



Determination of water vapor transmission rate (WVTR) of HDPE bottles for pharmaceutical products

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ABSTRACT

The objective of this study was to investigate the effects of experimental conditions for measuring the water vapor transmission rate (WVTR) of high-density polyethylene (HDPE) bottles using a steady-state sorption method. Bottles were filled with desiccant, closed with caps and heat induction sealed, and then stored in stability chambers at controlled temperature and relative humidity. Weight gain of the bottles was determined every 1 or 2 weeks until a linear weight gain profile was obtained. WVTR of the bottles was determined from the slope of the linear portion of the weight gain versus time profile. The effects of desiccants and temperature/humidity were studied. Results show that, with a sufficient amount of anhydrous calcium chloride in bottles, a negligibly low and sufficiently constant headspace humidity is maintained, and a steady-state permeation rate is achieved. For all 8 sizes of bottles used in this study, steady-state was achieved in 1 or 2 weeks after the experiment was started. This method provided reproducible WVTR data for HDPE bottles. Apparent moisture permeability of all 8 sizes of bottles was $(2.3 \pm 0.3) \times 10^{-7}$, $(2.6 \pm 0.2) \times 10^{-7}$, and $(3.4 \pm 0.2) \times 10^{-7}$ cm²/s at 25 °C, 30 °C, 40 °C, respectively. Moisture permeability determined from the current study was similar to data reported in the literature, indicating that the steady-state weight gain method can be used to obtain reliable WVTR of containers for pharmaceutical products.

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1. Introduction

Plastic containers, such as high-density polyethylene (HDPE), polypropylene (PP), and polyethylene terephthalate (PET) bottles, are widely used for packaging pharmaceutical products. These plastic containers are permeable to moisture vapor. Moisture ingress and the subsequent sorption of moisture by packaged products may lead to chemical or physical instability, or dissolution problems for some moisture-sensitive products. Loss of moisture for liquid products by permeation during storage may also lead to a change in product quality. Therefore, it is important to characterize the moisture permeability of pharmaceutical containers. In practice, moisture permeability of containers is commonly measured via the determination of water vapor transmission rate (WVTR). Upon the availability of reliable container WVTR and the properties of drug products related to gain or loss of water content, appropriate packaging could be designed to provide proper protection of products from moisture. For example, a modeling method can be used to predict *a priori*, the moisture uptake by packaged solid pharmaceuticals in various packaging designs during shelf life (Chen and

Li, 2003). Post-approval packaging changes for moisture-sensitive products can also be made readily if the new packaging can provide the same or better protective properties than the approved container closure system (FDA, 1999; PQRI, 2005).

Compendial methods for determination of moisture permeation are currently described in the USP(671) (USP29-NF24) for dispensing of pharmaceutical products. For multiple-unit containers, the USP method uses a single weight gain measurement via the use of control bottles. Data in literature have shown that results obtained by the USP method may be highly variable. For example, the standard deviation of the USP results was higher than the mean value (Taborsky and Grady, 2001; Chen and Li, 2003) in some cases. In one case, the value obtained at 25 °C/75%RH was higher than that at 40 °C/75%RH (Taborsky and Grady, 2001). A high variability in permeability renders the data of little scientific value either for packaging design or for justification of post-approval container changes. Obviously, the method needs to be modified such that accurate and reproducible results can be obtained and that clear conclusions can be drawn when WVTR values are compared.

Our previous study (Chen and Li, 2003) showed that the steady-state weight gain method could provide reproducible WVTR results for HDPE bottles. In this study, we expanded the study, verified the assumption of “sink” condition for steady-state permeation, and

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investigated the effects of desiccants and experimental conditions for determination of WVTR for different sizes of HDPE bottles.

2. Theoretical

For well-sealed plastic containers without gross defects, the mechanism of moisture ingress into the containers is mainly diffusion of water molecules through the container wall (PQRI, 2005). If the container wall is approximated as a homogeneous planar barrier with a constant diffusion coefficient, D , of water vapor at constant temperature, and if it is assumed that the concentration of water at the surface of the outside wall is kept at a constant level of C_o , the concentration at the inside wall surface is kept at essentially zero or a “sink” condition, and the initial concentration of water in the wall material is uniform at a level of C_i , the moisture permeation into the container can be determined by either measuring the quantity of water permeating through the wall into the “sink”, or by monitoring the amount of water entering the outer surface of the wall material. If the quantity of water permeating through the wall is measured, Eq. (1) can be used to describe the permeation process (Crank, 1986).

