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

INTRODUCTION

Topically applied drug products fall into two general categories: those applied to achieve local action and those applied to achieve systemic effects after absorption through the skin into the blood circulation. Local action can occur at or on the surface of the application site (e.g., stratum corneum); in the underlying tissues (e.g., epidermis and/or dermis); and in subcutaneous tissues (e.g., muscle or joint). Topically applied drug products include, but are not limited to, creams, gels, ointments, pastes, suspensions, lotions, foams, sprays, aerosols, solutions, and topical and transdermal delivery systems (TDS). The definitions and descriptions of these dosage forms, as well as brief information on their composition and/or manufacturing processes, can be found in *Pharmaceutical Dosage Forms* ⟨1151⟩.

Procedures and acceptable criteria for testing topically applied drug products can be divided into those that assess general product quality attributes and those that assess product performance. The product quality attributes include the following: description, identification, assay (strength), impurities, physicochemical and structural properties, uniformity of dosage units, water content, pH, apparent viscosity, microbial limits, antimicrobial preservative content, antioxidant content, sterility (if applicable), penetration enhancer content, and other tests that may be product specific. Product performance testing assesses drug release and other attributes that affect drug release from the finished dosage form.

This chapter provides lists of consolidated common product quality test requirements in a concise and coherent fashion. This chapter applies, in whole or in part, when referenced in a drug product monograph (see *General Notices, 3.10 Applicability of Standards*) and includes the quality tests for the specific route of administration. The quality tests listed can be used as appropriate by manufacturers toward the development of new drug product monographs for submission to *USP–NF*.

TDS release their active ingredients by different mechanisms. They can be passive or active. This chapter covers only the tests related to passive TDS.

PRODUCT QUALITY TESTS FOR TOPICAL AND TRANSDERMAL DRUG PRODUCTS

Additional Procedure for Products Packaged in Containers with a Non-Metered Pump

For some tests (e.g., viscosity, assay, etc.), with the exception of the uniformity in containers test, samples need to be collected from the pumped-out product. In these instances, the samples should be collected as follows:

1. Remove cap from container.
2. Fully depress and release the actuator, disposing of any material dispensed, and allowing the pump actuator to return to the initial position after each actuation. Repeat the sequence, as indicated in the patient instructions, until a full amount of material is dispensed.
3. Collect the next material dispensed as the sample. Generally, collect NMT the amount needed to perform a single analysis (for the assay test, typically NMT 2 actuations).

Universal Tests

Universal tests [see International Council for Harmonisation (ICH) guidance *Q6A—Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, available at www.ich.org] are listed as follows and are applicable to all topically applied drug products.

DESCRIPTION

A qualitative description of the drug product should be provided. The acceptance criteria should include the final acceptable appearance of the finished dosage form and packaging. A visual examination should identify changes in color, adhesive migration (i.e., cold flow; see *Cold Flow Test*) for TDS, separations, crystallization, and others that are specific to the drug product. The description should specify the content or the label claim of the article. For TDS, a visual examination should also be done to assess potential use issues with the product. The examination should include an assessment of the difficulty of removing the TDS from the pouch (e.g., due to adhesive migration adhering the system to the pouch); inability to remove the TDS from the pouch without damage to the system; and adhesive residue remaining on the pouch after removal of the TDS. This is not a compendial test but is part of the manufacturer's specification for the drug product.

IDENTIFICATION

Identification tests are discussed in *General Notices, 5.40 Identification*. Identification tests should establish the identity of the drug or drugs present in the article and should discriminate between compounds of closely related structures that are likely to be present. Identification tests should be specific for the drug substance(s) (e.g., infrared spectroscopy). Near-infrared (NIR) or Raman spectrophotometric methods also could be acceptable for the identification of the drug product (for additional information, see *Near-Infrared Spectroscopy—Theory and Practice ⟨1856⟩* and *Raman Spectroscopy—Theory and Practice ⟨1858⟩*). Identification solely by a single chromatographic retention time is not specific.

