Briefing

⟨3⟩ **Topical and Transdermal Drug Products—Product Quality 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 used to evaluate the in vitro drug release. 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.

(PDF: M. Marques.) RTS—C71036

Add the following:

■⟨3⟩ TOPICAL AND TRANSDERMAL DRUG PRODUCTS—PRODUCT QUALITY TESTS

i. **Introduction**
ii. **Glossary of Terms**
iii. **Product Quality Tests for All Topically Applied Drug Products**
   a. **Product Quality Tests for Topical Drug Products Intended for Local Action**
   b. **Product Quality Tests for Transdermal Drug Products**
iv. **Product Performance Test for Topical Drug Products**
v. **In Vitro Drug Release from Semisolid Dosage Forms**
   a. **Theory**
   b. **Application of In Vitro Drug Release**

I. INTRODUCTION

Drug products topically administered via the skin fall into two general categories: those applied to achieve local action and those to achieve systemic effects. Local action can occur at or on the surface of the skin (the stratum corneum) and also in the epidermis and/or dermis. Locally acting drug products include creams, gels, ointments, pastes, suspensions, lotions, foams, sprays, aerosols, and solutions. Creams, ointments, and gels are generally referred to as semisolid dosage forms. Drug products applied to the skin to achieve systemic effects are referred to as self-adhering transdermal patches or transdermal drug delivery systems (TDS).

Quality tests with procedures and acceptable criteria for both types of topically administered drug products can be divided into those that assess general quality attributes and those that assess performance. The former include identification, assay (strength), content uniformity, pH, microbial limits, and minimum fill. The latter assess drug release from the finished dosage form. For locally acting topical drug products, a product performance test exists only for semisolid formulations. TDS are physical devices that are applied to the skin and vary in their composition and method of fabrication. They release their active ingredients by different mechanisms. Several product performance tests are available to assess in vitro drug release from TDS. Performance tests considered for topically applied products may also be applicable to drug products of similar composition when administered by other routes of administration, e.g., ophthalmic drug products.

II. GLOSSARY OF TERMS

Definitions of topical drug products, brief information about their manufacture, and a glossary of dosage form names can be found in the general information chapter *Pharmaceutical Dosage Forms* ⟨1151⟩.

Absorption Bases—This class of bases may be divided into two groups: bases that permit the incorporation of aqueous solutions with the formation of a water-in-oil emulsion (e.g., *Hydrophilic Petrolatum* and *Lanolin*, both *USP*), and water-in-oil emulsions that permit the incorporation of additional quantities of aqueous solutions (e.g., *Lanolin*, *USP*). Absorption bases also are useful as emollients.

Choice of Base—The choice of an ointment base depends on many factors, such as the action desired, the nature of the medicament to be incorporated and its bioavailability and stability, and the requisite shelf life of the finished product. In some cases, it is necessary to use a base that is less than ideal in order to achieve the stability required. Drugs that hydrolyze rapidly, for example, are more stable in hydrocarbon bases than in bases that contain water, even though they may be more effective in the latter.

Collodion—Collodion (pyroxylin solution; see *USP* monograph *Collodion*) is a solution of nitrocellulose in ether and acetone, sometimes with the addition of alcohol. As the volatile solvents evaporate, a dry celluloid-like film is left on the skin. Because the medicinal use of a collodion depends on the formation of a protective film, the film should be durable, tenacious in adherence, flexible, and occlusive.

Creams—Creams are semisolid dosage forms that contain one or more drug substances dissolved or dispersed in a suitable base. This term traditionally has been applied to semisolids that possess a relatively soft, spreadable consistency formulated as either water-in-oil or oil-in-water emulsions. However, more recently the term has been restricted to products consisting of oil-in-water emulsions or aqueous microcrystalline dispersions of long-chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable.

Emulsions—Emulsions are viscid multiphase systems in which one or more liquids are dispersed throughout another immiscible liquid in the form of small droplets. When oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated an oil-in-water emulsion. Conversely, when water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated a water-in-oil emulsion. Emulsions are stabilized by emulsifying agents that prevent coalescence, the merging of small droplets into larger droplets and, ultimately, into a single separated phase. Emulsifying agents (surfactants) act by concentrating at the interface between the immiscible liquids, thereby providing a physical barrier that reduces the tendency for coalescence. Surfactants also reduce the interfacial tension between the phases, facilitating the formation of small droplets upon mixing. The term emulsion is not used if a more specific term is applicable, e.g., cream or ointment.

