

BRIEFING

**⟨725⟩ Topical and Transdermal Drug Products—Product Performance Tests.** Two new *USP* general chapters on Topical and Transdermal Drug Products address the quality and performance aspects of topical dermal pharmaceutical dosage forms. The general chapters are *Topical and Transdermal Drug Products—Product Quality Tests* (3), which covers the basic quality control tests for these dosage forms and *Topical and Transdermal Drug Products—Product Performance Tests* (725), which covers the apparatus and procedures to be used to evaluate the in vitro drug release. The HPLC procedure for the hydrocortisone analysis was validated using a Symmetry C18 brand of packing L1. Comments and suggestions regarding these two general chapters should be sent to Margareth Marques at MRM@usp.org no later than July 31, 2009. USP is planning a workshop on these general chapters and the comments and suggestions received.

(BPC: M. Marques.)    RTS—C71037

**Add the following:**

■ **⟨725⟩ TOPICAL AND TRANSDERMAL  
DRUG PRODUCTS—PRODUCT  
PERFORMANCE TESTS**

- i. **Introduction**
- ii. **Performance Test for Topical Drug Products—  
In Vitro Drug Release Using the Vertical Diffusion Cell**
  - a. **Apparatus**
  - b. **Calculation of Release Rate (Flux) and  
Amount of Drug Released**
  - c. **Performance Verification Test Method for  
USP Hydrocortisone Cream Reference  
Standard Product**

- iii. **Product Test for Transdermal Drug Products**
  - a. **Apparatus 5—Paddle over Disk Method**
  - b. **Apparatus 6—Rotating Cylinder Method**
  - c. **Apparatus 7—Reciprocating Holder Method**
- iv. **Product Quality Tests**

**I. INTRODUCTION**

A performance test for topical drug products must be able to measure drug release from the finished dosage form. It must be reproducible and reliable, and although it is not a measure of bioavailability, the performance test must be capable of detecting changes in the finished product's drug release characteristics that have the potential to alter the biological performance of the drug in the dosage form. This product performance test is provided to determine compliance with drug release requirements where specified in individual monographs.

**II. PERFORMANCE TEST FOR TOPICAL (SEMISOLID)  
DRUG PRODUCTS—IN VITRO DRUG RELEASE  
USING THE VERTICAL DIFFUSION CELL**

The vertical diffusion cell (VDC) system is a simple, reliable, and reproducible means of measuring drug release from semisolid (cream, ointment, and gel) dosage forms. Typically, 200–400 mg of a cream, ointment, or gel is spread evenly over a suitable synthetic, inert support membrane. The membrane, with its application side up, is placed in a VDC (typically a 15-mm diameter orifice), e.g., a Franz cell. Diffusive communication between the delivery system and the reservoir takes place through an inert, highly permeable support membrane. The membrane keeps the product and the receptor medium separate and distinct. Membranes are chosen to offer the least possible diffusional resistance and not to be rate controlling. The release rate experiment is carried out at  $32 \pm 1^\circ$ , except in the case of vaginal creams when

the temperature should be  $37 \pm 1^\circ$ . Sampling generally is performed during 4–5 h, and the volume withdrawn is replaced with fresh receptor medium. To achieve sink condition, the receptor medium must have a high capacity to dissolve or carry away the drug, and the receptor media should not exceed 10% of the concentration of the standard at the end of the test. The test is done with groups of six cells. Results from 12 cells—two runs of 6 cells—are used to document the release rate.

### II. a. Apparatus

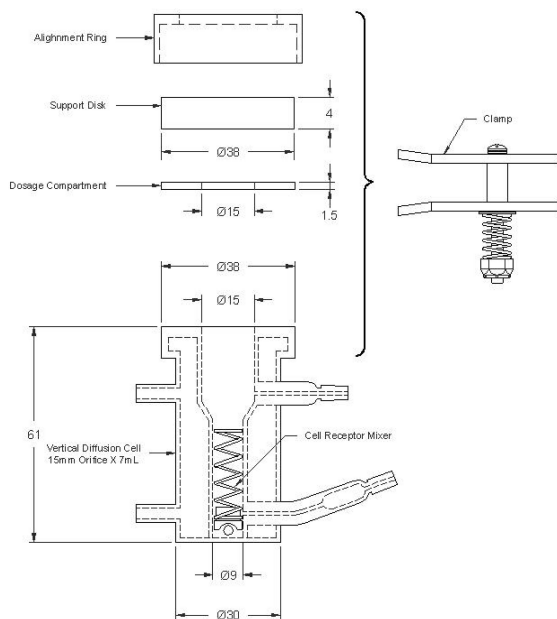


Fig. 1. Vertical Diffusion Cell.

