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Dissolution Workstation Software Update—Evolving with Your Needs

As the need for a truly compliant solution in the lab grows, it's important to consider new ideas and inspect the data-gathering environment as a whole. Dissolution testing—often performed in an isolated setting, free from analytical instrumentation—is regularly overlooked when it comes to data integrity. This can be a costly mistake. It's critical to ensure not only that you've protected your dissolution environment, but also that the data coming from this environment is protected as well.

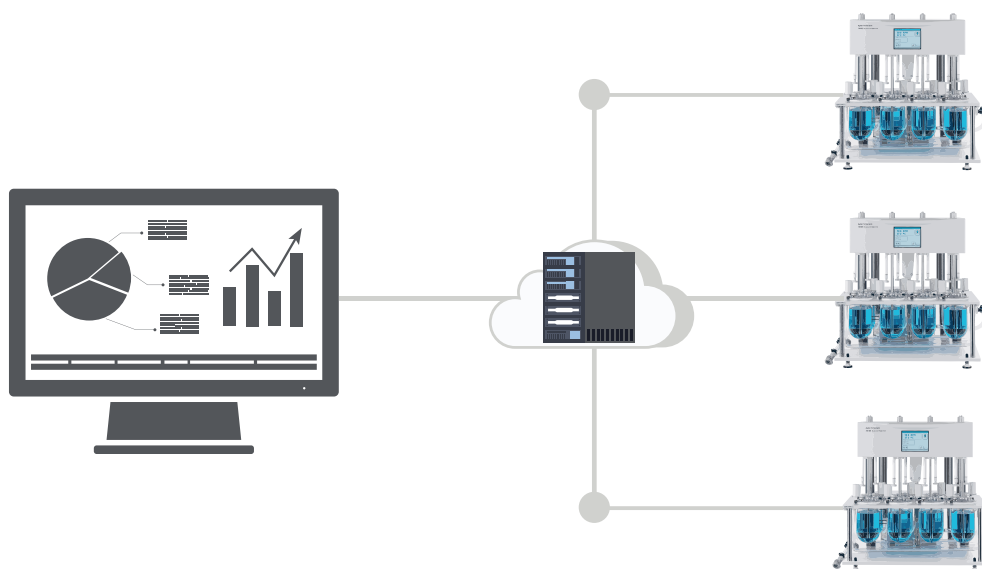
Anyone performing dissolution testing knows the dissolution environment can get a little untidy. Filling and emptying vessels, taking and filtering samples, changing media, rinsing accessories, etc. are all potential opportunities to make a mess. The apparatus itself is designed to withstand a good bit of exposure to these activities on a daily basis, but another component is appearing now more than ever in this space typically reserved for lab supplies: the PC.

Compliance related to 21 CFR Part 11 focuses primarily on the security of electronic records, attribution of work, and electronic signatures. While every "system"—be it hardware, software, firmware, etc.—has its own tools to facilitate a compliant environment, a software solution is universally accepted as the easiest to implement.

For this reason, Agilent Dissolution Workstation Software has taken the need for the PC out of the cluttered dissolution environment. The new version introduces a way to conveniently maintain all your dissolution system and method information from outside the laboratory. You can even load your method and start your test from any networked PC.

It works like this:

1. Select the system and dissolution method from any PC using Dissolution Workstation Software.
2. Enter relevant parameters and press START. (The command is sent from the PC to the 708-DS. The START button displays on the 708-DS.)
3. Inspect the dissolution environment and confirm that the dissolution apparatus is ready for testing (media, dosage forms, etc.).
4. To begin the test, press START on the 708-DS.



By creating a PC-free dissolution environment, you not only eliminate the chance of catastrophe, but also enhance compliance, organization, and overall data integrity. This latest software update incorporates the following enhancements:

- Windows 10 compatibility
- Links to individual Certificates of Conformance for accessories
- Expanded report-filtering criteria
- Remote-start capability
- Sample timing integrity check
- Manual 708-DS system enhancements

Contact your Agilent representative for more information about [Dissolution Workstation Software](#). You can also send a message to Agilent dissolution experts at dissolution.hotline@agilent.com to request a personal demonstration of the software and any other hardware solutions.

The 400-DS Just Got Even Better

Karen Krauel-Göllner, Product Manager, Dissolution Systems

The 400-DS, a small-volume modified compendial Apparatus 7, was initially developed for drug-eluting stent testing under accelerated conditions. Until today, the 400-DS has been utilized for testing a large variety of other products requiring ultra-low 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 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. A further additional benefit is the capability to run tests at elevated temperatures of up to 55 °C.

