BRIEFING

⟨1724⟩ Performance Tests for Topical Drug Products. Based on comments received, it is proposed to transfer parts of the General Chapter *Topical and Transdermal Drug Products - Product Product Performance Test* ⟨725⟩, published in *PF* 35(3) [May - June 2009] to a new informational chapter.

(BPC05 M. Marques) RTS—C87463

Add the following:

■⟨1724⟩ PERFORMANCE TESTS FOR TOPICAL DRUG PRODUCTS

I. INTRODUCTION

Product performance tests are conducted to assess drug release from finished pharmaceutical dosage forms. Although product performance tests are not a measure of bioavailability, these tests have the ability to detect changes in drug release from drug products that may have the potential to alter the biological performance of the drug in the dosage form. Those changes may be related to the active or to the excipients present in the formulation, physical and/or chemical attributes of the finished formulation, manufacturing variables, shipping and storage effects, aging effects and other formulation and/or process factors critical to the performance of the pharmaceutical dosage form.

Several product performance test procedures for in vitro drug release from transdermal systems are described in the General Chaper *Drug Release* ⟨724⟩

At present, of the various topical semisolid dosage forms, a product performance test is available only for creams, ointments, and gels. The test employs a vertical diffusion cell (VDC) system. The description and procedures for VDC systems are detailed in the General Chapter *Drug Release* ⟨724⟩. The VDC system is commonly used as a product development tool for screening product formulations. It also may be used to assure product sameness after process and/or formulation changes in approved semisolid dosage forms (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* (available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070930.pdf).

This chapter provides general information for testing in vitro performance of topical semisolid drug products.

II. IN VITRO PRODUCT PERFORMANCE TEST

II.A VERTICAL DIFFUSION CELL TEST METHOD

Theory - The vertical diffusion cell (VDC) is a reliable and reproducible means of measuring drug release from semisolid dosage forms. A thick layer of the semisolid product under evaluation is placed in contact with dissolution (receptor) medium in a reservoir. Diffusive communication between the delivery system and the dissolution (receptor) medium 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. Samples are withdrawn from the reservoir at various times. In most cases, a four to six-hour period is all that is needed to characterize drug release from a semisolid and, when this is the case, samples are usually withdrawn hourly.

After a short lag period, release of drug from the semisolid dosage form in the VDC is kinetically described by diffusion of a chemical out of a semi-infinite medium into a sink. The momentary release rate tracks the depth of

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penetration of the forming gradient within the semisolid. Beginning at the moment when the receding boundary layer's diffusional resistance assumes dominance of the kinetics of release, the amount of the drug released, M, becomes proportional to

$$\sqrt{t}$$

(where t = time) for solution, suspension, or emulsion semisolid system alike. The momentary rate of drug release, dM/dt, becomes proportional to

$$\frac{1}{\sqrt{t}}$$

, which reflects the slowing of drug release with the passage of time.The reservoir is kept large so that drug release into a medium remains highly dilute over the entire course of the experiment relative to the concentration of drug dissolved in the semisolid. In this circumstance, drug release is said to take place into a diffusional sink.

When a drug is totally in solution in the dosage form, the amount of drug released as a function of time can be described by Equation 1:

$$M=2xC_0\sqrt{\frac{Dt}{\pi}}$$

where M is the amount of drug released into the sink per cm^3, C_0 is the drug concentration in the releasing matrix, and D is the drug diffusion coefficient through the matrix.

A plot of M versus

$$\sqrt{t}$$

will be linear with a slope of

$$2xC_0\sqrt{\frac{D}{\pi}}$$

.

Equation 2 describes drug release when the drug is in the form of a suspension in the dosage form:

$$M=\sqrt{2\times D_m\times C_S\left(Q-\frac{C_S}{2}\right)\times t}$$

, where C_s is the drug solubility in the releasing matrix, D_m is the drug diffusion coefficient in the semisolid matrix, and Q is the total amount of the drug in solution and suspended in the matrix. When $Q >> C_s$, Equation 2 simplifies to Equation 3:

$$M=\sqrt{2\times Q\times D_m\times C_s\times t}$$

. A plot of M versus

$$\sqrt{t}$$

will be linear with a slope of

$$M=\sqrt{2\times Q\times D_m\times C_s}$$

.