(All measurements are expressed in mm unless noted otherwise.)

The VDC assembly consists of two chambers (a donor chamber and a receptor chamber), separated by a donor compartment and held together by a clamp (see *Figure 1*). This type of cell is commonly used for testing the *in vitro* release rate of topical drug products such as creams, gels, and ointments. Alternative diffusion cells that conform to the same general design and size can be used.

The VDC body normally is made from borosilicate glass, although different materials may be used to manufacture the body and other parts of the VDC assembly. None of the materials should react with or absorb the test product or samples.

In the donor compartment, the semisolid dosage form sample sits on a synthetic membrane within the cavity of the dosage compartment that is covered with a glass disk.

The diameters of the orifices of the donor chamber and the dosage compartment, which defines the dosage delivery area for the test, should be sized within  $\pm 5\%$  of the specified diameter. The receptor chamber orifice should never be smaller than the orifice of the donor chamber and should be fabricated to the same size as the donor chamber orifice. The design of the VDC should facilitate proper alignment of the dosage compartment and receptor orifices.

The thickness of the dosage compartment normally is 1.5 mm. This thickness should be sized within  $\pm 10\%$  of the specified thickness.

The cell body should be manufactured consistently, with uniform height and geometry. Cells should appear the same, and their internal receptor volumes should fall within  $\pm 5\%$  of their specified volume.

**Volume**—Before conducting testing, determine the true volume of each receptor chamber in the VDC. The volume of each VDC should be determined with the internal stirring device in place.

**Temperature**—The temperature of the receptor media during the test should remain within  $\pm 1.0^\circ$  of the target temperature (typically  $32^\circ$ ).

**Speed**—The rotational speed tolerance is  $\pm 10\%$  from the target speed (normally 600–800 rpm). The speed selected should ensure adequate mixing of the receptor media during the test.

**Sampling Time**—Samples should be taken at the specified times within a tolerance of  $\pm 2\%$  or  $\pm 2$  minutes, whichever is greatest.

**Qualification**—The qualification of the apparatus is demonstrated by verifying the test temperature and speed requirements are met, along with a performance verification test (PVT). The PVT is passed if two tests of six cells comply with FDA's requirements of a 90% confidence interval (see FDA *Guidance for Industry: Nonsterile Semisolid Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation*, May 1997, available at [www.fda.gov/cder/guidance/1447fnl.pdf](http://www.fda.gov/cder/guidance/1447fnl.pdf)). The PVT is performed by one analyst testing the specified reference standard in duplicate. The first test with six cells is performed and is defined as the reference. The second test of six cells is defined as the test. The PVT is passed if the second test passes the 90% confidence interval with reference to the first reference test.

**Procedure**—Unless otherwise specified in the individual monograph, degas the medium using an appropriate technique. With the stirring device in place, fill the VDC with the specified media and allow time for it to come to a temperature of  $32^\circ$ . If necessary, saturate the membrane in the specified media (generally receptor media) for 30 minutes. Place the membrane on the dosage compartment and invert. Apply the material that will be tested into the cavity of the dosage compartment, and spread the material out to fill the entire cavity of the dosage compartment.

Assemble each of the prepared dosage compartments to each VDC with the membrane down and in contact with the receptor media. During this application it is important to ensure that there are no bubbles under the membrane. When all dosage compartments and the remaining components are in place, turn on the stirring device, which constitutes time zero.

Follow the specified sampling procedure, and collect an aliquot from each VDC for analysis. Ensure that during the sampling process bubbles are not introduced into the cell. Exercise care during sampling and replenishment of the medium in order not to introduce bubbles.

