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Standard Test Methods for Measuring Water Vapor Transmission Rate (WVTR) of Pharmaceutical Bottles and Blisters[1]

This standard is issued under the fixed designation D7709; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

~~ε[1] NOTE—Section X1.3 and Table X1.1 were corrected editorially in September 2011.~~

1. Scope

1.1 The three test methods described herein are for measurement of water vapor transmission rates (WVTRs) of high-barrier multiple-unit containers (bottles), high-barrier single-unit containers (blisters), and quasi-barrier single-unit containers used for packaging pharmaceutical products. The containers are tested closed and sealed. These test methods can be used for all consumer-sized primary containers and bulk primary containers of a size limited only by the dimensions of the equipment and the weighing capacity and sensitivity of the balance.

1.2 These test methods are intended to be of sufficient sensitivity and precision to allow clear discrimination among the levels of barrier packages currently available for pharmaceutical products.

1.3 There are three methods: Method A is for bottles, Method B is for formed barrier blisters, and Method C is for formed quasi-barrier blisters. Methods B and C can be adapted for use with flexible pouches.

1.4 These test methods use gravimetric measurement to determine the rate of weight gain as a result of water vapor transmission into the package and subsequent uptake by a desiccant enclosed within the package. The packages are exposed to environments typical of those used for accelerated stability testing of drug products in the package (typically 40°C/75 % relative humidity [RH]).

1.5 For these methods, balance sensitivity, amount of desiccant, number of blisters per test unit, and weighing frequency were developed in an experiment based on Test Methods E96/E96M.

1.6 Test Methods E96/E96M gives specific instruction on the interactions among weighing frequency, number of data points necessary to establish steady state, minimum weight gain in a weighing period, and balance sensitivity.

1.7 The test methods in this standard were developed specifically for pharmaceutical bottles and blisters as closed container-closure systems. The experiment from which the methods were developed provided an inter-laboratory study from which the precision and bias statement was written. The packages in the study were small bottles and blisters used regularly for pharmaceutical solid oral dosage forms.

1.8 In spite of the specific nature of their application, the test methods in this standard should be suitable for other pharmaceutical packages and most types and sizes of other consumer packages.

1.9 The values stated in SI units are to be regarded as the standard. No other units of measurement are included in this standard. The units of measure for bottles are milligrams per bottle per day (mg/bottle-day) and for blisters, milligrams per blister cavity per day (mg/cavity-day). These units may be used for both standard and referee testing.

1.10 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E96/E96M Test Methods for Water Vapor Transmission of Materials

3. Terminology

3.1 *Definitions:*

[1] This test method is under the jurisdiction of ASTM Committee D10 on Packaging and is the direct responsibility of Subcommittee D10.32 ~~on Consumer, Pharmaceutical and Medical Packaging.~~

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

3.1.1 *barrier blister*, *n*—blister made from high-barrier material, formed and sealed so that the water vapor transmission rate (WVTR) (when tested at 40°C/75 % RH) is less than 1.0 mg/cavity-day.

3.1.2 *blister*, *n*—formed, lidded and sealed plastic dome that contains the solid oral product (usually one unit).

3.1.2.1 *Discussion*—Synonymous with *cavity*.

3.1.3 *card*, *n*—contiguous group of blisters formed and sealed with lid in place.

3.1.3.1 *Discussion*—The card is a production geometry that is a convenient quantity for a dosage regimen. The number of blisters per card commonly ranges from one to ten but may be more. From a marketing and production point of view, the card is the basic, irreducible number of blisters in a market or clinical trial package. The blister card may sometimes be referred to as the container.

3.1.4 *cavity*, *n*—see **blister** .

3.1.5 *container*, *n*—(*1*) bottle that contains multiple units of drug product, or (*2*) a card of blisters formed and sealed with lid.

3.1.6 *quasi-barrier blister*, *n*—blister made from low-barrier materials formed and sealed so that the WVTR (when tested at 40°C/75 % RH) is greater than 1.0 mg/cavity-day.

3.1.6.1 *Discussion*—An example of this is 250 µm (10 mil) poly(vinyl chloride) (PVC) formed into size zero blisters and sealed with aluminum foil lid.

3.1.7 *test specimen (or specimen)*, *n*—(*1*) *for bottles*, the bottle is the test specimen and (*2*) *for blisters*, the blister card is the test specimen.