ASSAY

A specific and stability-indicating test should be used to determine the strength (active pharmaceutical ingredient content) of the drug product. This assay requirement can be satisfied for topical products containing antibiotics by a standard microbiological method (see *Antibiotics—Microbial Assays ⟨81⟩*). In cases when the use of a nonspecific assay (e.g., *Titrimetry ⟨541⟩*) is justified, other supporting analytical procedures should be used to achieve overall specificity.

IMPURITIES

Process impurities, synthetic byproducts, impurities associated with the adhesive (e.g., residual monomers), residual solvents (see *Residual Solvents ⟨467⟩*), and other inorganic and organic impurities may be present in the drug substance and in the excipients used in the manufacture of the drug product and should be assessed and controlled. Impurities arising from the degradation of the drug substance and those arising during the manufacturing process of the drug product also should be assessed and controlled.

Specific Tests

In addition to the *Universal Tests* listed previously, the following *Specific Tests* should be considered on a case-by-case basis.

UNIFORMITY OF DOSAGE UNITS

This test is applicable for TDS and for topical dosage forms intended for systemic delivery, or where tight control of the dose is necessary to limit local irritation or undesired systemic exposure, packaged in single-unit containers, such as packets (see *Uniformity of Dosage Units ⟨905⟩*). The uniformity of dosage units specification is not intended to apply to solutions, suspensions, emulsions, ointments, or gels in single-unit containers intended for local action following external, cutaneous administration.

WATER CONTENT

A test for water content should be included when appropriate (see *Water Determination ⟨921⟩*). This test is generally formulation dependent. Therefore, it is not included in the compendial drug product monograph but is part of the manufacturer's specification for the drug product.

MICROBIOLOGICAL QUALITY

Microbiological examination of nonsterile drug products is performed according to the methods given in *Microbiological Examination of Nonsterile Products—Tests for Burkholderia cepacia Complex ⟨60⟩* (as appropriate for aqueous formulations), *Microbial Enumeration Tests ⟨61⟩*, and *Tests for Specified Microorganisms ⟨62⟩*, as appropriate, unless the formulation itself is demonstrated to have antimicrobial properties. Recommended acceptance criteria for nonsterile pharmaceutical products based on total aerobic microbial count and total combined yeasts and molds count are given in *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use ⟨1111⟩*.

ANTIMICROBIAL PRESERVATIVE CONTENT

Acceptance criteria for antimicrobial preservative content in multiple-unit 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⟩*).

PENETRATION ENHANCER CONTENT

If an excipient is claimed to be a penetration enhancer, a test and acceptance criteria for its content should be established.

ANTIOXIDANT CONTENT

If antioxidants are present in the drug product, tests of their content should be established unless oxidative degradation can be detected by another test method such as impurity testing. Acceptance criteria for antioxidant content should be established. They should be based on the levels of antioxidant necessary to ensure the product's stability at all stages throughout the product's proposed usage and shelf life.

STERILITY

Depending on the use of the dosage form (e.g., products that will be applied to open wounds or burned areas), sterility of the product should be demonstrated as appropriate (see *Sterility Tests ⟨71⟩*).

pH

When applicable, topically applied drug products should be tested for pH. Because some topically applied drug products contain very limited quantities of water or aqueous phase, pH measurements may not always be warranted. This test is generally formulation

dependent. Therefore, it is not included in the compendial drug product monograph but is part of the manufacturer's specification for the drug product.

PARTICLE SIZE

When the finished product contains a suspended solid drug substance, the product should be examined for particle size. The particle size of the active drug substance(s) in topically applied drug products is usually established and controlled at the formulation development stage. However, topically applied drug products should be examined for evidence of particle alteration (i.e., change in drug polymorphic form, appearance of particles, size, shape, morphology, agglomeration, or aggregation) of the drug substance that may occur during the course of product processing and storage. These types of tests are generally formulation dependent. Therefore, such tests are not included in compendial drug product monographs but are part of the manufacturer's specification for the drug product.

CRYSTAL FORMATION

When the drug substance is dissolved in the finished product, the product should be microscopically examined for evidence of crystal formation of the active drug substance. This test is generally formulation dependent. Therefore, it is not included in the compendial drug product monograph but is part of the manufacturer's specification for the drug product. It is recommended that the potential for the drug product to form crystals of drug substance be examined during product development.