With some cells it is acceptable to have up to three bubbles under the membrane if the bubbles are less than 1 mm in diameter. With some cells, bubbles may be removed from the receptor chamber during the test by tipping the cell as long as this process is required only one time per position.

## II. b. Calculation of Rate (Flux) and Amount of Drug Released

Creams and ointments are considered extended-release preparations. Their drug release largely depends on the formulation and method of preparation. The release rate of a given drug product from different manufacturers is likely to be different. It is assumed that the drug release of the product is linked to the clinical batch.

Unless otherwise specified in the individual monograph, the release requirements are met if the following have been achieved.

The amount released ( $\mu\text{g}/\text{cm}^2$ ) at a given time ( $t_1$ ,  $t_2$ , etc.) is calculated for each sample as follows:

$$\text{Amount Released } t_1 = A_U / A_S \cdot C_S \cdot 1,000 \cdot V_C / A_O$$

$$\text{Amount Released } t_2 = A_U / A_S \cdot C_S \cdot 1,000 \cdot V_C / A_O + (AR_{t_1} \cdot V_S / V_C)$$

where

$A_U$  = area of the current sample

$$\text{Amount Released } t_n = \frac{A_U}{A_S} \cdot C_S \cdot 1000 \cdot \frac{V_C}{A_O} + \sum_{i=1}^{n-1} \left( AR_{t_{i-1}} \cdot \frac{V_S}{V_C} \right)$$

$A_S$  = average area of the standard

$C_S$  = concentration of the standard (mg/mL)

$V_C$  = volume of the diffusion cell (mL)

$A_O$  = area of the orifice ( $\text{cm}^2$ )

$AR$  = amount released ( $\mu\text{g}/\text{cm}^2$ )

$V_S$  = volume of the sample aliquot (mL).

For each cell the individual amount released is plotted vs time, and the slope of the resulting line (rate of drug release, flux) is determined. The average of 6 + 6 slopes represents the drug release of the dosage form and serves as the standard for the drug product.

## II. c. Performance Verification Test of VDC Systems using the USP Hydrocortisone Cream

### Reference Standard

**Materials and Equipment**—USP Hydrocortisone Cream RS; 25-mm, 0.45- $\mu\text{m}$  hydrophilic polysulfone membrane filters (1); vacuum filtration apparatus consisting of a filter holder with a medium or fine-porosity sintered glass holder base, funnel with a 250-mL capacity, and magnetic stirrer; small and smooth jeweler's forceps; depression porcelain color plate; diffusion cell system with six diffusion cells and temperature control circulator; and sampling syringe or device and collection vials.

### Procedure

**Receptor Medium**—Mix 60 mL of Alcohol with 140 mL of water to prepare a 30% alcoholic media. Degas the media by filtering through a 47-mm, 0.45- $\mu\text{m}$  membrane by vacuum filtration. Assemble the filtration apparatus placing a magnetic stir bar (approximately 1 in.  $\times$  0.25 in.) in the receiving flask. Place the apparatus on a magnetic stirring plate, and spin the bar at a moderate rate. Apply vacuum and pass the media through the filter while stirring. After all media have passed through the filter, continue stirring while maintaining a vacuum for 2 minutes. Applying vacuum and stirring beyond 2 minutes may change the composition of the water-alcohol media. Care should be taken to ensure that the period of time that the media is under vacuum after the filtration is complete is limited to 2 minutes.

Immediately transfer the degassed receptor medium to a suitable receptor medium bottle and stopper. Place the receptor medium bottle in the jacketed beaker and allow the media to equilibrate for 30 minutes before use.

## Preparation of Apparatus

Set the circulating bath to a temperature (typically 32.5°) that will maintain the temperature in the diffusion cells at 32° during the test. Place the appropriate magnetic stirrer in each diffusion cell. Allow the system to equilibrate for at least 30 minutes before beginning the test.

## Membrane Preparation

Thirty minutes before use, prepare at least seven membranes. Using a Pasteur pipette, apply receptor medium to the surface of each membrane until covered. Allow the membranes to equilibrate for 30 minutes to saturate the membranes.