Because safe liquid handling is an important concern for Agilent and very often the 400-DS is used with solvents, we have added some additional hardware and software features. This now allows the use of up to 100% of select solvents to be used as media. These added benefits include: Better leak detection and leak handling, and added ventilation in the instrument.

We recommend all existing 400-DS customers have their equipment updated. This upgrade is being provided free of charge to current owners. Please contact your Agilent representative for more details.

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



Agilent 400-DS

Tips for Dissolution Testing of Transdermal Systems

Bryan Crist, Scientific Affairs Manager, Dissolution Systems

Transdermal systems (TDS) have provided numerous advantages for the systemic delivery of drugs through non-invasive means via the skin, such as:

- Providing controlled blood levels of potent drugs without the peak-and-valley fluctuations in blood levels that are common with orally administered drugs.
- Avoiding first-pass metabolism of the drug associated with oral drug delivery from passing through the liver before reaching systemic circulation.
- The ability to remove the system from the skin if toxicity or side effects begin to appear in the patient.

Dissolution apparatus have been modified over the years to provide means for in-vitro drug-release testing of TDS, which are contained in USP General Chapter <724> Drug Release. The three configurations are: USP Apparatus 5

(paddle over disk), USP Apparatus 6 (rotating cylinder), and USP Apparatus 7 (reciprocating holder, for small systems). [See Figures 1, 2 and 3.]

In each apparatus, the transdermal system is attached and lowered into the typical 1-liter dissolution vessel and operated to determine the rate at which the drug releases. However, successful testing of TDS remains dependent on technique. We hope the tips that follow will lead to meaningful test procedures, reduce variability, and simplify precise drug-release testing.

First, a few basics that apply to all three of the USP apparatus. Drug-release testing for TDS is performed at skin temperature of 32 °C instead of 37 °C, so media must be maintained at this temperature ± 5 °C. The dissolution media must also be well deaerated. Otherwise, bubbles will form on the surface of the



Figure 1: USP Apparatus 5
(paddle over disk)



Figure 2: USP Apparatus 6
(rotating cylinder)



Figure 3: USP Apparatus 7
(reciprocating holder)

active area of a patch, preventing the drug from moving through the controlled release surface and resulting in suppressed and variable release rates. The TDS must be mounted as flat as possible, without wrinkles, to ensure consistent delivery. The use of membranes such as Cuprophane, mentioned in the <724> chapter, may be used to mount the system securely to the apparatus without restricting the release rate. In most cases, the TDS may be attached to the apparatus using medical adhesives, double-sided tape, or other means outlined in specific USP monographs. Whatever adhesive you use, you must validate that the adhesive does not interfere with the analysis of the active ingredient. In all cases, the adhesive is applied to the backing of the patch so it may be securely attached to the apparatus with the active side of the patch facing the media. Finally, the active area of the patch must fit within the area of the holder or device it is attached to. In some cases, the adhesive backing will extend past the active area of the patch and this may be carefully removed to allow the active area to fit onto the holder or device.

The <724> chapter has continued to evolve slightly over the last seven years, and, unfortunately, some of the detail on mounting the system to the apparatus has been removed. We are providing these tips to help you perform consistent and meaningful drug-release testing of TDS. The procedures you use should be meticulously detailed and validated.

If a new product is being developed, the apparatus you choose typically depends on the size of the active area of the TDS. For small systems, Apparatus 5 or 7 may be used, depending on the potency of the drug. Highly potent systems may have very little active drug, so it may be difficult to see the active drug in Apparatus 5's one-liter vessel. The reciprocating holders for Apparatus 7 will be an advantage here because of the small-volume vessels range from 50 to 300 mL—and the holders will generally accommodate patch sizes up to about 25 mm in diameter or around 5 cm². [See Figure 4.] Apparatus 5 uses a disk comprised of a stainless steel support ring, a screen, and a retaining ring to hold it together. The diameter of the Apparatus

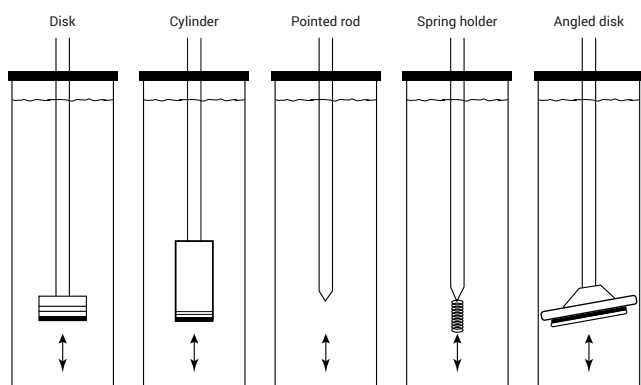


Figure 4: Reciprocating holders (disk, angled disk, and cylinder)