Coarse particles may dissolve so slowly that the moving boundary layer recedes to some extent behind the particles. That situation introduces noticeable curvature in the

$$\sqrt{t}$$

plot because of a particle size effect.

During release rate experiments, every attempt should be made to keep the composition of the formulation intact over the releasing period.

In Vitro Drug Release Using the VDC - The VDC system is composed of 6 cell units. Each VDC cell assembly consists of two chambers, a donor chamber and a receptor chamber, separated by a membrane and held together by a clamp or other means (see *Apparatus 8*, under *Drug release* ⟨724⟩). Other diffusion cells, that are similar in general design, can also be used. In the donor compartment, the semisolid dosage form sample sits on a synthetic, inert, highly permeable support membrane. For Apparatus 8a, the sample sits on the support membrane within the cavity of the sample chamber covered with a glass disk.

Typically, 200 to 400 mg of the semisolid sample is used. Diffusive communication between the semisolid sample and the reservoir takes place through the support membrane. The membrane keeps the drug product sample and receptor medium separate and distinct. The release rate experiment is carried out at $32 \pm 2^{\circ}$, except in the case of vaginal creams when the temperature should be $37 \pm 2^{\circ}$. Sampling generally is performed over a 4 - 6 hours time period, and the volume withdrawn is replaced with fresh receptor medium. To achieve sink condition, the receptor medium must have a high capacity to dissolve the drug, and the drug concentration in the receptor medium should not exceed 10% of the concentration of the drug dissolved at the end of the test. For each cell, the amount of drug released ($\mu g/cm^2$) at each sampling time (t_1, t_2, etc.) is determined , and the amount released plotted versus

$$\sqrt{t}$$

. The slope of the resulting line is a measure of the rate of drug release, or flux. The test is conducted with a group of 6 cells per test run. The average of 12 slopes (i.e., 2 runs of 6 cells) is a measure of the drug release rate from the dosage form and serves as the standard for the drug product tested.

II.A.B VERTICAL DIFFUSION CELL APARATUS

The vertical diffusion cell (VDC) assembly consists of two chambers, a donor chamber and a receptor chamber, separated by a membrane and held together by a clamp or other suitable means. Usually a set of six cell assemblies are operated together at one time (i.e., single run). A heating jacket or a suitable device should be used to maintain the temperature within the cell. This type of cell is commonly used for testing *in vitro* drug release rate from topical drug products such as creams, gels, and ointments. Alternative diffusion cell types that conform to the same general cell design and size can be used (see Figure 5 - model A, Figure 6 - model B, and Figure 7 - model C).

