4010 Determination of Water Vapor Transmission of Packaging Materials and Containers for Pharmaceutical use

This method is applicable to determining the water vapor transmission (WVT) of packaging materials or containers for pharmaceutical use, including, but not limited to films, sheeting and containers. The WVT refers to the amount of water vapor transmitted in a certain time through a test specimen induced by the specific water vapor pressure difference, under specified temperature and humidity conditions.

This method consists of gravimetric method, electrolytic analysis method and infrared detector method.

Method 1 Gravimetric method

Based on the weight changes, e.g., weight gains of desiccant or weight losses of aqueous solution, this method mainly includes two methods to obtain the WVT.

1 Weight gain method

This method is to determine the WVT of materials or containers under specified temperature and relative humidity (RH) conditions, usually calculated by the weight gains of desiccant. In general, weight gain method could be further classified into two methods, e.g., cup method and container method.

(1) Cup method The test specimen is fixed to a specially designed water permeable cup containing desiccant, and the WVT of the film or sheeting for pharmaceutical use could be calculated by the weight increments of the cup. Cup method is generally applicable to the thin films or sheeting with the WVT not less than 2g/ (m^2·24h).

Apparatus Constant climate chamber The temperature precision should be ±0.6℃, the RH precision should be ±2%, and the air velocity should be in the range of 0.5-2.5m/s. After the door of the chamber is closed, the specified temperature and humidity should be recovered within 15 minutes.

Analytical balance The balance should have a sensitivity of 0.1mg.

Water permeable cup The cup assembly should be constructed of any corrosion-resistant material with light weight, impermeable to water or vapor. The effective measurement area should not be less than 25cm^2. The cup assembly as shown in figure 1 could be used, and when meeting the requirements of this test, the cup assembly with other structure or in other shape could also be employed.

Test conditions Include but not limit to the generally applied conditions as follows:

A: 23℃±2℃, 90%RH ± 5%RH.

B: 38℃±2℃, 90%RH ± 5%RH.

C: 23℃±2℃, 50%RH ± 5%RH.

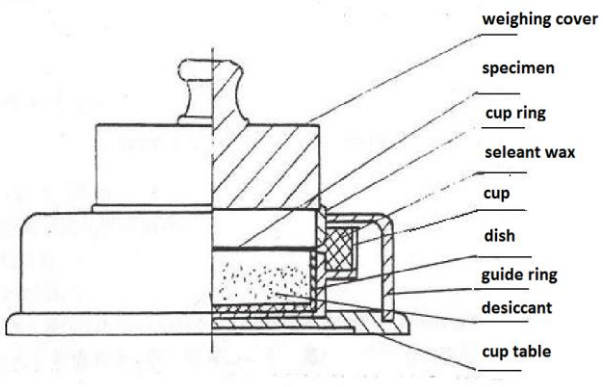

Fig. 1 Water permeable cup assembly

Procedure Choose three pieces of the test specimens, which should be of uniform thickness and free from wrinkles, creases, pinholes and other defects. When the cup assembly as shown in figure 1 applied, punch the test specimens with a disc-punching knife respectively. The diameter of each cut specimen should be between that of the cup ring and the cup. Add desiccant into clean dishes, and the suitable amount added should be up to about 3 mm away from the surface of the specimen. Put the dishes containing desiccant into cups, then place the cups on cup holders, and locate one specimen in the middle of each cup. After adding the cup ring, fix the position of each specimen with the guide ring, and then add the weighing cover. Be cautious to remove the guide ring and pour the molten sealant into the groove of each cup for no cracks and bubbles allowed in the solidified sealant. After the sealant solidified, remove the weighing covers and the cup holders, and wipe off the sealant stuck on the edge and the bottom of the water permeable cups. When other kinds of cup assembly are used, seal the cups according to the corresponding product instructions. Weigh the sealed water permeable cups after being kept at an ambient temperature of 23℃±2℃ for 30 minutes. Put the cups into the constant climate chamber with adjusted temperature and humidity. Take the cups out of the chamber 16 hours later, and put them into adesiccator at an ambient temperature of 23℃±2℃. Weigh the cups after being stabilized for 30 minutes, then put them into the constant climate chamber again. The time interval between each two following weighings could be 24, 48 or 96 hours, and before each weighing, the cups should be placed in the desiccator at an ambient temperature of 23℃±2℃ and stabilized for 30 minutes. End the test only if the difference between two consecutive mass increments is no more than 5%. Perform the blank test with a specimen at the same time. Calculate the WVT with the following equation:

$$WVT = \frac{24 \times (\Delta m_1 - \Delta m_2)}{A \times t}$$

Where: *WVT* is the water vapor transmission, g/(m^2·24h);

t is the time interval during which mass increment was stable, h;

Δm_1 is the mass increment of the test specimen in the time interval, g;

Δm_2 is the mass increment of the blank specimen in the time interval, g;

A is the areaof the test specimen through which water vapor transmitted, m^2.