$$Q_{t,d} = \frac{DC_o}{h} \left(t + \frac{C_i h^2}{2DC_o} - \frac{h^2}{6D} \right) - \frac{2hC_o}{\pi^2} \sum_{n=1}^{\infty} \frac{(-1)^n}{n^2} \exp\left(-\frac{n^2 \pi^2 Dt}{h^2}\right) - \frac{4C_i h}{\pi^2} \sum_{m=1}^{\infty} \frac{1}{(2m+1)^2} \exp\left(-\frac{(2m+1)^2 \pi^2 Dt}{h^2}\right) \quad (1)$$

where $Q_{t,d}$ is the amount of moisture diffused through unit surface area of the wall at time t , D is the diffusion coefficient of water in the wall, h is the wall thickness, and C_o and C_i represent the water concentration at the outside surface of the wall and the initial concentration in the wall, respectively.

If the amount of water entering the outer surface of the wall material is measured, such as via the measurement of weight gain of containers per USP(671), the measured quantity per unit surface area, $Q_{t,wg}$, includes the amounts of water absorbed by the wall and the backing material in the closure, and the amount of water diffused through the wall into a “sink” created by desiccant. In this case, Eq. (2) can be used to describe the permeation process.

$$Q_{t,wg} = \frac{DC_o}{h} \left(t - \frac{C_i h^2}{2DC_o} + \frac{h^2}{3D} \right) - \frac{2hC_o}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(-\frac{n^2 \pi^2 Dt}{h^2}\right) + \frac{4C_i h}{\pi^2} \sum_{m=0}^{\infty} \frac{1}{(2m+1)^2} \exp\left(-\frac{(2m+1)^2 \pi^2 Dt}{h^2}\right) \quad (2)$$

Eqs. (1) and (2) show that at the early time, the moisture permeation profiles are not linear with time because the exponential terms in the equations are non-negligible at short times. Eqs. (1) and (2) also show that the moisture permeation profiles are affected by the initial water concentration in the wall material, regardless of the location of determination. Therefore, permeability cannot be reliably determined from early time point by a single weight gain measurement. However, if the permeation process is allowed to proceed for a longer time with sufficient data points, WVTR may be determined using the simplified form of Eq. (1) or (2), regardless of the initial water concentration in the wall. Taking the weight gain method as an example, in the first case where $C_i = 0$, and at $t \rightarrow \infty$ when steady-state is achieved, the weight gain resulting from the diffusion through unit surface area in Eq. (2) can be simplified to

$$Q_{t,wg} = \frac{DC_o}{h} \left(t + \frac{h^2}{3D} \right) \quad (3)$$

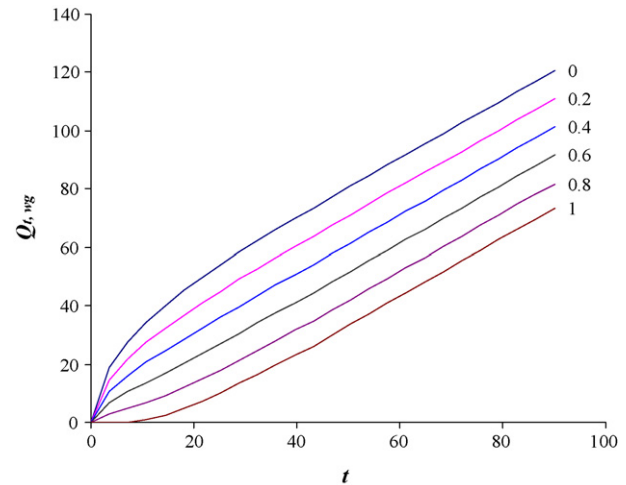


Fig. 1. Schematic of weight gain curves of containers filled with desiccants and stored at constant temperature and humidity. Numbers at the end of the curves are the values of C_i/C_o . The x- and y-axis are in arbitrary scales.

In the second case, where $C_i = C_o$, and at $t \rightarrow \infty$, Eq. (2) simplifies to

$$Q_{t,wg} = \frac{DC_o}{h} \left(t - \frac{h^2}{6D} \right) \quad (4)$$

The dependency of initial weight gain on the initial water concentration and the advantages of using steady-state weight gain data are further depicted in Fig. 1. The figure shows that the initial weight gain profiles range from a burst when the wall is initially dry ($C_i = 0$) to a delay when the wall is initially equilibrated with water ($C_i = C_o$). However, if the permeation process is allowed to proceed for a sufficiently long time to achieve steady-state permeation, the rate of weight gain at the later time points is the same regardless the initial wall conditions, as long as temperature and driving force remain unchanged. Therefore, reliable container permeability can be determined from the steady-state weight gain data.