## Sample Preparation

Carefully lift one membrane at its very edge with jeweler's forceps. Place the membrane on a paper tissue and blot any extreme excess solution (a slight excess solution is desired). Carefully place the membrane in the center of the dosage compartment. Place the dosage compartment, with the membrane centered on the underside, onto a tissue and press down on the compartment. Apply an appropriate amount of USP Hydrocortisone Cream RS (between 200 and 400 mg) on top of the membrane and inside of the dosage compartment cavity. Use a spatula to carefully smooth the material over the membrane, filling the entire cavity of the dosage compartment. Wipe any excess material from the surface of the dosage compartment. Repeat for a total of six sample preparations.

## Performing the Test

Fill the diffusion cells with receptor media, and allow time to equilibrate to 32°. Ensure that the stirrers are not rotating and that there is a positive meniscus covering the complete top of each diffusion cell. Place the glass disk on top of the dosage compartment against the sample. Place the dosage compartment/glass disk assembly on the top of the diffusion cell, avoiding bubbles. Inspect under the membrane for bubbles. Assemble the cell. Repeat for each cell. Begin the test according to the following test parameters: temperature: 32°; stir speed: 600–800 rpm; total test time: 6 hours; sampling times: 1, 2, 3, 4, and 6 hours.

## Sampling Procedure

At each of the stated sampling times, collect a sample from each cell as follows: stop the stirrer 30 seconds before sampling. Repeat sampling procedure for each cell in order from 1 to 6. Replace the medium. After the sixth cell has been sampled, resume the stirrer rotation.

## High-Performance Liquid Chromatography (HPLC) Hydrocortisone Analysis

USP Hydrocortisone RS; acetonitrile; water; alcohol, 95%; 47-mm, 0.45- $\mu$ m polysulfone membrane filters; 50 mm  $\times$  3.9 mm, 5- $\mu$ m packing L1.

## Procedure

### Mobile Phase Preparation

Prepare and degas a sufficient volume of mobile phase to complete the analysis of the samples collected. For each 1 L of mobile phase mix 200 mL of acetonitrile with

800 mL of water. If necessary, adjust the mobile phase composition to achieve an approximate retention time of 7 minutes for the hydrocortisone peak.

### Standard Preparation

Prepare a stock standard solution at a concentration of approximately 0.20 mg/mL of USP Hydrocortisone RS in alcohol. For example, a solution of 20 mg of hydrocortisone in 100 mL of alcohol is suggested. Prepare a working standard solution by making a 5-fold dilution of the stock standard in a solution of 30 : 70 alcohol:water mixture. For example, dilute 2 mL to 10 mL.

### Chromatographic Conditions

**Wavelength**—242 nm; flow rate: 1 mL/min; injection volume: 10  $\mu$ L; run time: 10 minutes; column: 5 cm  $\times$  3.9 mm, 5- $\mu$ m packing L1; mobile phase: 20 : 80 acetonitrile:water. Begin the analysis by making five replicate injections of the working hydrocortisone standard solution for system suitability.

**System Suitability Requirements**—Relative standard deviation: < 2%; tailing factor: NMT 1.5. Make single injections of each of the samples obtained during the in vitro release testing. Bracket injections of samples with single standard injections after the analysis of the 2-, 4-, and 6-hour samples. Calculate the results as specified.

## III. PERFORMANCE TESTS FOR TRANSDERMAL DRUG PRODUCTS

As with topical drug products, a performance test for transdermal drug products also must have the ability to measure drug release from the finished dosage form, must be reproducible and reliable, and must be capable of detecting changes in the finished product's drug release characteristics that have the potential to alter the desired pharmacologic effect(s) of the active ingredient.

Such changes could be related to active or inactive/inert ingredients in the formulation or physical dosage form, physical or chemical attributes of the finished preparation, manufacturing variables, shipping and storage, age, and other characteristics that are critical to quality.

When based on sound scientific principles, product performance tests can be used for pre- and postmanufacturing purposes such as during the product research and development phase, basic quality control, demonstration of product similarity, or demonstration of compliance with FDA Guidelines (e.g., approval and postapproval changes in the dosage form).