Take the arithmetic mean of three specimens as the test result, and the measurement of each specimen should not deviate from the mean value by more than ±10%.

Notes (1) *Sealant* Sealant should not soften and deform when exposed at the condition of 38℃ and 90%RH. If the exposed surface area is 50cm^2, the mass of the sealant should not change more than 1 mg in 24 hours. For example, (a) the ratio of a mixture of paraffin wax (with the melting point of 50-52℃) and beeswax is about 85 to 15, (b) the ratio of a mixture of paraffin wax (with the melting point of 50-52℃) and viscous polyisobutene (with low degree of polymerization) is about 80 to 20.

(2) *Desiccant* The diameter of anhydrous calcium chloride in granular form would be 0.60-2.36mm. It should be dried at 200℃±2℃ in an oven for 2 hours before use. If other kinds of desiccant, such as silica gel, molecular sieve, etc., are applied, they should be activated effectively before use.

(3) After each weighing, the cups should be shaken slightly to mix the desiccant up and down.

(4) The overall weight increments of the desiccant should not exceed 10% at the end of the test.

(5) The blank test refers to the test following the same procedure as the test specimen except for that there is no desiccant in the cup.

(6) When validated as equivalent, the apparatus withthe functions of temperature and humidity controlling and automatic continuous weighing, may be employed.

(2) Container method Used to measure the amount of water vapor transmitted through container under specified temperature and RH conditions, container method is generally applicable to the containers for oral solid preparations, for example, plastic bottles for solid oral dosage.

Apparatus Constant climate chamber The temperature precision should be ± 0.6℃, the RH precision should be ±2%, and the air velocity should be in the range of 0.5-2.5m/s. After the door of the chamber is closed, the specified temperature and humidity should be recovered within 15 minutes.

Analytical balance The sensitivity should be 0.1mg (When weighing more than 200g, the sensitivity could be no greater than 1mg. And weighing more than 1000g, the sensitivity could be no greater than 0.01% of the weight).

Test conditions Include but not limit to the generally applied conditions as follows:

A: 40℃±2℃, 75%RH ± 5%RH.

B: 30℃±2℃, 65%RH ± 5%RH.

C: 25℃±2℃, 75%RH ± 5%RH.

Procedure Take a quantity oftest containers, wipe each container with dry silk cloth, repeat to open and close the closures 30 times. Add desiccant into the containers as follows: for the containers with a volume of 20ml or more, add desiccant to 13mm away from the mouth of the containers; for the containers with a volume of less than 20ml, add desiccant to 2/3 of the volume of the containers.Then tightly close the containers immediately. Fill other two containers with same amount of glass beads as the desiccant to be used as the reference. When cap liners are employed, heat-seal the bottles under the suitable condition and make sure the effectiveness of heat-sealing. If necessary, remove the caps and paper boards to avoid the possible interference. Weigh each container accurately, then place the containers in a constant climate chamber and keep for the time period specified in the general chapterof each category. Take out the containers and wipe each container with dry silk cloth. Weigh each container after being kept at ambient temperature for 45 minutes. Calculate the WVT with the following equation:

$$WVT = \frac{1000}{nV}\left[\left(T_t - T_i\right) - \left(C_t - C_i\right)\right]$$

Where: WVT is the water vapor transmission of the test container, mg/ (24h·L);

V is the volume of the container, ml;

T_i is the initial weight of each test container, mg;

C_i is the initial average weight of reference containers, mg;

T_t is the final weight of each test container, mg;

C_t is the final average weight of reference containers, mg;

n is the number of tested days, day.

Note desiccant Anhydrous calcium chloride in granular form, whose diameter should be in the range of 2.36-4.75mm, is generally used, and should be dried at 200℃±2℃ in an oven for 2 hours before use. If other kinds of desiccant, such as silica gel, molecular sieve, etc., are applied, they should be activated effectively before use.