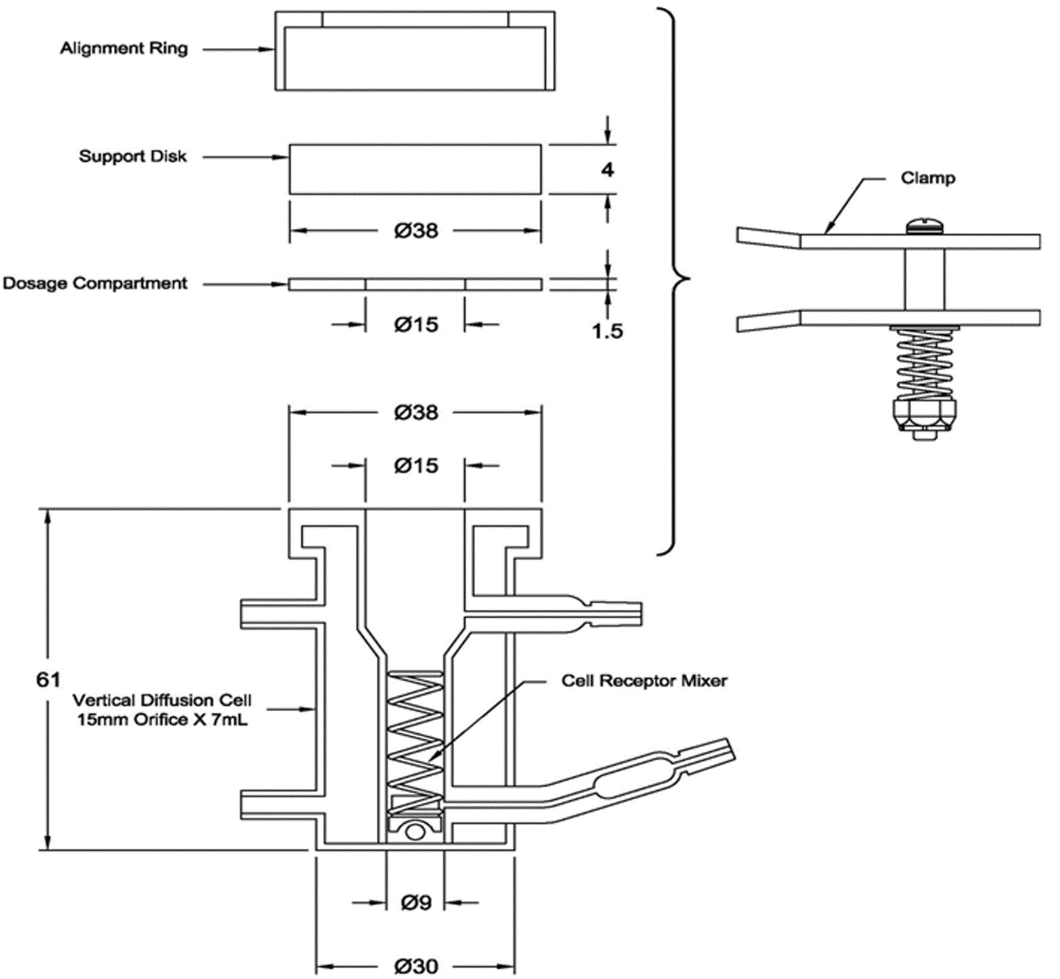

Figure 5 - Vertical Diffusion Cell - model A

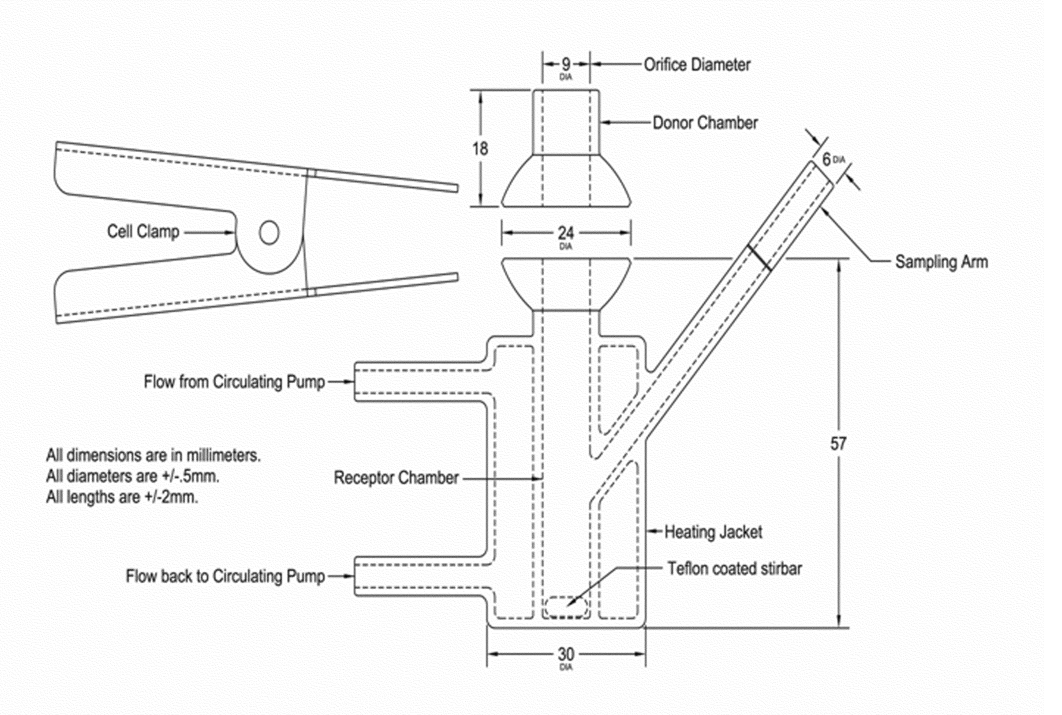

Figure 6 - Vertical Diffusion Cell - model B

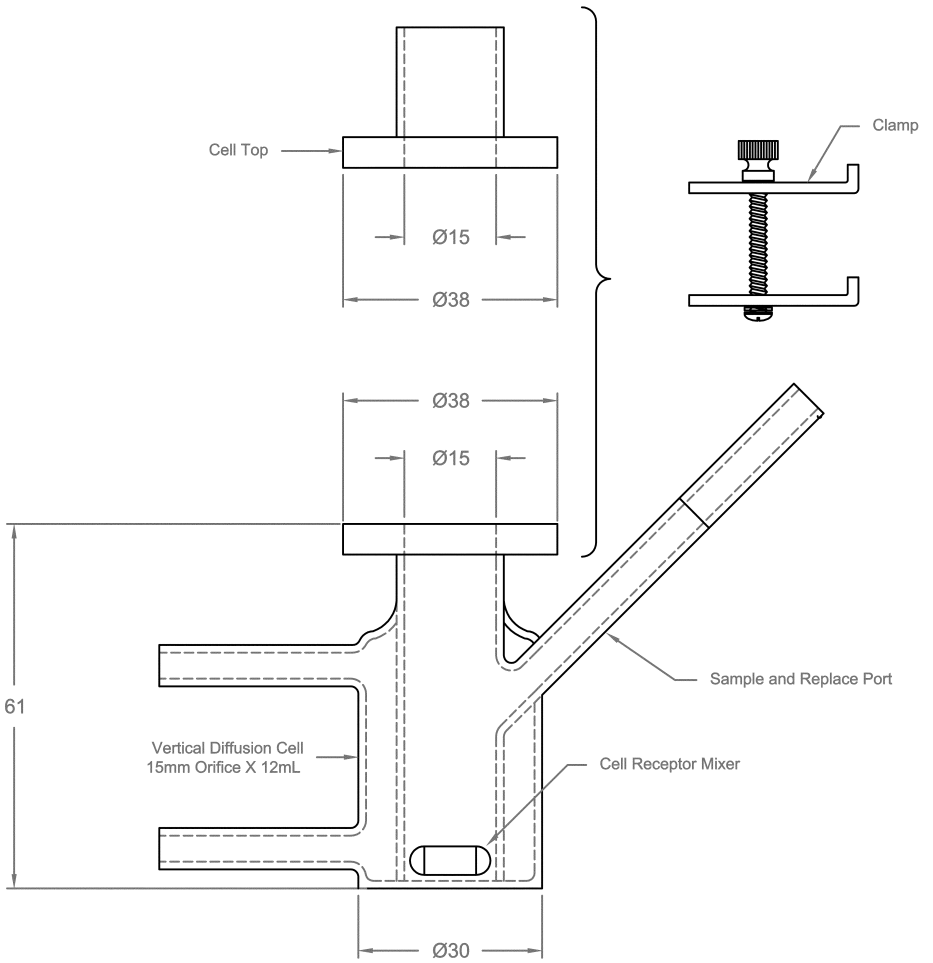

Figure 7- Vertical Diffusion Cell - model C

The VDC body (i.e., donor and receptor chambers) 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 cell assembly materials should react with, or adsorb, or absorb the test product or samples. The semisolid dosage form is placed on a membrane within the cavity of the dosage chamber that can be occluded. The diameters of the orifices of the donor chamber and the receptor chamber, which defines the dosage delivery surface area for the test should be sized within ± 5% of the specified diameter. However, the diameter of the donor chamber orifices may vary depending on the application. The receptor chamber orifice should never be smaller than the orifice of the donor chamber but should be fabricated to the same size as the donor chamber orifice. The design of the VDC should facilitate proper alignment of the donor chamber and the receptor orifice. The receptor chamber should be manufactured consistently with uniform height and geometry. The cells should appear the same, and their internal receptor volumes should fall within ± 5% of their specified volume.