In vitro drug release testing of transdermal patches can be carried out using USP Apparatus 5, Apparatus 6, or Apparatus 7. In general, researchers have found that Apparatus 5, the modified paddle method, is simpler and is applicable to most types, sizes, and shapes of transdermal delivery systems. At this time, no PVT Reference Standard exists for Apparatus 5, 6, or 7.

### III. a. Apparatus 5 (Paddle Over Disk Method)

**Apparatus**—Use the paddle and vessel assembly from *Apparatus 2* as described in *Dissolution* (711), with the addition of a stainless steel disk assembly (2) designed for holding the transdermal system at the bottom of the vessel. Other appropriate devices may be used, provided they do not absorb, react with, or interfere with the specimen being tested (3). The temperature should be maintained at  $32 \pm 0.5^\circ$ . During the test maintain a distance of  $25 \pm 2$  mm between the paddle blade and the surface of the disk assembly. The vessel may be covered during the test to minimize evaporation. The disk assembly for holding the transdermal system is designed to minimize any dead volume between the disk assembly and the bottom of the vessel. The disk assembly holds the

system flat and is positioned so that the release surface is parallel with the bottom of the paddle blade (see *Figure 2*).

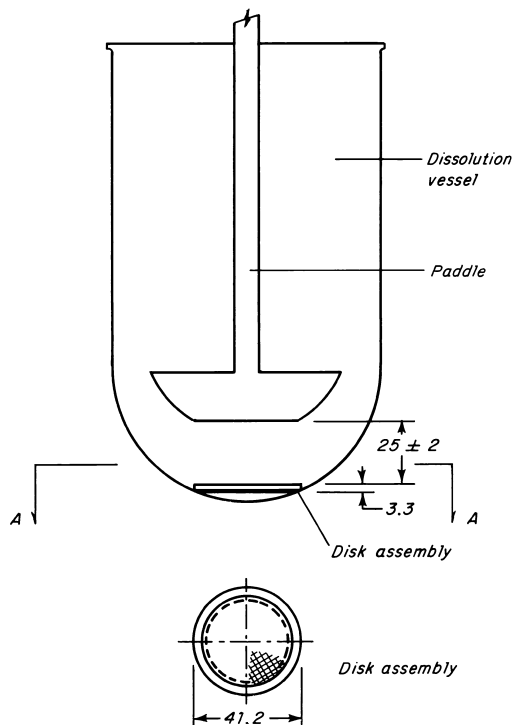


Fig. 2. Paddle over Disk.

(All measurements are expressed in mm unless noted otherwise.)

**Performance Verification Test and Dissolution Medium**—Proceed as directed for *Apparatus 2* in *Dissolution* (711).

**Procedure**—Place the stated volume of the *Dissolution Medium* in the vessel, assemble the apparatus without the disk assembly, and equilibrate the medium to  $32 \pm 0.5^\circ$ . Apply the transdermal system to the disk assembly, ensuring that the release surface of the system

is as flat as possible. The system may be attached to the disk by applying a suitable adhesive to the disk assembly. Dry for 1 minute. Press the system, release surface side up, onto the adhesive-coated side of the disk assembly. If a membrane<sup>3</sup> is used to support the system, it should be applied in such a way that no air bubbles occur between the membrane and the release surface. Place the disk assembly flat at the bottom of the vessel with the release surface facing up and parallel to the edge of the paddle blade and surface of the *Dissolution Medium*. The bottom edge of the paddle should be  $25 \pm 2$  mm from the surface of the disk assembly. Immediately start operation of the apparatus at the rate specified in the monograph. At each sampling time interval, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the blade, not less than 1 cm from the vessel wall. Perform the analysis on each sampled aliquot as directed in the individual monograph, correcting for any volume losses, as necessary. Repeat the test with additional transdermal systems.

**Sampling Time**—The test time points, generally three, are expressed in hours. Specimens should be withdrawn within a tolerance of  $\pm 15$  minutes or  $\pm 2\%$  of the stated time; select the tolerance that results in the narrowest time interval.

**In Vitro Release Criteria**—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table 1* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either  $L_1$  or  $L_2$ .