2 Weight loss method

This method refers to measuring the weight loss in percentage of the water in the containers within a certain time under specified temperature and RH conditions. This method is generally applicable to containers for liquid oral dosage, liquid topical dosage and infusion, etc.

Apparatus Constant climate chamber The temperature precision should be

±0.6℃, the RH precision should be ±2%, and the air velocity should be in the range of 0.5-2.5m/s. After the door of the chamber is closed, the specified temperature and humidity should be recovered within 15 minutes.

Analytical balance The sensitivity should be 0.1mg (When weighing more than 200g, the sensitivity could be no greater than 1mg. And weighing more than 1000g, the sensitivity could be no greater than 0.01% of the weight).

Test conditions Include but not limit to the generally applied conditions as follows:

A: 40℃±2℃, 25%RH±5%RH.

B: 25℃±2℃, 40%RH±5%RH.

C: 30℃±2℃, 35%RH±5%RH.

Procedure Take a quantity of test containers, add nominal volume of water into the containers, and tighten the closures. When cap liners are employed, heat-seal the bottles under the suitable condition and make sure the effectiveness of heat-sealing. If necessary, remove the caps and paper boards to avoid the possible interference. Weigh accurately, and place the containers in a constant climate chamber and keep for 14days. Take out the containers, Weigh each container accurately after being kept at ambient temperature for 45 minutes. Calculate the percentage of water loss with the following equation:

$$\text{The percentage of water loss (\%)} = \frac{W_1 - W_2}{W_1 - W_0} \times 100\%$$

Where: the percentage of water loss, %;

W_1 is the initial weight of each test container with water, g;

W_0 is the weight of each blank container, g;

W_2 is the final weight of each test container with water, g.

For the test specimens of the sealed packages filled with liquid, such as infusion products or liquid preparations for oral use, etc., take a quantity of test specimens and weigh accurately, then place the specimens in a constant climate chamber and keep for 14 days. Take out the test specimens, weigh accurately after being kept at ambient temperature for 45 minutes. Calculate the percentage of water loss with the following equation:

$$\text{The percentage of water loss (\%)} = \frac{W_1 - W_2}{W_1} \times 100\%$$

Where: the percentage of water loss is the WVT of the container, %;

W_1 is the initial weight of each test container with water solution, g;

W_2 is the final weight of each test container with water solution, g.

Method 2 Electrolytic analysis method

This method refers to the WVT analysis method for calculating the total amount of water vapor transmitted through the unit area of test specimen in a certain time by the numerical values of the electrolytic currents when water vapor contacting with electrode is electrolyzed to hydrogen and oxygen.

Apparatus The water vapor transmission tester is mainly composed of:

Transmission cell The upper chamber of high humidity generally contains a ground glass plate soaked in a saturated salt solution to maintain the constant humidity environment at one side of the specimen, and the lower chamber is connected to an electrolytic cell.

Electrolytic sensor The water vapor brought to the cell could be quantitatively determined.

Test conditions Include but not limit to the generally applied conditions as follows:

A: 23℃±0.5℃, 85%RH±2%RH.

B: 38℃± 0.5℃, 65%RH±2%RH.

Procedure Choose three pieces of the test specimens, which should be of uniform thickness and free from wrinkles, creases, pinholes and other defects. Condition the specimens at 23℃±2℃ and 50%±10%RH for at least 4 hours. Conduct the test according to the operation manual of the instrument. End the test when the displayed values keep stable (generally speaking, if the fluctuation amplitude of three consecutive current sampling values is not more than 5%, the steady state could be regarded as being reached). The RH needed could be adjusted bysalt solutions. The common preparations for temperature and humidity condition are shown in Table 1.

Table 1 Preparationsfor relative humidity

temperature	relative humidity	solution
23℃	85%	saturated solution of KCl
38℃	90%	saturated solution of KNO_3

The WVT could be calculated directly with the computer analysis software of the tester, or calculated according to the following equation:

$$WVT = 8.067 \times \frac{I}{A}$$

Where: WVT is the water vapor transmission of the test specimen, g/ (m^2·24h);

A is the transmission area of the test specimen, m^2;

I is the electrolytic current, Ampere;

8.067 is the constant, g/ (Ampere·24h).

Take the arithmetic mean of three specimens as the test result. Except for the specimen of high barrier property (the WVT result is less than or equal to 0.5g/ (m^2·24h)), the measurement of each specimen should not deviate from the mean value by more than ±10%. When the test result is less than or equal to 0.5g/ (m^2·24h), the measurement of each specimen should not be greater than 0.5g/ (m^2·24h).