Taking the container surface area into consideration, it can be shown that at constant temperature, WVTR through the container wall at steady-state can be found by differentiation of either Eq. (3) or (4). The result can be represented by Eq. (5).

$$WVTR = \frac{AdQ_{t,wg}}{dt} = \frac{ADC_o}{h} \quad (5)$$

where A is the surface area and h is the thickness of a container.

In practice, water concentration on the outer surface of the container wall C_o is not measured. Instead, C_o can be assumed to be proportional to the equilibrium external water concentration in the air C_{air} by partition theory as:

$$C_o = KC_{air} \quad (6)$$

where K is the partition coefficient of water vapor between the wall material and the air.

Moisture concentration in the air, C_{air} , can be calculated using the ideal gas law based on the actual and the saturated water vapor pressure under the experimental condition using Eq. (7).

$$C_{air} = \frac{18,000 \times p}{RT} = \frac{180 \times p_s \times \%RH}{RT} \quad (7)$$

where p and p_s are the actual and the saturated water vapor pressure in the air at temperature T , respectively, %RH is the percent relative humidity, and R is the gas constant. The value of 18,000 is the molecular weight of water in mg/mol.

Substituting Eqs. (6) and (7) into Eq. (5), WVTR can be expressed by Eq. (8).

$$WVTR = \frac{ADC_o}{h} = \frac{ADKc_{air}}{h} = \frac{180ADKp_s \times \%RH}{hRT} = \frac{180App_s \times \%RH}{hRT} \quad (8)$$

where P is the apparent moisture permeability of container, which is the product of diffusion coefficient and partition coefficient of moisture in the container material.

3. Experimental methods

3.1. Equipment

An electronic digital caliper (Pro-Max, Fowler) was used to measure the external surface area and wall thickness of HDPE bottles. An oven (Yamato DKN600) was used for drying desiccants. Stability stations that complied with ICH guidelines (ICH, 2003) at 25 °C/60%RH, 30 °C/65%RH, and 40 °C/75%RH were used to store bottles for permeability studies. A Secure Pak torque tester (Model 25, MRA) was used to close HDPE bottles with caps. A heat induction sealer (Model LM 3766-09, Enercon) and a vacuum leak tester (Model 1100, Uson) were used to seal and test the bottles to assure the seal integrity. Metal screen strays with diamond shape screen holes of 7 mm × 7 mm were used to hold the HDPE bottles in the stability chambers. A dual sensitivity balance with 0.01 and 0.1 mg readability (AG245, Mettler) was used to determine the weight gain of bottles. Data recorders (MicroRHTemp-EB, MageTech) were used to record the relative humidity and temperature in sealed HDPE bottles containing desiccant during permeation studies. Accuracy of the recorders was verified by using the recorders to measure the humidity over saturated lithium chloride solutions in desiccators at 25 and 40 °C prior to the use for bottles. Measured relative humidity over the lithium chloride solution was accurate to within 1%RH compared with standard values.

3.2. Materials

Square HDPE bottles (Marlex 5502BN) and matching caps (polypropylene or HDPE) used in this study were obtained from the inventory system of Abbott Laboratories. Descriptions of the bottles and closures are listed in Table 1. Anhydrous calcium chloride (4–8 mesh, JT Baker, Catalog No. 1313-07), and Desi Can (Bentonite Clay, 1 g, U.D. Belen) were used as desiccants for the moisture permeation study. The desiccants were heated at 110 °C for 7 h and allowed to cool in a sealed HDPE drum before use.

3.3. Procedure

3.3.1. Determination of bottle thickness and surface area

Three bottles of each size were cut horizontally and then vertically using a scalpel. Thickness of the bottle wall was measured

at a total of 18 locations along the cut edges using a digital caliper. External surface area of each size of the bottles was also measured using the same caliper.

3.3.2. Determination of humidity in bottles

A MicroRHTemp-EB data recorder was placed in each of the six, 4 oz HDPE bottles containing approximately 13 g of anhydrous calcium chloride. The bottles were sealed using a heat induction sealer and vacuum tested to ensure the integrity of the sealing. Three such sealed bottles were stored at 25 °C/60%RH and the other 3 bottles at 40 °C/75%RH. Relative humidity and temperature in the sealed bottles were recorded every 8 h for 70 days. Weight gain of the bottles was determined every 1 or 2 weeks. At the end of the study, the induction seal was removed and the recorders retrieved. Data was downloaded to a personal computer using software by MageTech.