Page 7 of 28 — Time: 16:22 — Date: 2/5/09 Instance: g:/Pf/Production/Final PF35(3)/m4034.xml Template: s:/Pf/Template/PFRRedesign/PFR-pf-server-2009.3f

Acceptance Table 1

Level	Number Tested	Criteria
$L_1$	6	No individual value lies outside the stated range.
$L_2$	6	The average value of the 12 units ( $L_1 + L_2$ ) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range.
$L_3$	12	The average value of the 24 units ( $L_1 + L_2 + L_3$ ) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average of the stated range, and none of the units is outside the stated range by more than 20% of the average of the stated range.

### III. b. Apparatus 6 (Rotating Cylinder Method)

**Apparatus**—Use the vessel assembly from *Apparatus 1* as described in *Dissolution* <711>, but replace the basket and shaft with a stainless steel cylinder stirring element and maintain the temperature at  $32 \pm 0.5^\circ$  during the test. The shaft and cylinder components of the stirring element are fabricated from stainless steel to the specifications shown in *Figure 3*. The dosage unit is placed on the cylinder at the beginning of each test. The distance between the inside bottom of the vessel and the cylinder is maintained at  $25 \pm 2$  mm during the test.

**Dissolution Medium**—Use the medium specified in the individual monograph (see *Dissolution* <711>).

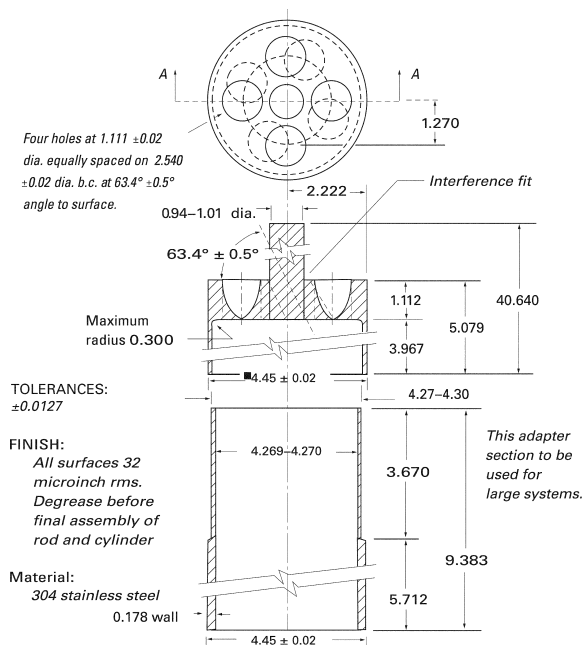


Fig. 3. Cylinder Stirring Element (5).

(All measurements are expressed in cm unless noted otherwise.)

**Procedure**—Place the stated volume of the *Dissolution Medium* in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, and equilibrate the *Dissolution Medium* to  $32 \pm 0.5^\circ$ . Unless otherwise directed in the individual monograph, prepare the test system before the test as follows: remove



the protective liner from the system, and place the adhesive side on a piece of Cuprophan (4) membrane that is not less than 1 cm larger on all sides than the system. Place the system, Cuprophan-covered side down, on a clean surface, and apply a suitable adhesive (6) to the exposed Cuprophan borders. If necessary, apply additional adhesive to the back of the system. Dry for 1 minute. Carefully apply the adhesive-coated side of the system to the exterior of the cylinder so that the long axis of the system fits around the circumference of the cylinder. Press the Cuprophan covering to remove trapped air bubbles. Place the cylinder in the apparatus, and immediately rotate at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a quantity of *Dissolution Medium* for analysis from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating cylinder, not less than 1 cm from the vessel wall. Perform the analysis as directed in the individual monograph, correcting for any volume losses as necessary. Repeat the test with additional transdermal drug delivery systems.

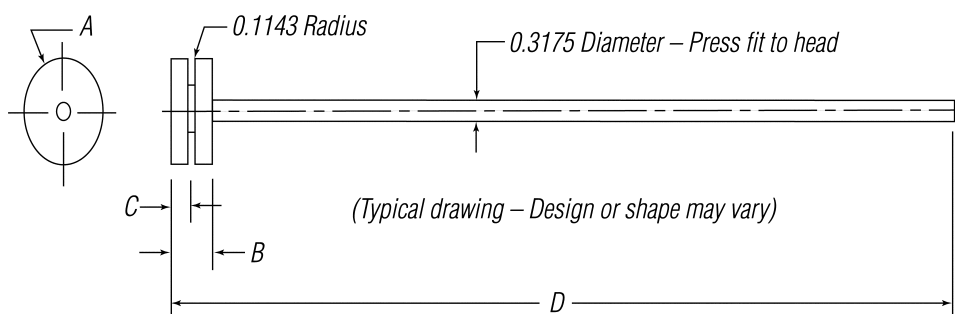
**Sampling Time**—Proceed as directed for *Apparatus 5 (Paddle Over Disk Method)*.