3.1.7.1 *Discussion*—For blisters, more than one card (or specimen) may be grouped into a test unit for conducting the test.

3.1.8 *test unit*, *n*—(*1*) *for bottles*, the bottle is the test unit as well as being the test specimen and (*2*) *for blisters*, the test unit is a group of test specimens (cards) processed together for temperature and humidity exposure and weighing at each time point.

3.1.8.1 *Discussion*—The purpose of the test unit for blisters is to gain the advantage of additive weight gain resulting from more blisters than are on a single card. Detailed discussion of this point is available in Test Methods E96/E96M. The term *test unit* when applied to bottles is simply to maintain congruence of naming among the three test methods.

4. Summary of Test Method

4.1 In Method A for bottles, desiccant is placed in the bottle which is then closed in the normal manner including any membrane (tamper-evident or otherwise) sealed in place. The desiccant-filled bottle is stored in an environment at 40°C/75 % RH. The desiccant-filled bottle is weighed at prescribed time intervals until steady-state weight gain is obtained. Once steady state is obtained, the bottles are weighed at five consecutive time points.

4.2 In Method B for barrier blisters, desiccant is placed in the blister and the lid material is sealed in place using equipment that is capable of filling and properly sealing the containers (or cards). The desiccant-filled blister card is stored in an environment at 40°C/75 % RH. The card of desiccant filled blisters is weighed at prescribed time intervals until steady-state weight gain is obtained. Once steady-state is obtained, the blister cards are weighed at five consecutive time points.

4.3 WVTR for Methods A or B is calculated using linear regression of the weight versus time. The number of blisters tested depends on the barrier characteristics of the material, the size of the blister, and the sensitivity of the balance used in the test.

4.4 4.4 In Method C for quasi-barrier blisters, desiccant is placed in the blister and the lid material is sealed in place using equipment that is capable of correctly filling and sealing the containers (or cards). The desiccant-filled blister card is stored in an environment at 40°C/75 % RH. The desiccant-filled blister card is weighed at zero time and 48 h (two days). At this time, the difference in weight (the weight gain) in mg/cavity-day is taken as the WVTR. The number of blisters tested depends on the barrier characteristics of the material, the size of the blister, and the sensitivity of the balance used in the test.

NOTE 1—For this test method, the requirement of five consecutive weighings is waived because the desiccant quickly becomes saturated when packed in a quasi-barrier package and stored at 40°C/75 % RH. During development of this test method, it appeared that after the second day the weight gain displayed a curvilinear profile typical of approaching saturation of the desiccant. To obtain five weighings within two days is an unwieldy process and is likely to lack precision.

5. Significance and Use

5.1 The purpose of these test methods is to obtain reliable values for WVTR that can be used to discriminate among barrier packages for pharmaceutical products. These test methods will establish a WVTR value that represents the water vapor transmission of the container closure system being evaluated. They are intended for use in evaluating or comparing, or both, the water vapor barrier performance of alternative packages for use in packaging of pharmaceutical products.

5.2 While these methods were developed for a specific, limited application, they should be suitable for most types and sizes of consumer packages.

6. Apparatus

6.1 For weighing the test units in Method A, use a balance that has sufficient capacity to weigh the total of bottle, cap, and desiccant throughout the period of the test. The balance shall have sensitivity adequate to measure small differences in weight from one time point to the next. The balance sensitivity shall be smaller than 5 % of the differences in weight from one time point to the next. (For example, during development of this test method, a balance with capacity of 110 g and sensitivity of 0.1 mg was found to be acceptable for a 60 CC bottle.)

6.2 For weighing the test specimens in Methods B and C, use a balance that has sufficient capacity to weigh the closed, sealed blister test unit throughout the period of use. The balance shall have sensitivity adequate to measure small differences in weight from one time interval to the next. The balance sensitivity shall be smaller than 5 % of the differences in weight from one time interval to the next. (For example, during development of this method, a balance with capacity of 110 g and sensitivity of 0.1 mg was found to be acceptable. Test Methods B and C may require that the blister cards (containers) be bundled in multiples to achieve periodic weight gains of sufficient magnitude to use the balance sensitivity. When so bundled, these cards are called test units. Test Methods E96/E96M specify that the weight gain in each weighing period shall be 20 times the sensitivity of the balance.