3.3.3. Determination of WVTR and moisture permeability of bottles

HDPE bottles were filled with dry calcium chloride to a level of not less than two thirds of the bottle depth, closed with caps, sealed using a heat induction sealer and vacuum tested. The bottles were identified, weighed, spaced on screen trays, and stored in a stability chamber at 25 °C/60%RH. At predetermined time intervals, the bottles were retrieved from the stability chamber, allowed to equilibrate in the weighing lab for about 30 min, weighed, and returned to the chamber immediately after weighing. Weight gain profiles of the bottles were constructed. The WVTR of each bottle was determined from the slope of the linear portion of the weight gain profile by linear regression. Apparent moisture permeability, P , of the bottle was calculated from the WVTR, surface area, and thickness data of the bottles using Eq. (9).

$$p = \frac{WVTR \times hRT}{180Ap_s \times \%RH} \quad (9)$$

where h (cm) is the average thickness, and A (cm²) is the external surface area of the bottles. R is the gas constant ($R = 8.314 \times 10^6$ cm³ Pa/mol K), p_s (Pa) is the saturated water vapor pressure in the air at temperature T , and %RH is the percent relative humidity used for WVTR measurement.

The above experiment was also conducted at 30 °C/65%RH and 40 °C/75%RH for each size of bottles. Additional conditions of 25 °C/85%RH and 40 °C/50%RH were used to study the effect of humidity on WVTR and permeability of bottles.

Effects of type and amount of desiccant on WVTR were studied using 3 and 4 oz bottles with either anhydrous calcium chloride or clay desiccant. Study designs, test conditions, and results are listed in Table 2. Bottle descriptions and closures are the same as listed in Table 1. All bottles were induction sealed.

Table 1
HDPE bottles used for moisture permeation study

Bottle size/style	Finish	Surface area (cm ²)	Thickness (cm)	Cap ^a	Liner
40 cm ³ , blake	22/400	86.3	0.136	Click Loc III, CR	SafeGard 75 M
0.75 oz, square	24/400, squeeze lok	69.1	0.096	Squeeze lok, CR	Selig FS 1–20
1 oz, square	24/400, squeeze lok	87.1	0.104	Squeeze lok, CR	Selig FS 1–20
1.5 oz, square	24/400, squeeze lok	101.5	0.102	Squeeze lok, CR	Selig FS 1–7
3 oz, square	38/400, squeeze lok	157.5	0.132	Squeeze lok, CR	Selig FS 1–7
4 oz, square	38/400, squeeze lok	195.2	0.103	Squeeze lok, CR	Selig FS 1–20
5 oz, square	38/400, squeeze lok	228.2	0.103	Squeeze lok, CR	Selig FS 1–20
175 cm ³ , blake	38/400	233.9	0.108	Continuous screw thread	SafeGard 75 M

^a All caps are made of polypropylene, except the caps for the 40 cm³ bottles are made of high-density polyethylene for the outer layer and polypropylene for the inner layer.

Table 2
Effects of desiccants on WVTR and apparent moisture permeability of bottles

Bottle size	Desiccant/quantity	Test condition	WVTR (mg/day, mean \pm S.D.)	$P \times 10^7$ (cm ² /s, mean \pm S.D.)
3 oz	CaCl ₂ , 90 g	40 °C/75%RH	1.23 \pm 0.02	3.1 \pm 0.1
3 oz	Bentonite clay, 10 g	40 °C/75%RH	1.25 \pm 0.07	3.2 \pm 0.2
3 oz	CaCl ₂ , 90 g	40 °C/50%RH	0.83 \pm 0.03	3.2 \pm 0.1
3 oz	Bentonite clay, 10 g	40 °C/50%RH	0.87 \pm 0.05	3.3 \pm 0.2
4 oz	CaCl ₂ , 13 g	25 °C/60%RH	0.53 \pm 0.02	2.3 \pm 0.1
4 oz	CaCl ₂ , 90 g	25 °C/60%RH	0.59 \pm 0.01 ^a	2.6 \pm 0.1
4 oz	CaCl ₂ , 130 g	25 °C/85%RH	0.82 \pm 0.05	2.6 \pm 0.2
4 oz	CaCl ₂ , 13 g	40 °C/75%RH	2.25 \pm 0.05	3.6 \pm 0.1
4 oz	CaCl ₂ , 90 g	40 °C/75%RH	2.36 \pm 0.03	3.8 \pm 0.1

^a MVTR of the 4 oz bottle containing 90 g of calcium chloride is significantly higher than the same sizes of bottles containing 13 g of the same desiccant by *t*-test ($p < 0.01$).