**In Vitro Release Criteria**—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from

the system conform to *Acceptance Table 1* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either  $L_1$  or  $L_2$ .

### III. c. Apparatus 7 (Reciprocating Holder Method)

**Apparatus**—The assembly consists of a set of volumetrically calibrated or tared solution containers made of glass or other suitable inert material, a motor and drive assembly to reciprocate the system vertically and to index the system horizontally to a different row of vessels automatically if desired, and a set of suitable sample holders (see *Figure 4 (7)* and *Figures 5a* and *5b*). The solution containers are partially immersed in a suitable water bath of any convenient size that permits maintaining the temperature,  $T$ , inside the containers at  $32 \pm 0.5^\circ$  or within the allowable range, as specified in the individual monograph, during the test. No part of the assembly, including the environment in which the assembly is placed, should contribute motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating sample holder. An apparatus that permits observation of the system and holder during the test is preferable. Use the size container and sample holder specified in the individual monograph.



Dimensions are in centimeters

System <sup>a</sup>	HEAD			Material <sup>b</sup>	ROD		O-RING
	A (Diameter)	B	C		D	Material <sup>c</sup>	(not shown)
1.6cm <sup>2</sup>	1.428	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-113-V884-75
2.5cm <sup>2</sup>	1.778	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-016-V884-75
5cm <sup>2</sup>	2.6924	0.7620	0.3810	SS/VT	8.890	SS/P	Parker 2-022-V884-75
7cm <sup>2</sup>	3.1750	0.7620	0.3810	SS/VT	30.48	SS/P	Parker 2-124-V884-75
10cm <sup>2</sup>	5.0292	0.6350	0.3505	SS/VT	31.01	SS/P	Parker 2-225-V884-75

<sup>a</sup> Typical system sizes.

<sup>b</sup> SS/VT=Either stainless steel or virgin Teflon.

<sup>c</sup> SS/P=Either stainless steel or Plexiglas.

Fig. 4. Reciprocating Disk Sample Holder (7).

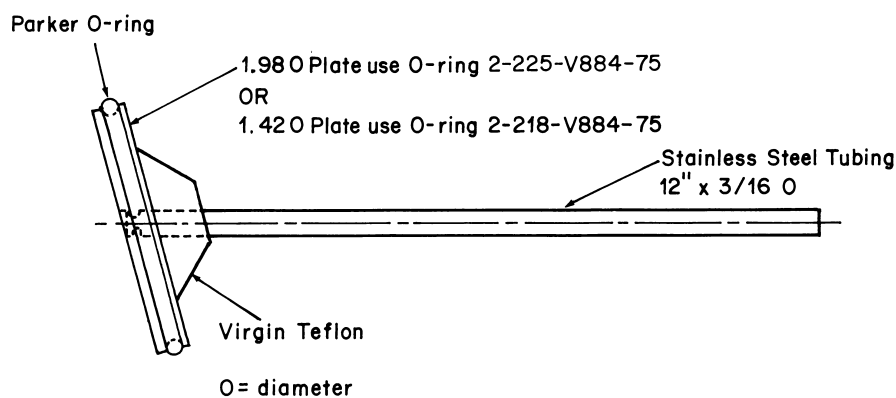


Fig. 5a. Transdermal System Holder—Angled Disk.