6.3 For exposure of packages to the test environment for Methods A, B, and C, use a chamber capable of maintaining 40 ± 2°C and 75 ± 5 % RH. The humidification should be achieved with de-ionized water, or equivalent means, to limit contamination from water impurities.

7. Reagents and Materials

7.1 *Purity of Reagents*—Reagent-grade chemicals shall be used in all tests. Unless otherwise indicated, it is intended that all reagents conform to the specifications of the Committee of Analytical Reagents of the American Chemical Society where such specifications are available.[3] Other grades may be used, provided it is first ascertained that the reagent is of sufficiently high purity to permit its use without lessening the accuracy of the determination.

7.2 *Desiccant for Method A*—During development of Method A, anhydrous calcium chloride in granular form was used as the desiccant. Other desiccants may be suitable; for example, a molecular sieve or silica gel. If calcium chloride in any form, including anhydrous, is ~~used,~~used it shall be pre-dried at 215 ± 5°C for 7¼ ± ¼ ~~) h to ensure that any calcium hexahydrate present is fully converted to the anhydrate. Cool the desiccant in a desiccator for at least 2 h before use.~~ h to ensure that any hexahydrate present is fully converted to the anhydrate. Cool the desiccant in a desiccator for at least 2 h before use.

NOTE 2—It has been shown[4] that anhydrous calcium chloride may contain calcium hexahydrate, which loses water only when the temperature reaches 200°C.

7.3 *Desiccant for Methods B and C*—During development of Method B, silica gel was used as the desiccant. It was used in a molded form to fit the size and shape of the blister used. Other desiccants may be suitable, for example, a molecular sieve. If silica gel is used, it shall be pre-dried in a circulating hot air oven at one of two conditions: 155 ± 5°C for 3¼ ± ¼ h or 150 ± 5°C for 4¼ ± ¼ h. Dry molecular sieve in a muffle furnace at 595 ± 25°C. Dry the 4A and 3A sieves for 3¼ ± ¼ h. Dry the 13X sieve for 5¼ ± ¼ h. Cool the desiccant in a desiccator for at least 2 h before use.

8. Sampling, Test Specimens, and Test Units

8.1 *Method A (Bottles)*—Use 15 bottles and 15 closures chosen to represent the package form to be tested. Reserve the bottles for preparation at the time of testing. The bottles and closures should be stored such that they will not be damaged; particularly the mating surfaces of bottle and closure. Prepare the test specimens by filling each bottle ⅔ with desiccant then close the container in the appropriate manner as quickly as possible, including any membrane seal (tamper-evident or otherwise), if appropriate. Filling of bottles shall be done in a low-humidity atmosphere (as low as possible, but not greater than 50% RH). Close screw caps in accordance with the torque recommendations in Table 1.

8.2 *Methods B and C (Blisters)*—Fill with pre-dried desiccant and seal the blisters on equipment that is capable of correctly filling and sealing the market or clinical trial package. The desiccant tablet should fill the cavity, but for practical considerations, multiple fragments may be used. If fragments are used, the total weight of desiccant shall be enough to meet the quantity required to avoid partial saturation of the desiccant before completion of the test.

8.3 Filling of blisters shall be done in a low-humidity atmosphere (as low as possible, but not greater than 50 % RH).

8.4 Desiccants shall not be exposed to room humidity for more than 30 min before sealing.

9. Calibration

9.1 The weighing balance used to weigh the containers shall be appropriately calibrated.

9.2 The environmental chamber shall be appropriately calibrated.

9.3 The oven(s) used for drying desiccant shall be appropriately calibrated.

10. Procedure

NOTE ~~2—All~~ 3—All samples should be handled in a manner that prevents contact with skin or skin secretions and contaminants. Tweezers, forceps, and powder-free laboratory gloves have been used successfully.

10.1 *Method A—Bottles*:

[3] Reagent Chemicals, American Chemical Society Specifications, American Chemical Society, Washington, DC. For suggestions on the testing of reagents not listed by the American Chemical Society, see Analar Standards for Laboratory Chemicals, BDH Ltd., Poole, Dorset, U.K., and the United States Pharmacopeia and National Formulary, U.S. Pharmacopeial Convention, Inc. (USPC), Rockville, MD.

[4] Chen, Yisheng and Yanxia Li, "Determination of Water Vapor Transmission Rate (WVTR) of HDPE Bottles for Pharmaceutical Products," *International Journal of Pharmaceutics*, 358 (2008) pp. 137–143.

