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PAGE 1
Dissolution Testing of Gels, Topical Creams & Ointments

PAGE 4
Dispelling a Myth: 6- versus 12-Position Dissolution Units

PAGE 6
Full-Flow Filters

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DISSOLUTION TESTING OF GELS, TOPICAL CREAMS & OINTMENTS

The apparatus for dissolution testing must deliver accurate and reproducible data and be easy to use. The Agilent Enhancer Cell (also described as the Immersion Cell in the USP) is a cost-effective way to meet these needs.

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Mandatory performance testing for semisolid drug products became official in the August 2013 First Supplement to USP 36 in USP general chapter <1724>. Similar to traditional pharmaceutical products such as tablets, product quality and performance tests for semisolid drug products must ensure their "identity, strength, quality, purity, comparability, and performance."[1] This USP general chapter discusses three types of equipment:

- Vertical diffusion cell (sometimes known as the Franz cell)
- Immersion cell (also known as the Enhancer Cell)
- Cell for USP Apparatus 4

You can use this equipment to evaluate the drug release from semisolid drug products such as creams, ointments, gels, and lotions. You commonly do tests during research and development, quality control, and for post-approval changes.

Figure 1 The Agilent Enhancer Cell assembly is available in three sizes to vary the amount of exposed surface area.

Achieve more reproducible data

Each of the three cell types is a viable solution for quality and performance testing of semisolid dosage forms. However, the Immersion, or Enhancer Cell, offers a distinct advantage over the others and has been shown to deliver more consistent and reliable data [2, 3, 4]. The Agilent Enhancer Cell assembly (Figure 1) consists of a polytetrafluoroethylene (PTFE) cell with adjustable volume and a screw cap to retain the skin or artificial membrane. You must control the available surface area because it is critical to achieving reproducible results. Control is accomplished by use of a "washer" with a defined opening of 4.0, 2.0, or 0.5 cm^2.

The cell body is designed to be adjustable to enable control of the volume of the reservoir within the cell body. The variable depth allows you to test semisolids, solutions, suspensions, or emulsions.

A membrane separates the dissolution media from the sample. The membrane should minimize the resistance to drug transport and should therefore be highly porous and of minimal thickness, and it should not bind with the active pharmaceutical ingredient (API). The proper membrane for your product should be chosen based on these characteristics.

Save time and expense with this easy-to-use apparatus

While data integrity is of utmost importance, the biggest advantage of the Agilent Enhancer Cell may be its ease of use. You can use the assembly with any dissolution apparatus configured for USP 2 (paddles); these are universal to most laboratories and thus save the expense of a dedicated instrument [5]. This familiar equipment shortens the learning curve and makes it possible to bring data online much faster [6]. In addition, you can use the Enhancer Cell in vessels that range from 200 mL up to conventional 1-liter volumes. Regardless of volume, the setup is easily automated for sampling and analysis with readily available systems, such as the Agilent 850-DS dissolution sampling station.

Because the Agilent Enhancer Cell is made of PTFE, it is inert and will not interact with the formulations in the cell. You avoid the problem with breakage, which is common with most glass diffusion cells. Unlike the Franz cell, the donor compartment of the Enhancer Cell that contains the formulation is temperature-controlled within the vessel.

In summary, the Agilent Enhancer Cell solution provides the laboratory with a proven robust technology that is used on a dissolution apparatus that is already familiar to the laboratory staff. The immersion of the Enhancer Cell into the temperature controlled environment provides necessary temperature stability to the doner compartment. This also seals the ointment or cream from atmospheric exposure that could alter the state of the drug product as it is exposed with the traditional vertical diffusion cell configuration. Lastly, the thickness of the drug product may be uniformly controlled with the adjustable surface plate.

The combination of ruggedness, temperature control, and atmospheric control ensures that the Enhancer Cell is well suited for required performance testing of ointments, creams, and gels.

Ordering Information

Quantity	Description	Part Number
6	Enhancer Cell, 4 cm^2 surface area membrane (one per position)	12-4000
1	Height spacer (1 cm) / alignment tool, for 4 cm^2 Enhancer Cell (only one required)	12-4020
1	Adjustment tool, for all Enhancer Cell sizes (only one required)	12-4015
6	Mini paddle, lower interchangeable, electropolished stainless steel	13-3608
6	TruAlign vessel, flat bottom, 200 mL (one per position)	12-5170
6	TruAlign vessel, 100/200 mL conversion kit (includes vessel adapter and evaporative cover)	12-6368

Table 1 Enhancer Cell Ordering Example: 708-DS conversion, 6 positions, 4 cm^2 Enhancer Cell.