Foams—Foams are emulsified systems packaged in pressurized containers or special dispensing devices that contain dispersed gas bubbles, usually in a liquid continuous phase, that when dispensed have a fluffy, semisolid consistency.

Gels—Gels (sometimes called jellies) are semisolid systems that consist of either suspensions composed of small inorganic particles or large organic molecules interpenetrated by a liquid. When the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system (e.g., *Aluminum Hydroxide Gel*, *USP*). In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes referred to as a magma (e.g., *Bentonite Magma*, *NF*). Both gels and magmas may be thixotropic, forming semisolids after standing and becoming liquid when agitated. They should be shaken before use to ensure homogeneity and should be labeled to that effect (see *Topical Suspensions*, below). Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid with no apparent boundary between the dispersed macromolecule and liquid.

Hydrocarbon Bases—Hydrocarbon bases, known also as oleaginous ointment bases, are represented by *White Petrolatum* and *White Ointment* (both *USP*). Only small amounts of an aqueous component can be incorporated into these bases. Hydrocarbon bases keep medicaments in prolonged contact with the skin and act as occlusive dressings. These bases are used chiefly for their emollient effects and are difficult to wash off. They do not ''dry out'' or change noticeably on aging.

Lotions—Although the term lotion may be applied to a solution, lotions usually are fluid, somewhat viscid emulsion dosage forms for external application to the skin. Lotions share many characteristics with creams. See *Creams, Topical Solutions,* and *Topical Suspensions*, herein.

Ointments—Ointments are semisolids intended for external application to the skin or mucous membranes. They usually contain less than 20% water and volatiles and more than 50% hydrocarbons, waxes, or polyols as the vehicle. Ointment bases recognized for use as vehicles fall into four general classes: hydrocarbon bases, absorption bases, water-removable bases, and water-soluble bases. Each therapeutic ointment possesses as its base one of these four general classes.

Ophthalmic Ointments—Ophthalmic ointments are semisolids for application to the eye. Special precautions must be taken in the preparation of ophthalmic ointments. They are manufactured from sterilized ingredients under rigidly aseptic conditions, must meet the requirements under *Sterility Tests* ⟨71⟩, and must be free of large particles. The medicinal agent is added to the ointment base either as a solution or as a micronized powder.

Pastes—Pastes are semisolid dosage forms that contain a high percentage (often $\geq$ 50%) of finely dispersed solids with a stiff consistency and intended for topical application. One class is made from a single-phase aqueous gel (e.g., *Carboxymethylcellulose Sodium Paste*, *USP*). The other class, the fatty pastes (e.g., *Zinc Oxide Paste*, *USP*), consists of thick, stiff ointments that do not ordinarily flow at body temperature and therefore serve as protective coatings over the areas to which they are applied.

Powders—Powders are solids or mixture of solids in a dry, finely divided state for external (or internal) use.

Sprays—Sprays are products formed by the generation of droplets of solution containing dissolved drug for application to the skin or mucous membranes. The droplets may be formed in a variety of ways but generally result when a liquid is forced through a specially designed nozzle assembly. One example of a spray dosage form is a metered-dose topical transdermal spray that delivers a precisely controlled quantity of solution or suspension on each activation.

Transdermal Delivery Systems (TDS)—TDS are self-contained, discrete dosage forms that, when applied to intact skin, are designed to deliver the drug(s) through the skin to the systemic circulation. Systems typically comprise an outer covering (barrier), a drug reservoir that may have a drug release-controlling membrane, a contact adhesive applied to some or all parts of the system and the system/skin interface, and a protective liner that is removed before the patient applies the system. The dose of these systems is defined in terms of the release rate of the drug(s) from the system and surface area of the patch and is expressed as mass per unit time for a given surface area. With these drug products, the skin typically is the rate-controlling membrane for the drug input into the body. The total duration of drug release from the system and system surface area also may be stated.

TDS work by diffusion: the drug diffuses from the drug reservoir, directly or through the rate-controlling membrane and/or contact adhesive if present, and then through the skin into the general circulation. Typically, modified-release systems are designed to provide drug delivery at a constant rate so that a true steady-state blood concentration is achieved and maintained until the system is removed. Following removal of the system, blood concentration declines at a rate consistent with the pharmacokinetics of the drug.

Topical Aerosols—Topical aerosols are products that are packaged under pressure. The active ingredients are released in the form of fine liquid droplets or fine powder particles upon activation of an appropriate valve system. A special form is a metered-dose aerosol that delivers an exact volume (dose) per each actuation.