Model A - The thickness of the sample chamber normally is 1.5 mm. This thickness should be sized within ± 10% of the specified thickness. The glass support disk is used to occlude the semisolid dosage form. Cell receptor mixer and stirrer magnet are used as the internal stirring mechanism.

Model B and C - A magnetic stirring bar is used as the internal stirring mechanism.

METHODS AND PROCEDURES

Procedures

Before initiating testing, determine the volume of each VDC with the internal stirring device in place.

The temperature of the receptor medium should be maintained at 32 ± 2°, or 37 ±2° for vaginal preparations, during the entire test.

The rotational stirring rate tolerance should be ± 5% of the rate in the method (normally 600 rpm). The rate of stirring should ensure adequate mixing of the receptor medium during the test period.

Samples should be obtained at the specified times in the method within a tolerance of ±2% or ±2 min, whichever is lower.

Unless otherwise specified in the method, the qualification of the apparatus has been verified when it has been determined that the test temperature and stirring rate are within their specified requirements and a satisfactory performance verification test (i.e., drug release rate) result.

Unless otherwise specified in the method, degas the medium using an appropriate technique. With the stirring mechanism in place, fill the receptor chamber with the specified medium with the stirrers rotating and a positive meniscus covering the top of each cell. Allow time for the medium to equilibrate to the specified temperature. Stop the stirrer before introducing the test sample into the cell. If necessary, saturate the membrane in the specified medium (generally receptor medium) for 30 min.

Model A - Place the membrane on the sample chamber and invert. Apply the material to be tested into the cavity of the sample chamber, spread the semisold out to fill the entire cavity of the sample chamber. Place the filled sample chamber on the receptor chamber with the membrane down and in contact with the receptor medium. During this procedure it is important to ensure that there are no bublles beneath the membrane. Then assemble the complete cell. When the assembly of all donor and receptor chambers and remaining cell components (i.e., disk, alignment ring and clamp) have been completed, turn on the stirring device, which constitutes the start of the test, time zero.

Models B and C - Place the membrane on the receptor chamber in contact with the receptor medium. During this procedure it is important to ensure that there are no bubbles beneath the membrane. Place the donor chamber on the membrane, attach the pinch clamp tight. Apply the material to be tested into the cavity of the donor chamber, and spread the material out to fill the entire donor chamber cavity. Unless otherwise specified in the method, occlude the donor compartment. When all components are in place, turn on the stirring device, which constitutes start of the test, time zero.

Procedure —Sampling is generally performed over a 4 - 6 hr time period. Follow the specified sampling procedure and collect an aliquot form each cell receptor chamber for analysis. With the stirrer stopped, replace the sampled volume with fresh medium warmed to the specific temperature using a sampling syringe, adn resume stirring. Ensure that during the sampling and medium replenishment process(es) that bubbles are not introduced into the cell.

Determine the amount of the drug in the sampled medium using a specific analytical method, e.g., HPLC.

II.A.C 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 manufacturing process. The re-

lease rate of a given drug product from different manufacturers is likely to be different. It is assumed that drug release from the product is linked to the clinical batch.