EMULSION GLOBULE SIZE

Because many semisolid dosage forms such as creams and lotions are multiphasic systems (e.g., emulsions) with co-existing oil and water/aqueous phases in the formulation, emulsion droplet size or globule size can be a critical quality attribute that characterizes the microstructure of these dosage forms. Therefore, control of the emulsion droplet and/or globule size should be considered a specific test for such products to ensure consistency, homogeneity, and physical stability in the drug product throughout the shelf life.

IN VITRO DRUG RELEASE TEST

For TDS, the in vitro drug release test is required as a batch-to-batch quality control. See *Drug Release* ⟨724⟩ for apparatus and test conditions. The development and validation report of the in vitro drug release test needs to include sufficient detail and data to facilitate the assessment of whether the method is adequate as a quality control test for batch release and stability testing.

For semisolid dosage forms, an in vitro drug release test (IVRT) is currently not mandatory for batch release. See *Semisolid Drug Products—Performance Tests* ⟨1724⟩ for appropriate contexts of use for an IVRT, as well as discussions on method development, experimental design, data analysis, suitable equipment and their qualification, as well as other practical information.

SPECIFIC TESTS FOR OPHTHALMIC DRUG PRODUCTS

See *Ophthalmic Products—Quality Tests* ⟨771⟩.

SPECIFIC TESTS FOR TOPICAL AEROSOLS

See *Topical Aerosols* ⟨603⟩.

SPECIFIC TESTS FOR TOPICALLY APPLIED SEMISOLID DRUG PRODUCTS

Minimum Fill

Single- and multiple-unit containers must meet minimum fill requirements as established by testing described in *Minimum Fill* ⟨755⟩. For single-unit containers where the test for ⟨905⟩ is applied, the test for ⟨755⟩ is not required.

Change to read:

Apparent Viscosity

Viscosity is a measure of a formulation's resistance to flow and is an assessment of a rheological property of a semisolid dosage form. The term "apparent viscosity" applies to non-Newtonian fluids, which comprise the majority of semisolid pharmaceutical dosage forms. For additional information, see *Rheometry* ⟨1911⟩ and *Measurement of* ▲*Yield Stress*▲ *(CN-1-Dec-2023) of Semisolids* ⟨1912⟩.

Measurement procedures should be developed as outlined in *Viscosity—Capillary Methods* ⟨911⟩, *Viscosity—Rotational Methods* ⟨912⟩, and *Viscosity—Rolling Ball Method* ⟨913⟩. For semisolids that show thixotropy and/or irreversible changes in viscosity after shearing, specific attention should be given to sample preparation procedures to minimize variability in the measurement of apparent viscosity caused by variable shear histories (e.g., mixing speed and temperature, filling operation, and sample handling). Furthermore, for some products it may be warranted to have apparent viscosity specifications at more than one stage of the manufacturing process (e.g., bulk in-process stage, final packaged product, etc.) or with more than one set of test conditions (e.g., high and low shear rates, different temperatures, etc.).

Apart from single-point viscosity measurements, more advanced rheological techniques (flow, oscillatory, creep, and stress relaxation testing) can be applied to develop a mechanistic understanding of a formulation and its structure. See ⟨1912⟩. These techniques may be useful for product development using the principles of quality by design or for comparative physicochemical and structural characterization of the test and reference products to support a demonstration of bioequivalence in an abbreviated new drug application. However, these techniques are not generally suitable for routine quality testing. Common parameters derived from rheological testing of semisolid pharmaceutical dosage forms that may be useful for characterization and comparison are the storage modulus, loss modulus, relaxation modulus, compliance, thixotropic index, and yield stress.

Acceptance criteria are product specific and defined to ensure that the apparent viscosity of each batch of semisolid drug product is within the the acceptable range determined during product development and is consistent between batches.

Uniformity in Containers

Topically applied semisolid drug products may show physical separation during manufacturing processes and during their shelf life. To ensure the integrity of the drug product, it is essential to evaluate the uniformity of the finished product. This test applies only to multiple-unit containers, such as tubes and jars. This test does not apply to more fluid topical drug products in multiple-unit containers, such as emulsions, lotions, two-phase gels, or topical suspensions, in which the labeling directs the user to mix the product (e.g., shake well) before use.