Method 3 Infrared detector method

This method is usually employed to determine the WVT of films or sheeting for pharmaceutical use. When the test specimen is mounted, the test chamber is divided into two parts. One side of the specimen is the low-humidity chamber, and the other side is the high-humidity chamber filled with water vapor at a known temperature. Due to the existence of a certain humidity difference, water vapor transmits from the high humidity chamber through the test specimen into the low humidity chamber, and then is transferred by the carrier gas into infrared detector to generate a certain amount of electrical signals. When the test reaches a steady state, the WVT of the test specimen is calculated by the electrical output signals.

Apparatus The infrared water transmission tester (Fig.2) is composed of humidity adjusting device, testing chamber, infrared detector, drying tube and flow meter. The humidity in the high humidity chamber can be regulated by the humidified carrier gas or the saturated salt solution. The infrared detector is connected with the low humidity chamber to measure the concentration of water vapor. The sensitivity of the infrared sensor to water vapor should be at least either 1μg/L or 1mm^3/dm^3.

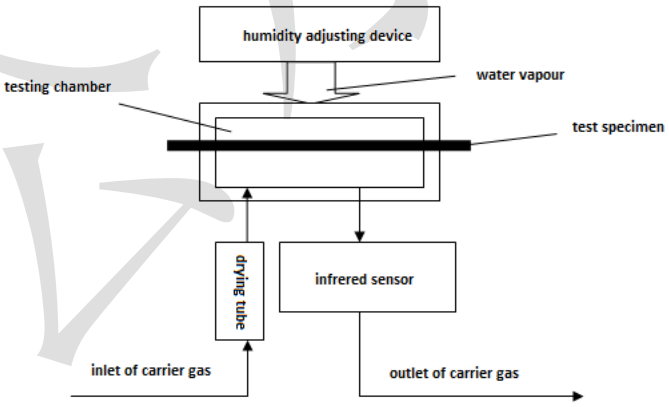

Fig. 2 Example ofinfrared water transmission tester

Test conditions Include but not limit to the generally applied conditions as follows:

A: 25℃±0.5℃, 90%RH±2%RH.

B: 38℃±0.5℃, 90%RH±2%RH.

C: 40℃±0.5℃, 90%RH±2%RH.

D: 23℃±0.5℃, 85%RH±2%RH.

E: 25℃±0.5℃, 75%RH±2%RH.

Procedure Choose three pieces of representative specimens of suitable size, which shouldbe of uniform thickness and free from wrinkles, creases, pinholes and other defects. Condition the specimens at 23℃±2℃ and 50%±10%RH for at least 4 hours, and then conduct the test. End the test when the displayed values keep stable (generally speaking, when the difference between two consecutive output voltage values or displayed WVT results is not greater than 5%, the steady state could be regarded as being reached. If the difference between two consecutive output values is still not within 5%, this should be indicated in the report). The WVT could be calculate directly with the computer analysis software of the tester, or calculated according to the following equation:

$$WVT = \frac{S \times (E_S - E_0)}{(E_R - E_0)} \times \frac{A_R}{A_S}$$

Where: WVT is the water vapor transmission of the test specimen, g/ (m^2·24h);

E_0 is the zero-drift voltage, V;

E_R is the steady-state voltage of the reference specimen,V;

Sis the WVT of the reference specimen, g/ (m^2·24h);

E_S is the steady-state voltage of the test specimen,V;

A_R is the transmission area of the reference specimen, m^2;

A_S is the transmission area of the test specimen, m^2.

Take the arithmetic mean of three specimens as the test result. Except for the specimen of high barrier property (the WVT result is less than or equal to 0.5g/ (m^2·24h)), the measurement of each specimen should not deviate from the mean value by more than ±10%. When the test result is less than or equal to 0.5g/(m^2·24h), the measurementof each specimen should not be greater than 0.5g/(m^2·24h).

Take the arithmetic mean of three specimens as the test result, rounding to the second place of decimals if the test result is less than 1, and to two significant figures if the test result is greater than 1.

Notes (1) Some specific test operations, e.g., the measurement of zero drift and the regulation of the carrier gas flow, should be performed based on the barrier performance of the tested materials, and according to the requirements of the instrument operation manual.

(2) Under the controlled conditions of temperature and humidity, the tester equipped with suitable container test stations could be employed further to determine the WVT of containers. Perform the test according to the instrument operation

manual.

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