Unless otherwise specified in the individual product specification, the release requirements are met if the following have been achieved:

Amount released ($\mu g/cm^2$) at a given time (t_1, t_2, etc.) is calculated for each sample:

Amount released at $t_1 = (A_U/A_S) \times C_S \times 1000 \times (V_C/A_0)$

Amount released at $t_2 = (A_U/A_S) \times C_S \times 1000 \times (V_C/A_0) + (AR_{t1} \times (V_S/V_C))$

$$\text{Amount released } t_n = (A_U/A_S) \times C_S \times 1000 (V_C/A_0) + \sum_{i=1}^{n-1} (AR_{tn-1} (V_S/V_C))$$

A_U = response (e.g., peak area, or peak height or absorbance) obtained from Sample solution

A_S = average response (e.g., peak area, or peak height or absorbance) obtained from of the Standard solution

C_S = concentration of the Standard solution (mg/mL)

V_C = volume of the diffusion cell (mL)

A_R = amount of drug released ($\mu g/cm2$)

A_0 = area of the orifice (cm2)

V_S = volume of sample taken (mL)

For each cell, the individual amount of drug released is plotted versus time, and the slope of the resulting line, rate of drug release or flux, is determined. The average of 12 (2 runs of 6 cells) slopes represents the drug release rate of the dosage form and serves as the standard for the drug product.

Application of Drug Release - The product performance test can be used to assess sameness of the drug product after post-approval changes or sucessive batch release comparison. This is illustrated by the following example in which the initial drug product batch is referred as Reference Batch (R) and the changed or subsequent batch is referred to as Test Batch (T). The individual amounts of drug released from R is plotted versus time, and the resulting slopes are determined. Those are the reference slopes. The process is repeated for the Test Batch (T).

The T/R slope ratios are calculated for each Test to Reference slope. This procedure is facilitated with a table where the values for the slopes for Test and Reference batches are listed down the left side and accross the top of the table, respectively. The T/R slope ratios are then determined. See example below.

	RS1	RS2	RS3	RS4	RS5	RS6
TS1	T S 1 / RS1	T S 1 / RS2	T S 1 / RS3	T S 1 / RS4	T S 1 / RS5	T S 1 / RS6
TS2	T S 2 / RS1	T S 2 / RS2	T S 2 / RS3	T S 2 / RS4	T S 2 / RS5	T S 2 / RS6
TS3	T S 3 / RS1	T S 3 / RS2	T S 3 / RS3	T S 3 / RS4	T S 3 / RS5	T S 3 / RS6
TS4	T S 4 / RS1	T S 4 / RS2	T S 4 / RS3	T S 4 / RS4	T S 4 / RS5	T S 4 / RS6
TS5	T S 5 / RS1	T S 5 / RS2	T S 5 / RS3	T S 5 / RS4	T S 5 / RS5	T S 5 / RS6
TS6	T S 6 / RS1	T S 6 / RS2	T S 6 / RS3	T S 6 / RS4	T S 6 / RS5	T S 6 / RS6

After the T/R ratios have been calculated, they are ordered from the lowest to the highest. The 8th and 29th T/R ratios are identified and converted to percent (multiplied by 100). To pass first stage testing, those ratios must be within the range of 75% to 133.33%.

If the results do not meet this criterion, 4 additional tests of 6 cells should be performed, resulting in 12 additional slope determinations for the product tested. The T/R slope ratios for all 18 slopes for the product tested are determined. All 324 individual T/R slope ratios are ordered from the lowest to the highest. To pass this second stage testing the 110th and 215th slope ratios must be within the range of 75% to 133.33%.

II.B HOLDING CELL

A sample of semisolid dosage form is placed in an inert holding cell with a suitable membrane separating the dosage form from the receptor medium. The holding cell is positioned at the bottom of a modified, reduced volume dissolution vessel of USP *Apparatus 2* type assembly and stirred with a minipaddle.

II.C USP APPARATUS 4 (FLOW-THROUGH CELL) WITH A TRANS-CAP SEMISOLID CELL

A sample of semisolid dosage form is placed in the trasn-cap cell with a suitable membrane separating the dosage form from the receptor medium. The trans-cap cell with membrane facing upward is inserted into the 22.6 mm flow cell of USP *Apparatus 4 (Flow-through Cell)* (see *Drug Release* ⟨724⟩).

II.D EXTRACTION CELL

A sample of semisolid dosage form is placed in an inert extraction cell with a suitable membrane separating the dosage form from the receptor medium. The test is performed using the USP *Apparatus 2* with the extraction cell positioned at the bottom of the dissolution vessel. ■2-S (*USP34*)