PRODUCTS PACKAGED IN TUBES

Visual uniformity: Carefully remove or cut off the bottom tube seal and make a vertical cut from the bottom to the top of the tube. Carefully cut the tube around the upper rim, open the two flaps, and lay the flaps open to expose the product.

Inspect the product visually for the presence of phase separation, change in physical appearance and texture (e.g., color change, crystallization, lumping), and other properties described in the product specification for *Description*. If there is no significant phase separation or change in physical appearance and texture, and if the product meets the *Description* criteria, the product passes the test. If the product exhibits significant phase separation or change in physical appearance or texture, the product fails the test.

Uniformity of active ingredient(s): The following procedures can be modified depending on the sensitivity of the quantitative procedure used to determine the amount of the drug substance(s) present in the formulation.

For multiple-unit tubes that contain 5 g or more of product

stage 1:

1. Using a single tube, after performing the test for *Visual uniformity*, remove an appropriate amount of the product from the top (i.e., cap end), middle, and bottom (i.e., seal end) portions of the tube. The sample size should be sufficient for at least one quantitative determination of the active ingredient(s) and should not exceed the maximum dose recommended by the product labeling for a single application.
2. Determine the amount of the active ingredient(s) in each portion of the product using any appropriate validated quantitative procedure, and evaluate the test results from the single tube using the *Stage 1* acceptance criteria outlined in number *3*.
3. *Stage 1* acceptance criteria are met if:
    - None of the 3 results are outside of the product assay range, and
    - The maximum difference in the amount of active ingredient(s) determined within the tube is NMT 10.0%. For example, if the 3 measurements within the tube are 97.0%, 95.2%, and 99.7%, the maximum difference would be 4.5% (i.e., 99.7% − 95.2% = 4.5%).
4. Proceed to *Stage 2* testing if *Stage 1* acceptance criteria are not met and none of the test results are outside the product assay range by more than 5.0% (e.g., if the product assay range is 90.0%–120.0%, the range will be 85.0%–125.0%), and the maximum difference in the amount of active ingredient(s) measured within the tube is NMT 10.0%. An example of a product that fails to meet *Stage 1* criteria: if the highest and lowest assay values were 106.0% and 94.7% of label claim, then the difference would be 106.0% − 94.7% = 11.3%.
5. Proceed to *Stage 3* testing if *Stage 1* acceptance criteria are not met, *Stage 2* acceptance criteria cannot be met, NMT 1 of the 3 test results is outside of the product assay range by more than ±5.0%, and the maximum difference of the amount of active ingredient(s) measured within the tube is NMT 15.0%.

stage 2:

1. Test an additional 2 tubes for *Visual uniformity* and *Uniformity of active ingredient(s)* for a total of 3 samples each from 3 tubes.
2. Determine the amount of the active ingredient(s) in each portion of the product using any appropriate validated quantitative procedure, and evaluate the test results from the 3 tubes using the *Stage 2* acceptance criteria.
3. *Stage 2* acceptance criteria are met if:
    - The *Visual uniformity* test is met for all tubes;
    - None of the 9 results (i.e., 3 each from 3 tubes) are outside of the product assay range by NMT 5.0%; and
    - The maximum difference of the amount of active ingredient(s) measured within each tube, for each of the samples tested, is NMT 10.0%.
4. Proceed to *Stage 3* testing if NMT 1 of the 9 test results is outside of the product assay range by ±5.0% and/or the maximum difference between the amount(s) of active ingredient(s) measured within each tube is more than 10% but NMT 15.0%.

stage 3:

1. If *Stage 2* has been completed, test an additional 7 tubes for *Visual uniformity* and *Uniformity of active ingredient(s)* for a total of 3 samples each from 10 tubes. If *Stage 2* was skipped, test an additional 9 tubes for *Visual uniformity* and *Uniformity of active ingredient(s)* for a total of 3 samples each from 10 tubes.
2. Determine the amount of active ingredient(s) in each portion of the product using any appropriate validated quantitative procedure, and evaluate the test results from the 10 tubes using the *Stage 3* acceptance criteria as outlined in number *3*.