Topical Solutions—Topical solutions are liquid preparations that usually are aqueous but often contain other solvents such as alcohol and polyols that contain one or more dissolved chemical substances intended for topical application to the skin or, as in the case of *Lidocaine Oral Topical Solution*, *USP*, to the oral mucosal surface.

Topical Suspensions—Topical suspensions are liquid preparations that contain solid particles dispersed in a liquid vehicle intended for application to the skin. Some suspensions labeled as lotions fall into this category.

Water-removable Bases—Water-removable bases are oil-in-water emulsions (e.g., *Hydrophilic Ointment*, *USP*) and are more correctly called creams (see *Creams*, above). They also are described as ''water-washable'' because they may be readily washed from the skin or clothing with water, an attribute that makes them more acceptable for cosmetic purposes. Some medicaments may be more effective in these bases than in hydrocarbon bases. Other advantages of the water-removable bases are that they can be diluted with water and that they favor the absorption of serous discharges in dermatological conditions.

Water-soluble Bases—This group of so-called ''greaseless ointment bases'' comprises water-soluble constituents. *Polyethylene Glycol Ointment*, *NF*, is the only pharmacopeial preparation in this group. Bases of this type offer many of the advantages of the water-removable bases and, in addition, contain no water-insoluble substances such as petrolatum, anhydrous lanolin, or waxes. They are more correctly called gels (see *Gels*, above).

III. PRODUCT QUALITY TESTS FOR ALL TOPICALLY APPLIED DRUG PRODUCTS

Universal tests are listed below and should be applied to all topically applied drug products.

Description—A qualitative description of the dosage form should be provided. The acceptance criteria should include the final acceptable appearance. If color changes during storage, a quantitative procedure may be appropriate. It specifies the content or the label claim of the article.

Identification—Identification tests are discussed in *Procedures* under *Tests and Assays* in the *General Notices and Requirements*. Identification tests should establish the identity of the drug or drugs present in the article and should discriminate between compounds of closely related structure that are likely to be present. Identity tests should be specific for the drug substances. The most conclusive test for identity is the infrared absorption spectrum (see *Spectrophotometry and Light-Scattering* ⟨851⟩ and *Spectrophotometric Identification Tests* ⟨197⟩). If no suitable infrared spectrum can be obtained, other analytical techniques can be used. Near infrared (NIR) or Raman spectrophotometric methods also could be acceptable for the sole identification of the drug product formulation (see *Near-infrared Spectrophotometry* ⟨1119⟩ and *Raman Spectroscopy* ⟨1120⟩). Identification solely by a single chromatographic retention time is not regarded as specific. However, the use of two chromatographic procedures for which the separation is based on different principles or a combination of tests in a single procedure can be acceptable. See *Chromatography* ⟨621⟩ and *Thin-layer Chromatographic Identification Test* ⟨201⟩.

Assay—A specific and stability-indicating test should be used to determine the strength (content) of the drug product. See *Antibiotics—Microbial Assays* ⟨81⟩, *Chromatography* ⟨621⟩, or *Assay for Steroids* ⟨351⟩. In cases when the use of a nonspecific assay is justified (e.g., *Titrimetry* ⟨541⟩), other supporting analytical procedures should be used to achieve overall specificity. A specific procedure should be used when there is evidence of excipient interference with the nonspecific assay.

Impurities—Process impurities, synthetic by-products, and other inorganic and organic impurities may be present in the drug substance and excipients used in the manufacture of the drug product. These impurities are controlled by the drug substance and excipients monographs. Organic impurities arising from the degradation of the drug substance and those arising during the manufacturing process of the drug product should be monitored.

In addition to the universal tests listed above, the following specific tests may be considered on a case-by-case basis.

Physicochemical Properties—These are properties such as *pH* ⟨791⟩, *Viscosity* ⟨911⟩, and *Specific Gravity* ⟨841⟩.

Uniformity of Dosage Units—This test is applicable for TDS and for dosage forms packaged in single-unit containers. It includes both the mass of the dosage form and the content of the active substance in the dosage form. The test can be performed by either content uniformity or weight variation (see *Uniformity of Dosage Units* ⟨905⟩).

Water Content—A test for water content should be included when appropriate (see *Water Determination* ⟨921⟩).

Microbial Limits—The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product. See *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩ and *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* ⟨62⟩).