4. Results and discussion

4.1. Humidity in bottles containing desiccants

Container moisture permeability measured by steady-state weight gain method is based on an assumption that a “sink” condition exists for water vapor in the container headspace. A perfect sink is difficult to achieve for a closed container. However, by using a sufficient amount of desiccant to effectively adsorb the water molecules from the headspace, the internal relative humidity (%RH), may be lowered to a negligible level and can, therefore, be considered a “sink” condition. Using verified data recorders, results for the 4 oz HDPE bottles containing approximately 13 g of desiccants showed that %RH in the sealed bottle varied in the range of 0%–2% at 25 °C, and 0%–3% at 40 °C over 10 weeks (Fig. 2). The internal humidity of 3%RH at the end of study represented approximately 4% error relative to the external humidity of 75%RH at 40 °C if the internal humidity is ignored. Fig. 2 also shows that the

internal humidity and hence the driving force remained practically unchanged during the study. These data showed that a “sink” condition was effectively achieved in the current study. These results agree well with data in literature that the relative humidity in the air dried by anhydrous calcium chloride was 1.6% at 25 °C (Baxter and Starkweather, 1916). It should be noted that 13 g of anhydrous calcium chloride occupied approximately 10% of the over flow volume of the 4 oz bottle. This small quantity was used for this size of bottles in order to demonstrate a worst-case scenario and to reserve space for placing a recorder in each bottle. When a larger quantity of desiccants is used in normal studies, a sink condition can be better maintained.

4.2. WVTR and permeability of HDPE bottles

Experimental data from the current study showed that weight gain profiles of HDPE bottles containing desiccant and stored under ICH conditions were biphasic. Examples are shown in Fig. 3. Bottle weight gain in the early phase for up to 1 or 2 weeks was substantially faster than later time points. The rapid weight gain in the early time points can be attributed mainly to sorption of water by the wall

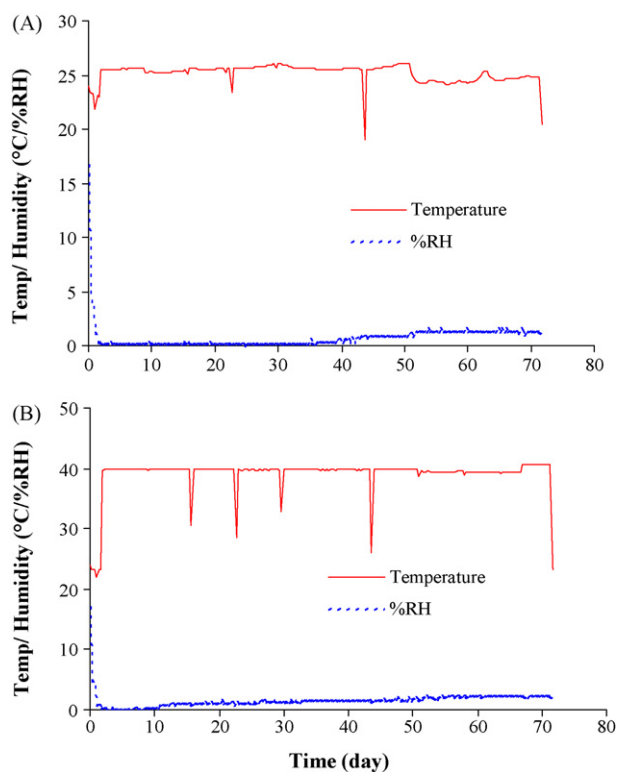


Fig. 2. Humidity and temperature in the headspace of 4 oz HDPE bottles containing 13 g of desiccant and stored at (A): 25 °C/60%RH, and (B): 40 °C/75%RH. Note: the temperature decreases during the study resulted from the removal of bottles from the stability stations for weighing.