3. *Stage 3* acceptance criteria are met if:
    - The *Visual uniformity* test is met for all tubes;
    - NMT 1 of the 30 test results is outside of the product assay range by ±5.0%; and
    - The maximum difference of the amount of active ingredient(s) measured within each tube, for each of the 10 tubes tested, is NMT 15.0%.

For multiple-unit tubes that contain less than 5 g of product

stage 1:

1. Using a single tube, after performing the test for *Visual uniformity*, remove an appropriate amount of product from the top (i.e., cap end) and bottom (i.e., seal end) portions of the tube. The sample size should be sufficient for at least one quantitative determination of the active ingredient(s) and should not exceed the maximum dose recommended by the product labeling for a single application.
2. Determine the amount of the active ingredient(s) in each portion of the product using any appropriate validated quantitative procedure, and evaluate the test results from the tube using the *Stage 1* acceptance criteria outlined in number *3*.
3. *Stage 1* acceptance criteria are met if:
    - Neither result is outside of the product assay range; and
    - The difference between the amount of active ingredient(s) determined for the 2 samples within the tube tested is NMT 10.0%. For example, if the 2 measurements within a tube were 95.2% and 89.7%, the difference would be 5.5%.

4. Proceed to *Stage 2* testing if *Stage 1* acceptance criteria are not met and neither of the test results are outside the product assay range by more than ±5.0% (e.g., if the product assay range is 90.0%–120.0%, the range will be 85.0%–125.0%), and the difference between the amounts of active ingredient(s) measured within the tube is NMT 10.0%.
5. Proceed to *Stage 3* testing if *Stage 1* acceptance criteria are not met, *Stage 2* acceptance criteria cannot be met, NMT 1 of the test results is outside of the product assay range by more than ±5.0%, and the difference between the amounts of active ingredient(s) measured within the tube is NMT 15.0%.

stage 2:

1. Test an additional 2 tubes for *Visual uniformity* and *Uniformity of active ingredient(s)* for a total of 2 samples each from 3 tubes.
2. Determine the amount of the active ingredient(s) in each portion of the product using any appropriate validated quantitative procedure, and evaluate the test results from the 3 tubes using the *Stage 2* acceptance criteria as outlined in number *3*.
3. *Stage 2* acceptance criteria are met if:
    - The *Visual uniformity* test is met for all tubes;
    - None of the 6 test results (i.e., 2 each from 3 tubes) are outside of the product assay range by ±5.0%; and
    - The difference between the amount of active ingredient(s) determined for the 2 samples within each tube, for each of the 3 tubes tested is NMT 10.0%.

4. Proceed to *Stage 3* testing if NMT 1 of the 6 test results is outside of the product assay range by ±5.0%, and/or the maximum difference between the amount(s) of active ingredient(s) measured within each tube is more than 10% but NMT 15.0%.

stage 3:

1. If *Stage 2* has been completed, test an additional 7 tubes for *Visual uniformity* and *Uniformity of active ingredient(s)* for a total of 2 samples each from 10 tubes. If *Stage 2* was skipped, test an additional 9 tubes for *Visual uniformity* and *Uniformity of active ingredient(s)* for a total of 2 samples each from 10 tubes.
2. Determine the amount of active ingredient(s) in each portion of the product using any appropriate validated quantitative procedure, and evaluate the test results from the 10 tubes using the *Stage 3* acceptance criteria as outlined in number *3*.
3. *Stage 3* acceptance criteria are met if:
    - The *Visual uniformity* test is met for all tubes;
    - 19 of 20 test results are within ±5.0% of the product assay range; and
    - The difference between the amount of active ingredient(s) determined for the 2 samples within each tube, for each of the 10 tubes tested, is NMT 15.0%.

PRODUCTS PACKAGED IN CONTAINERS OTHER THAN TUBES

For semisolid products packaged in a container other than a tube when the sampling method presented previously cannot be used, other sampling methods are acceptable, such as this method described for a jar:

1. Select a suitable syringe of sufficient length to extend to the bottom of the container.
2. Remove and set aside the syringe plunger, and cut off the bottom of the syringe barrel. Sampling should take place from a location to the left or right of the mid-line of the jar surface to preserve an undisturbed region on the other side for any additional investigation (see *Figure 1*).