Antimicrobial Preservative Content—Acceptance criteria for preservative content in multidose products should be established. They should be based on the levels of antimicrobial preservative necessary to maintain the product's microbiological quality at all stages throughout its proposed usage and shelf life (see *Antimicrobial Effectiveness Testing* ⟨51⟩).

Antioxidant Preservative Content—If antioxidant preservatives are present in the drug product, tests of their content normally should be determined.

Sterility—Depending on the use of the dosage form (e.g., ophthalmic preparations), sterility of the product should be demonstrated as appropriate (see *Sterility Tests* ⟨71⟩).

III. a. PRODUCT QUALITY TESTS FOR TOPICAL DRUG PRODUCTS INTENDED FOR LOCAL ACTION

Additional tests for locally acting topical dosage forms are provided in this section. Some of these may also be used for some nitroglycerin semisolids.

Viscosity—Rheological properties such as viscosity of semisolid dosage forms can influence their drug delivery. Viscosity may directly influence the diffusion rate of a drug at the microstructural level. Yet semisolid drug products with comparatively high viscosity still can exhibit high diffusion rates when compared to semisolid products of comparatively lower viscosity. These observations emphasize the importance of rheologic properties of semisolid dosage forms, specifically viscosity, on drug product performance.

Depending on its viscosity, the rheological behavior of a semisolid drug product may affect its application to treatment site(s) and consistency of treatment and thus the delivered dose. Therefore, maintaining reproducibility of a product's flow behavior at the time of release is an important product manufacturing control that manufacturers should use to maintain and demonstrate batch-to-batch consistency. Most semisolid dosage forms, when sheared, exhibit non-Newtonian behavior. Structures formed within semisolid drug products during manufacturing can show a wide range of behaviors, including shear thinning viscosity, thixotropy, and structural damage that may be irreversible or only partially reversible. In addition, the viscosity of a semisolid dosage form is highly influenced by factors such as the inherent physical structure of the product, product sampling technique, sample temperature for viscosity testing, container size and shape, and specific methodology employed in the measurement of viscosity.

A variety of methods can be used to characterize the consistency of semisolid dosage forms, including penetrometry, viscometry, and rheometry. With all methods significant attention is warranted to the shear history of the sample. For semisolids, viscometer geometries typically fall into the following categories: concentric cylinders, cone-plates, and spindles. Concentric cylinders and spindles typically are used for more fluid, flowable semisolid dosage forms. Cone-plate geometries are more typically used when the sample size is small or the test samples are more viscous and less flowable.

When contemplating what viscosity parameter(s) to test, one must consider the properties of the semisolid drug product both ''at rest'' (in its container) and as it is sheared during application. The rheological properties of the drug product at rest can influence the product's shelf life, and its properties under extensive shear can influence its spreadability and, therefore, its application rate that will affect the safety and efficacy of the drug product. Further, although it is necessary to precisely control the temperature of the test sample during the viscosity measurement, one should link the specific choice of the temperature to the intended use of the drug product (e.g., skin temperature for external application effects).

Because semisolid dosage forms frequently display non-Newtonian flow properties, formulators should give close attention to the shear history of the sample being tested, such as the shear applied during the filling operation, shear applied dispensing the product from its container, and shear when introducing the sample into the viscometer. The point of reemphasizing this aspect is that considerable variability and many failures to meet specifications can be directly attributed to a lack of attention to this detail rather than a change of viscosity (or flow properties) of the drug product.

Tube (Content) Uniformity—Tube uniformity is the degree of uniformity of the amount of active drug substance among containers, i.e., tubes containing multiple doses of the semisolid topical product. The uniformity of dosage is demonstrated by assay of top, middle, and bottom samples (typically 0.25–1.0 g) obtained from a tube cut open to withdraw respective samples for drug assay.

Various topical semisolid products may show some physical separation at accelerated storage temperatures because emulsions, creams, and topical lotions are prone to mild separation due to the nature of the vehicle.

The following procedure should be followed for testing tube uniformity of semisolid topical dosage forms:

1. Carefully remove or cut off the bottom tube seal and make a vertical cut up the face of the tube. Then carefully cut the tube around the upper rim and pry open the two ''flaps'' to expose the semisolid.

