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Do You Need Flexibility for Your Most Challenging Dissolution Needs?

Karen Krauel-Göllner, Product Manager, Dissolution

While the traditional basket and paddle apparatus (USP Apparatus 1 and 2) offers a convenient way to evaluate most oral drug formulations, you quickly run into problems when your dosage forms become more challenging in terms of solubility, lengths of the dissolution test, flexibility of the holder for your formulation, and the use of solvents. Also, the multiple changes of pH during the test, along with changes in agitation rates during the *in vitro* test are very cumbersome, if not impossible.

The Reciprocating Cylinder USP Apparatus 3, also known as the BIO-DIS, is excellent for developing controlled-release products because it can quickly and easily expose products to mechanical and physiochemical conditions that may influence the release of the products in the GI tract. The BIO-DIS Extended Release Tester was designed to test the dissolution rates of extended-release products or any dosage form requiring release profiling at multiple pH levels. The ability to transfer the product from one pH to another makes it an excellent candidate for delayed- and modified-release products.

Apparatus 3 allows the dosage form to be placed inside an inner tube that is then dipped in an outer vessel at varying speeds in up to six different media, simulating the pH changes that an orally ingested product would be exposed to in the GI tract (see Figure 1). By retaining the dosage form in the inner tube through the use of screens at the bottom (or top and bottom) of the inner tube, the vertical mixing action creates an environment where the dosage form constantly floats up and down inside the inner tube.

Figure 1: BIO-DIS and inner tube

While the Apparatus 3 is a great choice for delayed- and modified-release products, novel low dose and combination products may benefit greatly from the small volume, agitation, and versatility that the modified USP Apparatus 7 offers in the Agilent 400-DS.

The standard configuration of the Apparatus 7 (see Figure 2) already offers the option of smaller volumes, e.g. 50 mL, as well as the ability to change the pH during your run by moving through up to six rows. The standard Apparatus 7 is still an open system, however, and evaporation can become a challenge for extended dissolution tests.

Figure 2: Standard Apparatus 7

Agilent therefore developed the Agilent 400-DS (see Figure 3), a modified yet not entirely comparable version of the Apparatus 7. Initial development was for drug-eluting stent testing under accelerated conditions. The 400-DS has been utilized for testing a large variety of other products requiring ultralow volumes in the 5–10 mL range, with absolute control over evaporative losses and assurance of analytical sample integrity.

The unique design of the 400-DS combines 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 multiport 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. Another additional benefit is the capability to run tests at elevated temperatures of up to 55 °C.

Figure 3: 400-DS

Although the USP Chapter <724> states several holders for various dosage forms, there has been a need for modified holders over the years to accommodate novel dosage forms. These drug products may require different exposure, orientation, and agitation rates in the presence of specific volumes of dissolution medium to provide drug release in as biorelevant a process as possible.

We encourage customers with novel dosage forms requiring smaller volumes of media to contact us. Agilent already offers quite a variety of holders and many times an existing design can be utilized.

Figures 4 and 5 show you some of our holders for the 400-DS. The variety for the different formulations being run in the 400-DS is multifaceted.

The stent holder is the obvious choice for drug-eluting stents and so is the holder for pacemaker leads.

But already the stent holder has been used with dialysis bags (Reference 1). The contact lens holder (see F in Figure 5) is very versatile for small patches, which wrap around the center and are then fixed into place with the outer basket. We also used this holder successfully for an electro spun fleece in a customer demo.

Testing of microparticles can be done in the PEEK (see A in Figure 5) or mesh basket (see E in Figure 5), obviously depending on the particle size. The same holders are also used by our customers for implants, segments of vaginal rings (Reference 2), and gelling depot formulations.

Sometimes customizations of the holders are necessary, but ultimately you have the capability to work with a compendial USP 7 apparatus:

- at small volumes
- with the option to change media easily with the use of up to five media ports
- at accelerated temperatures
- with almost no evaporative loss
- with a built-in autosampler
- with 13 sample positions

Learn more about the 400-DS at www.agilent.com/chem/400-DS and/or contact your local Agilent representative.