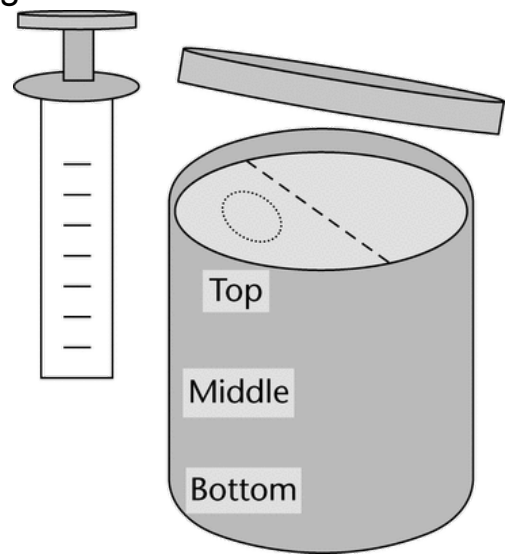

Figure 1. Sampling from a jar container.

3. Slowly push the syringe barrel into the container until it reaches the bottom. Then twist the syringe barrel containing the sample core, and remove the syringe from the container.
4. Insert the syringe plunger into the barrel, and carefully extrude the sample core onto a clean surface in three equal portions to represent the top, middle, and bottom portions of the container.
5. Remove an appropriate sample representative of the top, middle, and bottom portions of the container samples, and test according to the instructions outlined in *Products Packaged in Tubes*.

Delivered-Dose Uniformity in Metered-Dose Containers

The test for delivered-dose uniformity is required for drug products contained either in metered-dose containers or in premetered-unit presentations. The test for delivered-dose uniformity includes dose uniformity over the entire unit shelf life. Select 1 container. Using separate collection vessels, quantitatively collect delivered doses representing the initial, middle, and the final dose from the container. Appropriately discard doses not collected for testing. Determine the drug substance content of each of the 3 collected samples using an appropriate and validated quantitative procedure or the procedure indicated in the individual monograph. A dose in this test is defined as the minimum recommended number of actuations specified in the product labeling or in the instructions for use but NMT 2 actuations. The target-delivered dose is specified by the product label claim, unless otherwise specified in the individual monograph.

In-Process Testing

PUMP FUNCTIONALITY TEST FOR METERED- AND NON-METERED-DOSE CONTAINER CLOSURES

This test is conducted during product development to establish that the airless pumps are performing as intended. This test is product dependent. Therefore, it is part of the manufacturer's controls for the drug product and it is not included in compendial drug product monographs.

During the filling process for semisolid or liquid products packaged in a non-metered-dose container closure requiring an actuator to dispense the product (for example, an airless pump container), in-process testing to verify pump functionality should be examined. Example tests include pumps to prime and total amount dispensed.

Change to read:

SPECIFIC TESTS FOR TDS

TDS are formulated with an adhesive layer to ensure intimate contact with the skin and allow the delivery of the desired dose of the drug. Adhesives in TDS must permit easy removal of the release liner before use, adhere properly to human skin upon application, maintain adhesion to the skin during the prescribed period of use, and permit easy removal of the TDS at the end of use without leaving a residue or causing damage to the skin or other undesirable effect(s). Additionally, adhesives must be able to maintain the performance of the TDS throughout the shelf life of the drug product.

Testing of the physical properties of the TDS generally include peel adhesion, release liner peel, tack, cold flow, shear, and crystal formation (see *Crystal Formation*). The peel adhesion, release liner peel, and tack tests measure the adhesion properties of the TDS. Each of these tests measures the force required to separate the TDS from another surface. The cold flow and shear tests measure the cohesive properties of the TDS. These latter tests measure the resistance to flow of the adhesive matrix.

Acceptance criteria are product specific and defined to ensure that adhesion of each batch of TDS is within the range defined by the product design and is consistent between batches based on the product development specifications. Acceptance criteria should be established using in vitro testing results of representative batches, including clinical batches for which satisfactory in vivo adhesion performance has been demonstrated. Release and shelf life limits should be the same, unless justified.