References

1. U.S. Pharmacopoeia 36 / NF 31, 1st Supplement, <1724> Semisolid Drug Products, **2012**.
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BRYAN CRIST, SCIENTIFIC AFFAIRS MANAGER

DISPELLING A MYTH: 6- VERSUS 12-POSITION DISSOLUTION UNITS

A dissolution test is based on six results, and the apparatus typically includes a minimum of six positions to accommodate enough vessels to run a complete test. The number of units to test appears in the USP General Chapter <711> Dissolution, Acceptance Criteria tables for each type of dosage. This number and configuration appeared in scientific literature during the 1950s and 1960s and was officially included in the U.S. Pharmacopeial Forum in 1970. Often the acceptance criteria or comparison data requires several sets of 6 to obtain 12 or 18 results, which have historically been tested on 6-position apparatus. Interestingly, the number of tablets to be tested in the ICH Harmonized Pharmacopeia (EP, USP, and JP) is described as an assembly in the singular throughout the harmonized dissolution chapter.

In terms or regulatory requirements for dissolution testing, guidance from the U.S. Food and Drug Administration suggests that marketed dosage forms be tested for specification setting with 12 or more units. This number also correlates with FDA's required number of tests on human subjects (n≥12) to determine the bioavailability of products and in vitro/in vivo relationships. Specifications (Q) are based on 12 units and expressed as the percentage of label claim required for demonstrating a therapeutic effect, but this *does not imply that this testing must be done at the same time, or on a single dissolution apparatus with 12 positions*.

In summary, the number 12 is only a reference point of a minimum number of units to be tested to adequately set specifications and ensure bioequivalence between generic and reference drug products; it is not a requirement that your apparatus have 12 positions. Very often more units (18 or 24) may be tested to assure higher accuracy and precision in statistical comparison methods such as f_2. Dissolution apparatus are developed and used worldwide based on six positions as a matter of convenience and conformance. Twelve units are routinely tested on a single six-position apparatus by performing the method twice.

Considerations when choosing the number of place units per apparatus

Regulations

Although it is a requirement for f_2 comparison to use a minimum of 12 units, it is *not* a regulatory requirement to perform dissolution on a single 12-position system. There is no regulatory requirement to perform all numbers required for comparison at the same time.

Compendial requirement 1

Samples must be withdrawn only at specific times within 2% of the time they were dropped. You do not have a sample until it has been filtered to stop the dissolution process. This equates to pulling and filtering 6 samples in ± 36 seconds for a 30 minute timepoint, but this has to be done at the proper position. If you use a 12-position apparatus, you will need to collect and filter 12 samples within ± 36 seconds; this is only 3 seconds per position.

Compendial requirement 2

Because of the previous requirement, you may introduce dosage forms at consecutive intervals (for instance, every 30 seconds) to allow time to sample. You may stagger the tablets. However, you must drop the dosage forms into nonrotating medium. If someone introduces a tablet to the first vessel and starts the apparatus, all positions will rotate. The 12-position apparatus must have the ability to keep media from moving until each dose is introduced.

Flexibility

Two six-position units allow you to start and stop two independent tests at different times. With a single 12-position apparatus, you must run the same method speed and test length for the twelve individual positions. With six-position systems, you have the ability to start and stop two apparatus independent of one another.

Failure investigations

Two six-position apparatus will require less investigation and retesting in the event of a failure. If one tablet among the 12 fails due to a mechanical issue, do both batches need to be retested? With two independent apparatus there is less ambiguity in the event of a failure since a single test is associated with a single apparatus.

Adherence to stricter guidelines for enhanced mechanical qualification

The tighter specifications for mechanical qualification required by the ASTM and FDA will be more difficult to meet. We suggest you receive assurances that any 12- or 14-place system will pass the new MQ physical parameters. Vessel/shaft centering is now only 1.0 mm. If one position is off by more than 1.0 mm in the upper and lower portion of the vessel, the entire unit should be taken out of service until repaired, or readjusted and requalified.

Less downtime

If a single 12- or 14-place unit is removed from service for a mechanical or repair issue, you've lost the productivity of two smaller systems. If a problem occurs with one of two six-place units, you can still operate the other system.

Automation flexibility

Whether you are doing automated sampling, media replacement, or online UV-Vis or LC measurement, you can choose from a multitude of automation solutions available for six- or eight-place systems. If your testing needs change, the more independent approach can accommodate pathways for automation. Eight-position apparatus allow easy online integration because the spare vessels are used for blank and standard solutions during the test.