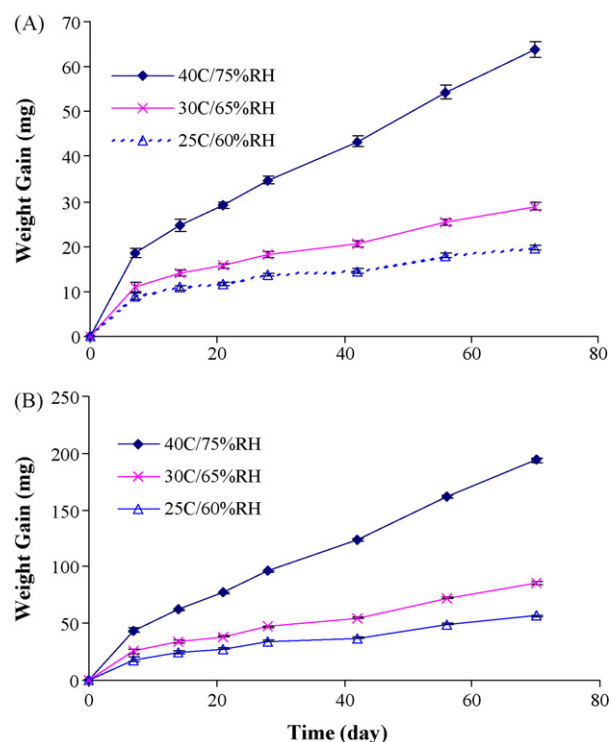


Fig. 3. Weight gain profiles of HDPE bottles under ICH conditions: (A) 1 oz and (B) 4 oz.

Table 3
Water vapor transmission rate (WVTR) and apparent moisture permeability of HDPE bottles

Bottle size	WVTR ^a (mg/day, mean \pm S.D., $n = 10$)			$P \times 10^7$ (cm ² /s, mean, $n = 10$)		
	25 °C/60%RH	30 °C/65%RH	40 °C/75%RH	25 °C	30 °C	40 °C
40 cm ³	0.15 \pm 0.01 ^b	0.26 \pm 0.01 ^b	0.70 \pm 0.02 ^b	2.0	2.5	3.3
0.75 oz	0.17 \pm 0.01	0.28 \pm 0.01	0.71 \pm 0.02	1.9	2.3	3.0
1 oz	0.21 \pm 0.01	0.34 \pm 0.01	0.92 \pm 0.01	2.1	2.4	3.3
1.5 oz	0.27 \pm 0.01	0.41 \pm 0.01	1.02 \pm 0.03	2.2	2.4	3.1
3 oz	0.36 \pm 0.01	0.53 \pm 0.02	1.28 \pm 0.02	2.5	2.6	3.3
4 oz	0.59 \pm 0.01	0.93 \pm 0.03	2.36 \pm 0.03	2.6	2.9	3.8
5 oz	0.68 \pm 0.02	1.12 \pm 0.03	2.82 \pm 0.05	2.6	3.0	3.9
175 cm ³	0.56 \pm 0.02 ^b	0.94 \pm 0.02 ^b	2.39 \pm 0.04 ^b	2.2	2.6	3.3
			Average	2.3	2.6	3.4
			S.D.	0.3	0.2	0.3

^a Determined using dry calcium chloride as desiccant.

^b $n = 6$.

and the closure, including sorption by the backing material behind the foil in the closure. The slower and linear weight gain in the later time points indicate that sorption by bottle material has reached equilibrium under the test conditions, and that steady-state permeation is reached. WVTR and apparent permeability determined from the slope of the linear weight gain profiles of different sizes of bottles are listed in Table 3. The table shows that, at a given temperature and humidity, WVTR increases as bottle size/surface area increases. WVTR also increases as the temperature and humidity are increased. When the test conditions were changed from 25 °C/60%RH to 40 °C/75%RH, the WVTR of a given size of bottle increased approximately four fold. When normalized by bottle surface area, thickness, and external water vapor concentration, the apparent permeability of the bottle material at a given temperature is consistent for different sizes of bottles. The relative standard deviation of permeability is approximately 10%–15% for all the data of 8 sizes of bottles. Apparent moisture permeability increases as temperature increases. When determined at 25, 30, and 40 °C, apparent moisture permeability of all the HDPE bottles used in this study are $(2.3 \pm 0.3) \times 10^{-7}$, $(2.6 \pm 0.2) \times 10^{-7}$, and $(3.4 \pm 0.2) \times 10^{-7}$ cm²/s, respectively. Response of permeability to temperature follows the Arrhenius equation (Fig. 4). From the slope of the Arrhenius plot, the activation energy of water vapor permeation through the HDPE material was calculated to be 21 kJ/mol. Validity of these data can be confirmed by comparison with data reported in literature. From Fig. 4, it can be determined that moisture permeability of HDPE material at 37.8 °C is 3.2×10^{-7} cm²/s, and the corresponding moisture permeation rate through unit area and thickness of