In addition to physical testing, this section also discusses the *Leak Test* applicable to form-fill-seal-type (reservoir or pouched) TDS.

Peel Adhesion Test

This test measures the force required to remove (peel away) a TDS attached to a standard substrate surface (e.g., polished stainless steel). The TDS is applied to the substrate using specified techniques for application and is conditioned at a specified temperature and time. Then the TDS is peeled away from the substrate with an instrument that allows for control of the peel angle (e.g., 90° or 180°) and peel rate (e.g., 300 mm/min), and the force profile is recorded. This procedure is repeated using a minimum of 5 independent samples yielding results from a suitable method. The product fails the test if the overall mean adhesion force is outside of the acceptable range determined during product development. During method development, suitable methods (including test panel surface) need to be identified. The method should allow the TDS to be removed entirely and cleanly, leaving no visually noticeable matrix residue on the substrate surface (i.e., an indication of adhesive failure).

Other failure modes (e.g., delamination at an interface, cohesive failure, etc.) are not indicative of true peel adhesion. The method should be developed to ensure an adhesive failure mode. Suitable methods do not result in undesired adhesion failures, including delamination at an interface (e.g., between a membrane and an adhesive layer or between two different adhesive layers of a bilayer product) or transfer of adhesive to the test panel (i.e., cohesive failure).

Release and shelf life limits should be the same, unless justified.

The geometry of a TDS (e.g., round or rectangular shaped) and its design (e.g., TDS with different surfaces such as an inner part and with a peripheral adhesive ring) should be considered in the method.

The substrate surface should be cleaned regularly and checked for scratches, as this may influence test results.

Release Liner Peel Test

This test measures the force required to separate the release liner from the adhesive layer of the TDS. The test is performed with a finished product sample. The test sample is conditioned using specific procedures (temperature and time). Then, the release liner is pulled away from the TDS with an instrument that allows for control of the peel angle (e.g., 90° or 180°) and peel rate (e.g., 300 mm/min), and the force profile is recorded. This procedure is repeated using a minimum of 5 independent samples. The product fails the test if the ▲overall▲ (ERR 1-Dec-2023) mean peel force is outside the acceptable range determined during product development.

Tack Test

A few tack test methods have been developed and the current predominantly used method is the probe tack method. It is up to the TDS manufacturer to decide which tack test is most appropriate for each drug product. The product fails the test if the overall mean of the maximum (tack) force results, using a minimum of 5 independent samples, is outside the acceptable range determined during product development. For additional discussion on the probe tack method, see *Probe Tack Test* ⟨1212⟩.

Cold Flow Test

Cold flow is the migration of the adhesive matrix beyond the edge of the TDS backing, and through the slit in the release liner, which may occur during the course of product processing and storage. Cold flow is an inherent property of TDS due to the use of pressure-sensitive adhesives that flow when force is applied (i.e., if the adhesive matrix did not flow, the TDS would not stick). The magnitude of the cold flow is generally dependent on the product formulation, packaging design, storage conditions, and storage time. Cold flow should be assessed using a combination of quantitative and qualitative methods. No single quantitative method has been identified to work universally for all TDS. The TDS manufacturer should determine the most suitable cold flow test, or tests, as cold flow may manifest differently for different products. Several different cold flow tests have been developed. Examples include the following:

- Linear measurement of the radial cold flow using microscopy
- Measuring the distance of migrated adhesive matrix at predefined and evenly spaced positions of a TDS
- Measuring cold flow by applying a reference plate in the size of the TDS plus the acceptable cold flow
- Swabbing and stripping the migrated part of the matrix and determining it gravimetrically or by assay of the drug substance
- Die cutting and punching out the original size of the TDS and determining the amount of migrated matrix on the outside
- Overall area determining methods of cold flow using image analysis tools

Acceptance criteria are product specific and defined to ensure that the cold flow of each batch of TDS is within the range determined during product development and is consistent between batches.