2. At the batch release and/or designated stability time point remove and test 0.25- to 1.0-g samples from the top, middle, and bottom of a tube. If assay values for those tests are within 90.0%–110.0% of the labeled amount of active drug, and the relative standard deviation (RSD) is not more than 6%, then the results are acceptable.
3. If at least one value of the testing described above is outside 90.0%–110.0% of the labeled amount of drug and none is outside 85.0%–115.0% and/or the RSD is more than 6%, then test an additional three randomly sampled tubes using top, middle, and bottom samples as described. Not more than 3 of the 12 determinations should be outside the range of 90%–110.0% of the labeled amount of drug, none should be outside 85.0%–115.0%, and the RSD should not be not more than 7%.
4. For very small tubes (e.g., 5 g or less), test only top and bottom samples, and all values should be within the range of 90.0%–110.0% of the labeled amount of drug.

pH—When applicable, semisolid drug products should be tested for pH at the time of batch release and designated stability test time points for batch-to-batch monitoring. Because most semisolid dosage forms contain very limited quantities of water or aqueous phase, pH measurements may be warranted only as a quality control measure, as appropriate.

Particle Size—Particle size of the active drug substance in semisolid dosage forms is determined and controlled at the formulation development stage. When applicable, semisolid drug products should be tested for any change in the particle size or habit of the active drug substance at the time of batch release and designated stability test time points (for batch-to-batch monitoring) that could compromise the integrity and/or performance of the drug product, as appropriate.

Ophthalmic Dosage Forms—Ophthalmic dosage forms must meet the requirements of *Sterility Tests* ⟨71⟩. If the specific ingredients used in the formulation do not lend themselves to routine sterilization techniques, ingredients that meet the sterility requirements described under *Sterility Tests* ⟨71⟩, along with aseptic manufacture, may be employed. Ophthalmic ointments must contain a suitable substance or mixture of substances to prevent growth of, or to destroy, microorganisms accidentally introduced when the container is opened during use, unless otherwise directed in the individual monograph or unless the formula itself is bacteriostatic (see *Added Substances* under *Ophthalmic Ointments* ⟨771⟩). The finished ointment must be free from large particles and must meet the requirements for *Leakage* and for *Metal Particles* in *Ophthalmic Ointments* ⟨771⟩. The immediate containers for ophthalmic ointments shall be sterile at the time of filling and closing. It is mandatory that the immediate containers for ophthalmic ointments be sealed and tamper-proof so that sterility is assured at time of first use.

III. b. PRODUCT QUALITY TESTS FOR TRANSDERMAL DRUG PRODUCTS

The product quality tests for TDS drug products include assay, content uniformity, homogeneity, and adhesive.

Uniformity of Dosage Units—This test is applicable for TDS and for dosage forms that are packaged in single-unit containers. It includes both the mass of the dosage form and the content of the active substance in the dosage form. It can be done by either content uniformity or weight variation (see *Uniformity of Dosage Units* ⟨905⟩).

Assay of excipient(s) critical to the performance of the product should be considered; e.g., residual solvent content can affect certain patches.

Adhesive Test—Three types of adhesive tests generally are performed to ensure the performance of the TDS dosage forms. These are the peel adhesion test, tack test, and shear strength test. The peel adhesion test measures the force required to peel away a transdermal patch attached to a stainless steel test panel substrate at panel angles of 90° or 180° following a dwell time of 1 minute and peel rate of 300 mm/minute.

The tack test is used to measure the tack adhesive properties of TDS dosage forms. With this test a probe touches the adhesive surface with light pressure, and the force required to break the adhesion after a brief period of contact is measured.

The shear strength or creep compliance test is a measure of the cohesive strength of TDS dosage forms. Two types of shear testing are performed: dynamic and static. During dynamic testing the TDS is pulled from the test panel at a constant rate. With the static test the TDS is subjected to a shearing force by means of a suspended weight.

Leak Test—A test that is discriminating and capable of detecting sudden drug release, such as leakage, from the TDS should be performed. Although form, fill, and seal TDS are more likely to display leak problems, all TDS should be checked for sudden drug release (dose dumping) during release testing of the dosage form.

IV. PRODUCT PERFORMANCE TEST FOR TOPICAL DRUG PRODUCTS

A performance test for topical drug products must have the ability 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 drug release characteristics from the finished product. The latter have the potential to alter the biological performance of the drug in the dosage form. Those changes may be related to active or inactive/inert ingredients in the formulation, physical or chemical attributes of the finished formulation, manufacturing variables, shipping and storage effects, aging effects, and other formulation factors critical to the quality characteristics of the finished drug product. Product performance tests can serve many useful purposes in product development and in postapproval drug product monitoring. They provide assurance of equivalent performance for products that have undergone postapproval raw material changes, relocation or change in manufacturing site, and other changes as detailed in the FDA's Guidance for Industry SUPAC-SS: *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). In this general chapter, a USP performance test for semi-solid dosage forms to support batch release is considered. Details of the procedure are provided in the general chapter *Topical and Transdermal Drug Products—Product Performance Tests* ⟨725⟩ (proposed).