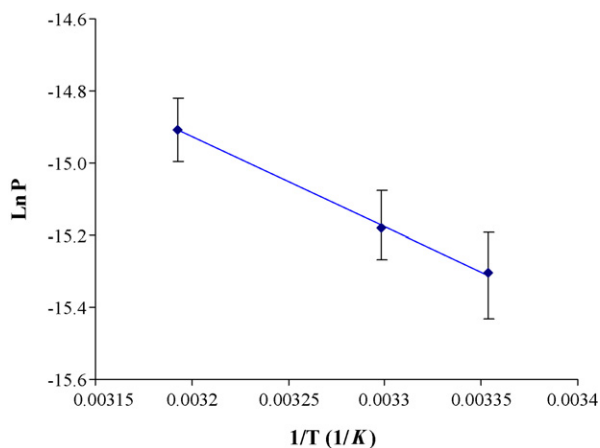


Fig. 4. Arrhenius plot of apparent moisture permeability of different sizes of HDPE bottles. Note: the solid line is the regression line of apparent permeability as a function of temperature: $\ln P = -6.923 - 2501.19/T$.

the material under a sink condition at 37.8 °C/90%RH can be calculated to be 1.30×10^{-11} g cm/cm² s. This result agrees well with a literature value of 1.37×10^{-11} g cm/cm² s for a pure HDPE film (Kamal and Jinnah, 1984), indicating that the current steady weight gain method can be used to determine valid WVTR and moisture permeability data for the plastic bottles.

4.3. Effects of desiccants

4.3.1. Quantity of calcium chloride

The effect of the quantity of anhydrous calcium chloride on WVTR was investigated by filling either 13, 90, or 130 g of the desiccant into a 4 oz HDPE bottle for WVTR measurement. These three levels of desiccant occupied approximately 10%, 70% and 100% of the overflow volume of the bottles. Results in Table 2 show that at 25 °C/60%RH, WVTR were 0.53 ± 0.02 and 0.59 ± 0.01 mg/day for the 13 and 90 g desiccant, respectively. At 40 °C/75%RH, WVTR was 2.25 ± 0.05 and 2.36 ± 0.03 mg/day for the two levels of desiccant, respectively. As expected by the nature of calculation, the difference in WVTR also appeared in apparent moisture permeability (Table 2). Although the difference in the absolute WVTR is small for different amount of desiccant, the difference is statistically significant by *t*-test ($p < 0.01$) for both test conditions. These results indicated that bottles must be filled with anhydrous calcium chloride to a level that is significantly higher than 10% of the bottle volume in order to avoid the risk of underestimation of WVTR.

When the bottles were nearly 100% filled with anhydrous calcium chloride (130 g) and tested at 25 °C/85%RH, the resultant apparent permeability was similar to that obtained with 70% fill (90 g) (Table 2), suggesting that the maximum effect of calcium chloride on WVTR has been reached when the desiccant fill is approximately 70% of the container volume. This result supports the practice of filling bottles with anhydrous calcium chloride to a level of not less than two thirds of the bottle depth for WVTR measurement.

Table 2 also shows that, for a given size of bottle, WVTR is proportional to %RH at constant temperature. When normalized by the water vapor concentration in the air and the geometry of the bottle, apparent moisture permeability is independent of %RH. This demonstrates that apparent permeability is not sensitive to water vapor concentration in the range studied, and that permeation rate is proportional to the external humidity.

4.3.2. Type of desiccant

Anhydrous calcium chloride is specified in USP (671) for measuring container WVTR. An alternative desiccant, bentonite clay, was investigated in this study for comparison. Either 90 g anhydrous calcium chloride or 10 g of bentonite clay per bottle was used for measuring the WVTR of 3 oz HDPE bottles. Results showed that

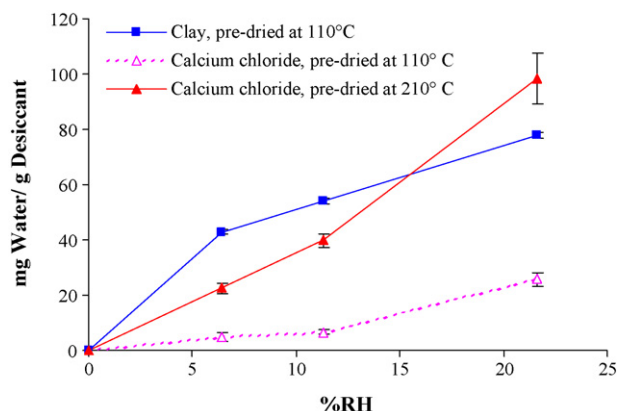


Fig. 5. Moisture sorption isotherm of anhydrous calcium chloride and clay desiccants at 25 °C.