Shear Test

The shear test measures the cohesive strength of a TDS. It can be measured under static (see *Static Shear Test*) or dynamic conditions. Shear testing may not be feasible for all TDS because the presence of multiple layers of adhesive in the system, the presence of a membrane or scrim, or the use of an emulsion adhesive system may result in the inability to achieve cohesive failure. TDS that are constructed with a peripheral adhesive ring or form-fill-seal TDS may not be suitable for this test. The TDS manufacturer should decide if a shear test is appropriate, and if so, which shear test is most appropriate for each drug product. Acceptance criteria are product specific and defined to ensure that the shear of each batch of TDS is within the range determined during product development and is consistent between batches.

Static Shear Test

For the static shear test, the time required to remove a standard area of the TDS from the substrate (i.e., stainless steel test panel) under a standard load (e.g., 250 g) is measured. The TDS is applied to a test panel, and the sample is subjected to a shearing force by means of a given weight suspended from the TDS. The test apparatus holds the test panels at 0°–2° from vertical to ensure that the TDS will not

experience peeling action when the weight is attached. Dwell time, weight used, test panel type, mode of failure, and sample size should be noted; the time taken for the TDS sample to detach from the test panel is reported. Cohesive failure, i.e., adhesive matrix is left on the TDS and on the substrate plate, should occur. Suitable methods do not result in undesired adhesion failures, including delamination at an interface, e.g., between a membrane and an adhesive layer, or between two different layers of a bilayer product.This procedure is repeated using a minimum of 5 independent samples yielding results from a suitable method. The product fails the test if the overall mean result, i.e., arithmetic mean or geometric mean as determined by the manufacturer, of each TDS batch is outside of the range determined during product development.

Leak Test

This test is applicable only for form-fill-seal-type (reservoir or pouched) TDS. Form-fill-seal TDS must be manufactured with zero tolerance for leaks because of their potential for dose dumping if leaking occurs.

In-process control methods to examine TDS for leaks or potential leaks are needed and require considerable development on the part of TDS manufacturers.

IN-PROCESS TESTING

During the manufacturing process, the presence of leakage (or potential for leakage) due to TDS perforation, cuts, and faulty seals resulting from failures such as air bubbles, gel splash, or misalignment of a TDS backing and release liner layers must be examined. Unless automated process analytical technology is implemented, in-process testing to identify these defects should be performed using the following test procedures.

Visual inspection:

- A specified number of TDS, defined on the basis of batch size, should be examined randomly.
- Each sampled TDS should be thoroughly visually inspected for leakage.
- The product fails if any of the TDS examined are detected with a leak.

Seal integrity: TDS seals should be stress tested to ensure that the application of pressure does not force seals to open, thereby leading to leakage.

- A specified number of TDS, defined on the basis of batch size, should be randomly examined.
- Each sampled TDS should be thoroughly visually inspected for leakage.
- Each sampled TDS is placed on a hard, flat surface and overlaid with a weight so that it is subjected to 13.6 kg. The weight should be left in place for 2 min. Upon removal of the weight, the TDS should be visually inspected for leakage.
- The product fails if the number of TDS detected with a leak is greater than the acceptable limit established by the manufacturer.

Packaged product testing: TDS may leak after they have been individually placed in the primary packaging material as a result of the packaging operation itself or by a user opening the packaging. Therefore, TDS should be tested for leakage after they have been manufactured and packaged in their primary packaging material.

- A specified number of TDS, defined on the basis of batch size, should be randomly examined after they have been placed in their primary packaging material.
- The sampled TDS should be removed from their packaging and thoroughly visually inspected for leakage.
- Each sampled TDS should then be uniformly wiped with a solvent-moistened swab. Both the backing side and the release liner side of the TDS should be wiped. The inside surface of the pouch should also be wiped. The swab(s) is then extracted and assayed for the drug.
- The product fails if the total amount of drug from the TDS, and the corresponding pouch, exceed the acceptable limit established by the manufacturer.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
<3> TOPICAL AND TRANSDERMAL DRUG PRODUCTS - PRODUCT QUALITY TESTS	Margareth R.C. Marques Principal Scientific Liaison	GCDF2020 General Chapters - Dosage Forms 2020

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