilent Technologies, publication number 5991-7715EN, 2016. https://www.agilent.com/cs/library/whitepaper/public/5991-7715EN.pdf

BRYAN CRIST, SCIENTIFIC AFFAIRS MANAGER

DISSOLUTION TESTING OF CHEWABLE TABLETS

The dissolution of chewable tablets has presented challenges for demonstrating a formulation's in vitro drug release. Although chewable formulations have been around for decades, understanding requirements for in vitro testing of these stubborn formulations has not been consistent in methodology. To assist with this situation, FDA Draft Guidance titled "Quality Attribute Considerations for Chewable Tablets" was issued in June of 2016 and it has provided strategies for testing products that may be, or must be, chewed to release the active ingredient under in vitro conditions.[1]



Chewable tablets with polymeric beads

USP chapter <1151> Pharmaceutical Dosage Forms further distinguishes between chewable tablets that "may" be chewed, for ease of administration, and those that "must" be chewed or crushed before swallowing to avoid choking or to ensure acceptable release of the active ingredient. Current thinking on in vitro dissolution testing of chewable tablets from guidance and compendial methods focus on the release of the drug from whole, non-crushed tablets. In other words, the in vitro dissolution testing of chewable tablets should follow principles of dissolution for conventional IR tablets and the API should release out of the tablet without chewing.[2]

Regulatory guidance recommends that intact chewable tablets should be tested in product development with four media; water, aqueous pH 1.2, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer, and the apparatus that should typically be used are USP Apparatus 1-3; basket, paddle and reciprocating cylinder. The FDA also encourages, during product development stages, evaluation not only in gastric and intestinal fluids in the fed and fasted state, but also hardness testing (30 to 120 seconds) while exposed to small quantities of simulated human saliva to gain a clearer picture of the tendency for the chewable to disintegrate when exposed to oral conditions on the tablet without chewing. The composition of simulated salivary fluid is available in the FDA draft guidance as well as their suggestion to target chewable tablet hardness of less than 12 kp during product development.

Additional recommendations suggest that chewable tablets should meet the same disintegration and dissolution specifications as IR tablets and thus dissolution testing should be conducted on intact chewable tablets because it is always possible that the tablet may be swallowed whole. Crushing of the tablets prior to dissolution testing is not recommended since there is no reported or validated method for this process.

Numerous monographs exist in the USP for dissolution testing of chewable tablets with several modifications observed over traditional non-chewable formulations: media may contain surfactant, and Apparatus 2-Paddle appears to be most commonly used with higher agitation (around 75 to 100 rpm). Q-times are often higher (from 45 to 60 minutes), and acceptance criteria is typically lower (around 70 to 75%).

The USP Dissolution Method Development and Validation chapter <1092> also suggests that Apparatus 3 – Reciprocating Cylinder had been found especially useful for chewable tablets in addition to soft gelatin capsules, delayed-release dosage forms, and non-disintegrating products.[3] Workshops held by FIP and AAPS have outlined guidelines for the dissolution testing of novel dosage forms, indicating that the reciprocating cylinder apparatus may be suitable for testing chewable tablets. The addition of glass beads would be required to provide more intensive agitation to the in vitro dissolution test.[4]

For additional information, a meeting of the Dissolution Discussion Group (DDG) was held 10 August 2017 on the subject of Dissolution Testing of Chewable Tablets. You will be able to download a recorded version of this meeting along with many other dissolution and drug release topics at the DDG site: www.dissolution.com

References:

[1] *Quality Attribute Considerations for Chewable Tablets*, FDA Draft Guidance for Industry, June 2006 https://www.fda.gov/downloads/Drugs/Guidances/UCM507098.pdf

[2] *USP <1151> Pharmaceutical Dosage Forms*, US Pharmacopeial Convention, Rockville, MD, USA; USP 40, 2017

[3] *USP <1092> The Dissolution Procedure: Method Development and Validation*, US Pharmacopeial Convention, Rockville, MD, USA; USP 40, 2017

[4] *FIP/AAPS Guidelines to Dissolution / in Vitro Release Testing of Novel / Special Dosage Forms*, Martin Siewert, Jennifer Dressman, Cynthia K. Brown, and Vinod P. Shah; AAPS :PharmSciTech 2003; 4 (1) Article 7, January, 2003

QUESTIONS YOU ASKED

Your question: We are facing a chromatographic problem because the dose of API in the tablet is not high enough to be quantified with our instruments. It seems that the mini-paddle can be used in small diameter vessels with 200 mL of medium or less, down to about 50 mL. However, since these microvessels are a non-compendial apparatus as well as the mini-paddle, what is the acceptable justification for using them? Which discriminative tests should we do?

Our answer: The good news is that it already appears that you have justified your path to small-volume testing by confirming that the low concentration of drug in your formulation cannot be analyzed with a standard volume dissolution apparatus; it just needs to be formalized to withstand regulatory scrutiny. A similar issue occurs with novel targeted drug delivery systems (stents and implants), and due to very low concentrations of the active ingredient, miniaturization of the dissolution environment is necessary.

Occasionally, large HPLC injection volumes may be used, but if you have LOQ issues for early time points, it may be best to try a small-volume apparatus. USP chapter <1092> may be of assistance here, but generally the justification of small-volume apparatus is through a process of using traditional dissolution apparatus and documenting failure by proving that you cannot analyze the samples because they are at the LOQ. Failure is just as important as success for justifying non-compendial drug release apparatuses. In your case, using a 50 mL volume may only get you to 10 times the LOQ, but this may be enough if you can demonstrate precision through repetitive testing, accuracy through spike and recovery studies, and specificity from excipients and related substances—and produce a rugged reproducible method that is as biorelevant as possible.

Since small-volume dissolution is not yet compendial, you should submit the specifications of the commercially available small volume vessels and paddle shafts, which are available from manufacturers. It is also a good idea to submit your method for ensuring qualification of your small volume apparatus. These are the primary components missing between a compendial and non-compendial apparatus and methodology.

ALLAN LITTLE, DIRECTOR OF MARKETING, DISSOLUTION SYSTEMS

NEW DISSOLUTION SOURCE BOOK NOW AVAILABLE

You can now download a copy or request a printed version of our new Dissolution Source Book.

The book includes our entire dissolution product line, from instruments to accessories. It is also filled with useful information regarding the various pharmacopeia, application tips, and information on educational courses as well as our service and qualification offering.

Download a PDF of the 2017-2018 Dissolution Source Book here:
www.agilent.com/cs/library/catalogs/public/5991-7981EN_Dissolution_Source_Book.pdf

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