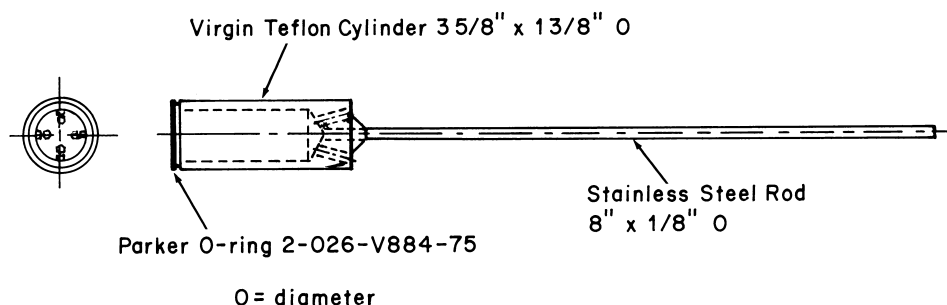


Fig. 5b. Transdermal System Holder—Cylinder

**Preparation A**—Attach the system to be tested to a suitable sample holder with 2-cyano acrylate glue.

**Preparation B**—Press the system onto a dry, unused piece of Cuprophane (4), nylon netting, or equivalent with the adhesive side against the selected substrate, taking care to eliminate air bubbles between the substrate and the release surface. Attach the system to a suitably sized sample holder with a suitable O-ring so that the back of the system is adjacent to and centered on the bottom of the disk-shaped sample holder or centered around the circumference of the cylindrical-shaped sample holder. Trim the excess substrate with a sharp blade.

**Preparation C**—Attach the system to a suitable holder as described in the individual monograph.

**Dissolution Medium**—Use the *Dissolution Medium* specified in the individual monograph (see *Dissolution* (711)).

**Procedure**—Suspend each sample holder from a vertically reciprocating shaker so that each system is continuously immersed in an accurately measured volume of *Dissolution Medium* within a calibrated container pre-equilibrated to temperature, *T*. Reciprocate at a frequency of about 30 cycles/minute with an amplitude of about 2 cm, or as specified in the individual monograph, for the specified time in the medium specified for each time point. Remove the solution containers from the bath, cool to room temperature, and add sufficient solution (water in most cases) to correct for evaporative losses.

Perform the analysis as directed in the individual monograph. Repeat the test with additional drug delivery systems as required in the individual monograph.

**Sampling Time**—Proceed as directed for *Apparatus 5 (Paddle Over Disk Method)*.

**In Vitro Release Criteria**—Drug release should be measured at least at three time points: the first time point around 1 hour, second around 50% of total drug release, and third around 85% drug release. Unless otherwise specified in the individual monograph, the requirements are met if the quantities of the active ingredients released from the system conform to *Acceptance Table 1* in *Drug Release* (724) for transdermal drug delivery systems, or as specified in the individual monograph. Continue testing through the three levels unless the results conform at either  $L_1$  or  $L_2$ .

#### IV. PRODUCT QUALITY TESTS

General product quality tests that are part of the compendial monograph such as identification, assay, content uniformity (uniformity of dosage units), impurities, pH, water content, and microbial limits; specific tests such as viscosity, tube (content) uniformity, and particle size for topical drug products; and adhesive and leak tests for transdermal drug products should be performed. For details of drug product quality tests for topical and

transdermal dosage forms, see the general chapter *Topical and Transdermal Drug Products—Product Quality Tests* (3).

## REFERENCES

1. Polysulfone membrane filter—possible supplier [www.pall.com](http://www.pall.com), marketed as Tuffryn filters.
2. Disk assembly (stainless support disk) may be obtained from [www.millipore.com](http://www.millipore.com).
3. A suitable device is the watchglass-patch-polytef mesh sandwich assembly available as the Transdermal Sandwich from [www.hansonresearch.com](http://www.hansonresearch.com).
4. Use Cuprophan, Type 150 pm,  $11 \pm 0.5\text{-}\mu\text{m}$  thick, an inert, porous cellulosic material, that is available from [www.medicell.co.uk](http://www.medicell.co.uk) or [www.varianinc.com](http://www.varianinc.com).
5. The cylinder stirring element is available from [www.varianinc.com](http://www.varianinc.com).
6. Use Dow Corning, MD7-4502 Silicone Adhesive 65% in ethyl acetate, or the equivalent.
7. The reciprocating disk sample holder may be purchased from [www.varianinc.com](http://www.varianinc.com). ■1S (USP33)