Figure 4: Holders for (left pacemaker leads and (right) stents

Figure 5: (A) PEEK basket, mesh end, (B) Flat bed holder, (C) Stent holder (5 mL), (D) PEEK basket assembly, (E) Mesh basket, (F) Contact lens holder, (G) Stent holder (10 mL), (H) Pacemaker lead holder

References:

1. Probst M, Schmidt M, Tietz K, Klein S, Weitschies W, Seidlitz A. In vitro dissolution testing of parenteral aqueous solutions and oily suspensions of paracetamol and prednisolone, *Int J Pharm*, 2017, **532** (1): 519-527; doi: 10.1016/j.ijpharm.2017.09.052.
2. Externbrink A, Eggenreich K, Eder S, Mohr S, Nickisch K, Klein S. Development and evaluation of accelerated drug release testing methods for a matrix-type intravaginal ring. *Eur J Pharm Biopharm*, 2017, **110**: 1-12; doi: 10.1016/j.ejpb.2016.10.012.

Improve Your Investigations by *Not* Making a Change

Dan Spisak, Product Manager, Dissolution

Determining the root cause for dissolution failures can be an arduous task with so many variables to consider. From the physical instrumentation to the analyst technique to the dosage form itself—any means to eliminate sources of error or improve traceability can help determine what might have gone wrong.

One easy process to implement involves dissolution accessories. Your lab can address accessory-specific issues by tracking and maintaining in individual vessels, paddle or basket shafts, baskets, and more.

All Agilent 708-DS Dissolution Apparatus now include a convenient card that can be affixed to the instrument. This card displays the serial numbers of relevant accessories and their position so that, after cleaning, the user can replace them into the same location. This enables traceability for investigative purposes and eliminates the variable that exists if the accessories are used interchangeably.

Position	Vessel	Paddle	Basket shaft	Basket	Receptor shaft
1					
2					
3					
4					
5					
6					
7					
8					

Questions? Contact the Agilent dissolution team for:
Method development assistance, regulatory guidance, and instrument-related support.

Email: dissolution.hotline@agilent.com Web: dissolution.chem.agilent.com

The card also displays contact information for Agilent's Dissolution Hotline (dissolution.hotline@agilent.com) and the Dissolution Exchange (dissolution.chem.agilent.com), where there's application assistance and resources ready to support your laboratory for anything related to dissolution. Be sure to look for this addition with any new 708-DS or contact your Agilent representative to install on any existing dissolution apparatus.

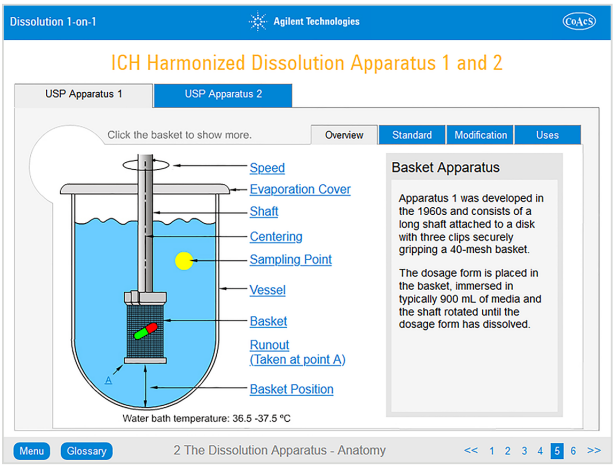
Where Did You Learn About Dissolution?

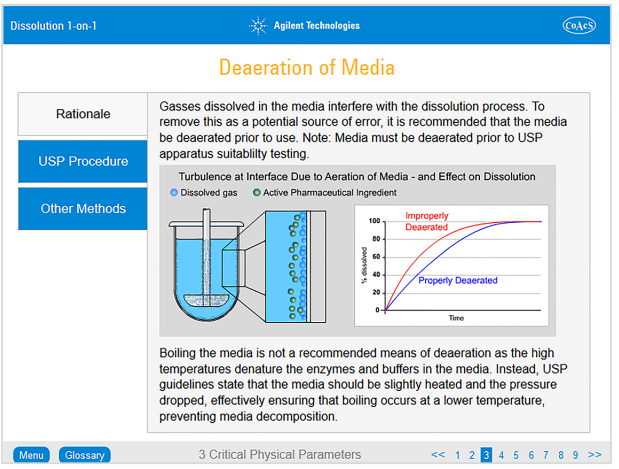
Allan Little, Director of Marketing, Dissolution