Figure 5: Mounting TDS onto rotating cylinder

5 disk is 41 mm and the active component must be securely mounted with the backing of the TDS attached to the screen with the active side facing up toward the rotating paddle. This apparatus is quite practical for many systems because it is an Apparatus 2 paddle system

and the only difference in setup is that the rotating paddle must be set at a height of 25 mm from the surface of the disk, not the bottom of the vessel.

For larger systems, the Apparatus 6 rotating cylinder offers a fairly large surface area. With the extension attached, TDS up to 10 x 14 cm may be attached to the outer circumference of the cylinder. Regarding the technique for attaching these larger systems to the rotating cylinder, some text that was contained in previous chapters of the USP provided additional information for the placement of the systems that is not contained in the current USP editions. Here's what you need to know:

- When applying the patch directly to the dialysis material Cuprophane, leave an extra 1 cm of border with the Cuprophane to securely mount the patch and keep it from peeling away from the cylinder during the test.

- The adhesive should be placed on the backing of the patch. While facing active side down, roll the cylinder onto the back of the patch to secure it without air bubbles. This may be best accomplished by rolling it on a mouse pad [See Figure 5.] to avoid damaging the TDS during mounting.
- The patch should be oriented on the cylinder so the long axis of the system fits around the circumference of the center portion of the cylinder.

Hopefully, these tips will make it easier to develop methods for drug-release testing of TDS, along with precise directions for the analysts so their testing will be consistent and accurately performed.

Reference:

USP General Chapter <724> Drug Release, USP 41, 2018, United States Pharmacopeial Convention, 12601 Twinbrook Parkway, Rockville, MD

Questions You Asked

Q. I have a new dissolution method that we have been using 0.45 micron filters for sampling. Is it possible that I may substitute 10 or 35 micron cannula tip filters in its place?

A. The main concern is that the pore size of the original filter is 0.45 micron and the proposed cannula tip filters have a wide range of porosity from 1 up to 70 microns. The primary challenge will be to assess if the proposed cannula tip filter retains undissolved API and stops the dissolution test or if it allows undissolved API to pass through the filter and continue to dissolve prior to testing. The latter outcome could yield a high bias to the continued dissolution of the drug, post-filtration.

A validation of the filter efficiency for your desired porosity will be required to determine if it actually stops the dissolution process. The best way to test the efficiency of a cannula tip filter in this case is to set up a trial run in a vessel with a single dose. Next, pull three 10 mL samples when the product is about 25% dissolved and pull another three 10 mL samples at about 75% dissolved (six samples total). These should be obtained through separate syringes and cannulas fitted with Full Flow Filters. The cannulas should be removed and the contents immediately dispensed into separate test tubes. To test, read one sample in a UV immediately upon filtering, then sonicate the next two test tubes for about 5 minutes. Read the second tube and sonicate the remaining tube another 5 minutes, then read the third tube. Repeat the same process for samples obtained when the product is about 75% dissolved. If all three readings are identical, success! This means undissolved product has not passed through the filter.

But if the sample readings get consecutively higher, undissolved drug is coming through and is dissolving post-filtration. If this happens, you will have to resort to a smaller micron filter.

Since the filter material may be different than the original filter, an adsorptivity study should also be conducted. These studies may be found in our [Filter Validation Protocol](#).

Q. I am developing a method for a product that is sticking to glass at the beginning of the test and is causing variability in test results. Will an acrylic vessel work better and hopefully reduce the variability I am seeing?

A. Usually, a product that sticks to glass will most likely stick to acrylic vessels as well. The variability that you are seeing is often caused by a tablet that is stuck to a region away from the center bottom of the vessel and in an area of high angular rotation, which will cause the tablet to disintegrate and dissolve more quickly

There are two things you should consider:

(1) Ensure that you are dropping the dose into non-rotating media as specified in the USP <711> Dissolution chapter.

(2) Perhaps view the variability as a justification to use a sinker, which will allow the tablet to slide down to the bottom center of the vessel prior to rotation of the shaft. Sinkers are often used where sticking tablets are encountered.

Learn more:

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