TABLE 1 Closing Torque for Screw-type Containers

Closure Diameter, mm[A]	Suggested Tightness Range with Manually Applied Torque, N · m	Suggested Tightness Range with Manually Applied Torque, in. · lbf
8	0.56	5
10	0.68	6
13	0.90	8
15	0.56 – 1.02	5 – 9
18	0.79 – 1.13	7 – 10
20	0.90 – 1.36	8 – 12
22	1.02 – 1.58	9 – 14
24	1.13 – 2.03	10 – 18
28	1.36 – 2.37	12 – 21
30	1.47 – 2.60	13 – 23
33	1.69 – 2.82	15 – 25
38	1.92 – 2.94	17 – 26
43	1.92 – 3.05	17 – 27
48	2.15 – 3.39	19 – 30
53	2.37 – 3.39	21 – 30
58	2.60 – 4.52	23 – 40
63	2.82 – 4.86	25 – 43
66	2.94 – 5.08	26 – 45

[A]For a closure having diameter between two diameters listed, use the torque range for the next larger diameter.

10.1.1 Bottles shall be received in the test laboratory, filled, and closed in accordance with Section 8.

10.1.2 Mark each container with a unique identifier. Mark with indelible ink on the container. Do not use a label.

10.1.3 Weigh each container at ambient temperature and RH. Record this weight for time zero.

10.1.4 Place all containers in the test chamber (40°C/75 % RH) within 1 h of weighing.

10.1.5 Weigh all containers at time intervals of 7 days ± 1 h.

10.1.5.1 Weigh the containers at 7, 14, 21, 28, and 35 days to get steady-state data points. (The time interval from Time 0 to Day 7 is the period of stabilization of permeation.)

10.1.5.2 Prior to weighing at each time interval, equilibrate the containers for about 30 min at the weighing temperature and RH. Limit the time out of the chamber to less than 2 h.

10.1.6 Record the weights in an appropriate manner for later computation of the regression line.

10.2 *Method B, Barrier Blisters (WVTR Less than 1.0 mg/day-cavity [at 40°C/75 % RH])*:

10.2.1 Blisters shall be received in the test laboratory and filled and closed in accordance with Section 8.

10.2.2 Mark each test unit with a unique identifier. Mark with indelible ink on the specimen. Do not use removable labels. A test unit is one or more blister cards.

10.2.3 Ten test units are required. Each test unit shall consist of a minimum of ten blister cavities. If the card contains less than ten cavities, bundle the cards to form a single test unit of at least ten cavities. (This is required to provide sufficient weight gain at each time interval.) See the following examples of some test unit quantities for blisters (not all inclusive):

Blisters per Card	Cards per Test Unit
4	3
5	2
10	1
30	1

10.2.3.1 Ultra-high barriers may not show the full measure of precision and sensitivity this method can provide. If the anticipated WVTR is 0.01 mg/day-cavity or less, each test unit should have more than 10 cavities, but no more than 30 cavities. Examples are foil-foil blisters or very small blisters formed from other materials. An alternative approach would be to double or triple the length of weighing intervals to allow a greater mass of water to accumulate in the desiccant.

10.2.4 Place all test units in the test chamber (40°C/75 % RH) within 1 h of weighing.

10.2.5 Weigh all test units at time intervals of 7 days ± 1 h.

10.2.5.1 Weigh the test units at 7, 14, 21, 28, and 35 days to get 5 steady-state data points. (The time interval from Time 0 to Day 7 is the period of stabilization of permeation.)

10.2.5.2 Prior to weighing at each time interval, equilibrate the containers for about 30 min at the weighing temperature and RH. Limit the time out of the chamber to less than 2 h.

10.2.6 Record the weights in appropriate manner for later computation of the regression line.

10.3 *Method C, Quasi-Barrier Blisters (WVTR Greater than 1.0 mg/day-cavity (at 40°C/75 % RH])*:

10.3.1 Blisters shall be received in the test laboratory and filled and closed in accordance with Section 8.

10.3.2 Mark each specimen with a unique identifier. Mark with indelible ink on the specimen. Do not use removable labels.

10.3.3 Ten test units are required. Each test unit shall consist of a minimum of ten blister cavities. If the card contains less than ten cavities, bundle the cards to form a single test unit of at least ten cavities. (This is required to provide sufficient weight gain at each time interval.) See 10.2.3 for examples of some test unit quantities for blisters.