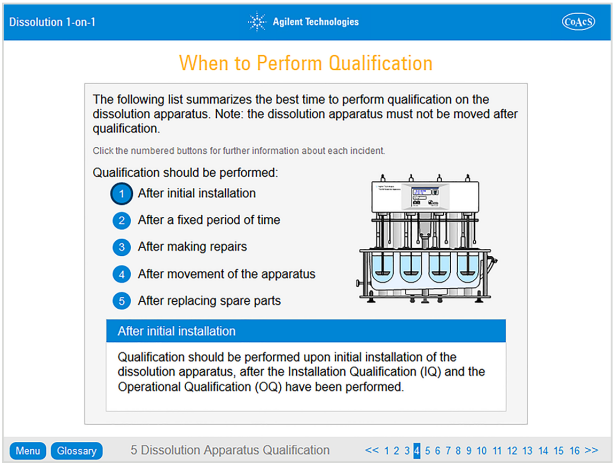
Chances are your first exposure to dissolution came as on-the-job training. Dissolution is not extensively covered at the university level; most analysts learn the technique from another colleague. Agilent has been providing dissolution training all the way back to the VanKel days. We believe it's not enough to provide the dissolution equipment, but also to make sure everyone knows how to properly use it. We began by offering a two-day, Fundamentals of Dissolution seminar and workshop. This was (and still is) a popular way to teach the theoretical and practical aspects of dissolution, however time availability was limited with face-to-face courses, so we also offer an online learning program: Dissolution 1-on-1. The course consists of seven chapters:

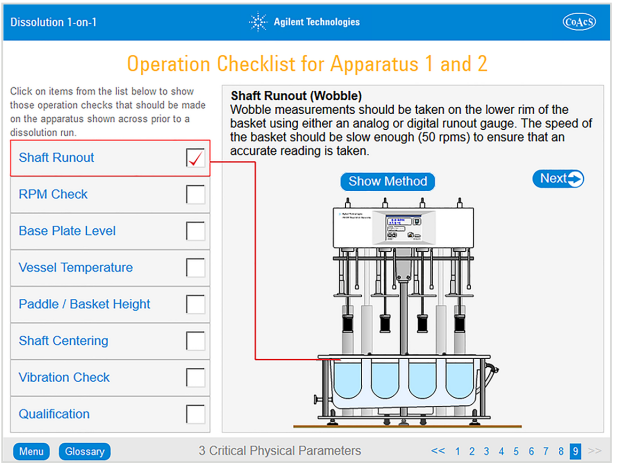
While there is a brief overview of the history of dissolution and the theory behind it, the bulk of the course is designed to build the practical knowledge base for dissolution analysts. Each chapter identifies the objectives as well as the recommended prerequisites to maximize knowledge transfer. The course is designed to be interactive. As the cursor is moved across the screen, various topics of interest are revealed.

These screen shots are a sample of the course material.









The course itself is free. Simply register and access the course material.

A proficiency test is also available, although there is a charge for this service. Managers can register their employees and then receive notification when they have successfully mastered the material. Discounts are available for large companies who wish to manage the training across their organization.

To learn more about the Dissolution 1-on-1 testing, visit dissolution.chem.agilent.com/learn/dissolution-1on-1/ and http://www.coacssoftware.com/dissolution2/

Questions You Asked

Q. I have a question concerning USP Chapter <1087> Apparent Intrinsic Dissolution with the Rotating Disk method. The diagram shows a rubber gasket between the shaft/holder and the dye. What is the purpose of the gasket, to keep media out of the holder and dye?

A. Yes you are correct. The gasket is a neoprene gasket that needs to be in place on top of the dye so when it is attached to the shaft/holder it provides a seal to keep media from entering the inside of the holder and wicking down the punch (which must also be left in place during the test). It's also necessary to prevent wetting the compact from the top, which could compromise the test results. Secondly, this keeps media from reaching the punch, which is hardened steel and could easily rust due to acidic components of the media and become difficult to withdraw from the dye. After use, the punch should be thoroughly rinsed, dried, and lightly oiled for storage between uses.

Q. I have an Enhancer Cell method that is described in USP <1724> Semisolid Drug Products – Performance Tests, Immersion Cell, Model A. I have evaluated the retaining ring, which seems to be larger than the 4.0 cm^2 surface area required. Why doesn't this match the USP?

A. The release area is actually controlled by the washer inner diameter (ID), not the ID of the Enhancer Cell body (reservoir) or the retaining ring. There are three size washers to represent 0.5 cm^2, 2.0 cm^2, and 4.0 cm^2, and they are all used with the same cell body and retaining ring.

Learn more:
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U.S. and Canada
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agilent_inquiries@agilent.com

Europe
info_agilent@agilent.com

India
india-lsca_marketing@agilent.com

Asia Pacific
inquiry_lsca@agilent.com

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