V. IN VITRO DRUG RELEASE FROM SEMISOLID DOSAGE FORMS

V. a. THEORY

The vertical diffusion cell (VDC) system is a simple, reliable, and reproducible means of measuring drug release from semisolid dosage forms. A thick layer (200–400 mg) of the test semisolid is placed in contact with a reservoir. 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. Samples are withdrawn from the reservoir at various times. In most cases, a 5- to 6-hour time period is all that is needed to characterize drug release from a semisolid, and when this is the case samples usually are withdrawn hourly.

After a short lag period, release of drug from the semisolid dosage form in the VDC system is kinetically describable by diffusion of a chemical out of a semi-infinite medium into a sink. The momentary release rate tracks the depth of 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 $\sqrt{t}$ = time) for solution, suspension, or emulsion semisolid systems alike. The momentary rate of release, *dM/dt*, becomes proportional to $1/\sqrt{t}$, which reflects the slowing of drug release with the passage of time. The reservoir is kept large so that drug release is into a medium that 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 within the dosage form, the amount of drug released as a function of time can be described by:

$$M = 2 \cdot Co\sqrt{D \cdot t / \pi}$$

where:

M = amount of drug released into the sink per cm^2

Co = drug concentration in releasing matrix

D = drug diffusion coefficient through the matrix.

A plot of *M* vs $\sqrt{t}$ will be linear with a slope of

$$2 \cdot Co\sqrt{D / \pi}$$

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

$$M = \sqrt{2 \cdot Dm \cdot Cs(Q - Cs/2)t}$$

where:

Dm = drug diffusion coefficient in the semisolid matrix

Cs = drug solubility in the releasing matrix

Q = total amount of the drug in solution and suspended in the matrix.

When $Q >> Cs$, Equation 2 simplifies to Equation 3.

$$M = \sqrt{2 \cdot Q \cdot Dm \cdot Cs \cdot t}$$

A plot of *M* vs $\sqrt{t}$ will be linear with a slope of $\sqrt{2QDmCs}$.

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 *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 during the releasing period.

V. b. APPLICATION OF DRUG RELEASE

Drug release results can be utilized for purposes such as ensuring product sameness after SUPAC-SS-related changes or successive batch release comparisons. This is illustrated by the following example in which the initial drug batch is referred to as Reference Batch (R) and the changed or subsequent batch is referred to as Test Batch (T). The individual amount released from R is plotted vs time, and the resulting slope is determined. These are the reference slopes (RS). The process is repeated to determine the test slopes (TS).

The T/R ratios are calculated for each Test to Reference Slope. This is facilitated if one creates a table where the TS are listed down the left side of the table and the RS are listed across the top of the table. The T/R ratios are then calculated and entered in the body of the table.

After the T/R ratios have been calculated they are ordered from lowest to highest. The 8th and 29th T/R ratios are extracted and converted to percent (multiply by 100). To pass the first stage these ratios must fall within the range of 75%–133.33%.

If the results do not meet this criterion, the SUPAC-SS Guidance requires that four more tests of six cells each should be run, resulting in 12 additional slopes per product tested. The T/R ratios are calculated for all 18 slopes per product tested. All 324 individual T/R ratios are calculated and ordered lowest to highest. The 110th and the 215th ratios are evaluated against the specification of 75%–133.33%.

Third stage testing is not suggested.■1S (*USP33*)

	RS1	RS2	RS3	RS4	RS5	RS6
TS1	TS1/RS1	TS1/RS2	TS1/RS3	TS1/RS4	TS1/RS5	TS1/RS6
TS2	TS2/RS1	TS2/RS2	TS2/RS3	TS2/RS4	TS2/RS5	TS2/RS6
TS3	TS3/RS1	TS3/RS2	TS3/RS3	TS3/RS4	TS3/RS5	TS3/RS6
TS4	TS4/RS1	TS4/RS2	TS4/RS3	TS4/RS4	TS4/RS5	TS4/RS6
TS5	TS5/RS1	TS5/RS2	TS5/RS3	TS5/RS4	TS5/RS5	TS5/RS6
TS6	TS6/RS1	TS6/RS2	TS6/RS3	TS6/RS4	TS6/RS5	TS6/RS6