Figure 2 The 708-DS dissolution apparatus is designed for reproducibility and ease of qualification, and is the ideal platform for standardizing dissolution testing.

ALLAN LITTLE, DIRECTOR OF MARKETING DISSOLUTION SYSTEMS

FULL-FLOW FILTERS

Filtration is an essential step in the dissolution process. Because dissolution continues until the sample is filtered, it is critical to filter immediately. The full-flow filter, when attached to a manual or automated sampling cannula, provides immediate filtration, which preserves the integrity of the dissolution sample.

The analysis of filtered samples is generally performed by a UV-Vis spectrophotometric or HPLC procedure. In short, the filtration step is the moment in time separating the dissolution phase from the analytical phase and has particular attributes to both phases of the dissolution test.

Whether a dissolution method is performed manually or automatically, the filter must be challenged in three primary areas: efficiency, adsorption and leachability. If a filter is being qualified as an equivalent filter, the efficiency challenge may be omitted unless the pore size of the filter has changed. If excessive absorption of the active drug occurs, if excipient interference is high, or if filters become clogged, alternative filters may be required.

Full-flow filters offer increased surface area to optimize the filter performance during a dissolution run. When used with Agilent automated sampling equipment (VK 8000 or 850-DS), the filters are back flushed after a sampling time point to minimize potential clogging. Full-flow filters are made of ultrahigh molecular weight polyethylene (UHMWPE) or, for even greater chemical resistance, polyvinylidene fluoride (PVDF).

Agilent full-flow filters are color coded to help visually differentiate the various pore sizes as well as UHMWPE versus PVDF. Both filter types can be used with 1/8 inch diameter cannulas and are available in a wide variety of pore sizes and package configurations.


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CERTIFICATE OF ANALYSIS

Figure 3 Certificates of Analysis are available upon request. Simply contact the Agilent Dissolution Hotline for copies at dissolution.hotline@agilent.com.

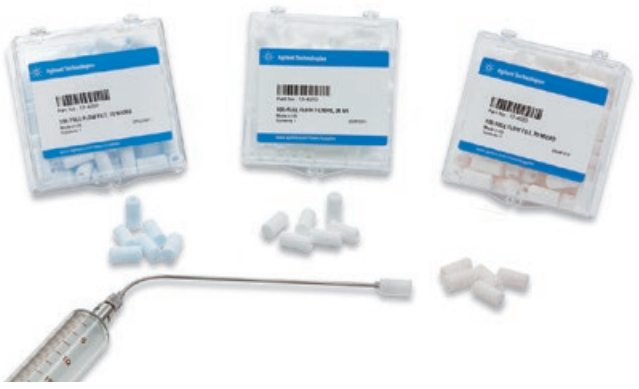

Figure 4 Full Flow Filters

Ordering Information

Agilent PN	Description	Color Code	Package Size
17-4003	Full-Flow Filter, UHMWPE, 1 µm	N/A	100/pkg
17-4004	Full-Flow Filter, UHMWPE, 4 µm	N/A	100/pkg
17-4000	Full-Flow Filter, UHMWPE, 10 µm	Blue	100/pkg
17-4001	Full-Flow Filter, UHMWPE, 10 µm	Blue	50/pkg
17-4005	Full-Flow Filter, UHMWPE, 10µm	Blue	1000/pkg
17-4010	Full-Flow Filter, UHMWPE, 35 µm	White	100/pkg
17-4011	Full-Flow Filter, UHMWPE, 35 µm	White	50/pkg
17-4015	Full-Flow Filter, UHMWPE, 35 µm	White	1000/pkg
17-4020	Full-Flow Filter, UHMWPE, 70 µm	Red	100/pkg
17-4021	Full-Flow Filter, UHMWPE, 70 µm	Red	50/pkg
17-4025	Full-Flow Filter, UHMWPE, 70 µm	Red	1000/pkg
17-4040	Full-Flow Filter, PVDF, 10 µm	Green	100/pkg
17-4045	Full-Flow Filter, PVDF, 10 µm	Green	1000/pkg
17-4050	Full-Flow Filter, PVDF, 35 µm	Yellow	100/pkg
17-4055	Full-Flow Filter, PVDF, 35 µm	Yellow	1000/pkg

Table 2 Agilent full-flow filters are available in a wide variety of pore sizes and package configurations.

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