either at 40 °C/50%RH or 40 °C/75%RH, the two desiccants resulted in similar WVTR ($p \geq 0.05$ by *t*-test) for the bottles (Table 2) under each condition even though the quantity of clay is significantly lower than anhydrous calcium chloride. These results indicate that clay is more effective in maintaining a sink condition than anhydrous calcium chloride under the experimental conditions.

In a follow up experiment, the moisture sorption isotherms of the anhydrous calcium chloride and clay desiccant, both pre-dried at 110 °C, were measured by equilibrating the dry desiccants in desiccators containing saturated salt solutions at 25 °C for 1 week, followed by measurement of weight gain. Deliquescence of calcium chloride occurred at and above 21.6%RH. Results showed that the equilibrium moisture sorption capacity of the anhydrous calcium chloride pre-dried at 110 °C was substantially lower than clay desiccant in the low humidity range (Fig. 5). At 6%RH/25 °C, moisture capacity of clay is about 8 times higher than calcium chloride when both are pre-dried at 110 °C. Obviously, the amount of desiccant needed to create and maintain a sink condition is inversely proportional to the moisture sorption capacity. Therefore, bentonite clay can be used in an amount of about one eighth of that anhydrous calcium chloride for WVTR measurement, particularly when space is limited for desiccant. The use of smaller amount of clay desiccant to create a sink condition has been supported by the results in the above that 10 g of clay resulted in similar WVTR as the use of 90 g of anhydrous calcium chloride for 3 oz bottles.

A review of the scientific literature indicates that calcium chloride can exist in multiple hydrates, and that the hexahydrate will lose water only when temperature reaches 200 °C (Budavari et al., 1989). Therefore, the same anhydrous calcium chloride was pre-dried at 210 °C for 7 h, and then exposed to different humidity in desiccators. Results showed that activation at 210 °C significantly improved the moisture sorption by the desiccant (Fig. 5). However, moisture sorption capacity was still lower than clay desiccant in the range of less than 10% relative humidity. These results showed that drying at 110 °C as specified in the current USP(671) is not sufficient to fully activate the commercial product anhydrous calcium chloride if the material has been exposed to moisture during shipping and storage. Such deficiency can be corrected by activation at 210 °C. If activation is kept at 110 °C for calcium chloride, a larger amount of the desiccant is needed to compensate for the incomplete activation.

4.4. Effects of balance sensitivity and data recording

The overflow volume of the bottles used in this study ranges from 29 ml for the 0.75 oz to 200 ml for the 175 cm³ bottles. A pre-

Table 4
Effects of test conditions on variability of bottle WVTR

Bottle size	Relative standard deviation of WVTR (%R.S.D.)		
	25 °C/60%RH	30 °C/65%RH	40 °C/75%RH ^a
40 cm ³	6.7	3.8	2.9
0.75 oz	5.9	3.6	1.4
1 oz	4.8	2.9	1.1
1.5 oz	3.7	5.3	1.0
3 oz	5.6	8.2	1.6
4 oz	5.1	4.3	1.3
5 oz	5.9	3.6	1.4
175 cm ³	3.6	2.1	1.7

^a %R.S.D. resulted from 40 °C/75%RH is significantly lower ($p < 0.01$) than that from 25 °C/60%RH and 30 °C/65%RH.

cision of 1 mg in weight gain data would be sufficient to meet the current USP(671) requirement for these bottles. Results in Table 3 show that WVTR of these bottles is smaller than 1 mg/day in many cases, especially at the conditions of 25 °C/60%RH and 30 °C/65%RH. To ensure the small values are measured accurately, weight gain data must be recorded with high precision. Such a need can be seen from the following example. The WVTR of the 3 oz bottle is 0.36 mg/day at 25 °C/60%RH. Assuming that 5% of error is acceptable in the results, the acceptable error in data rounding is only 0.126 mg/week if weight gain is measured every 7 days, not counting any other sources of error. That is, data recording must be precise to a level of 0.1 mg for such measurement. Obviously, weighing with a precision of 1 mg will lead to a large uncertainty in the WVTR result for these bottles.

Weighing uncertainty can be minimized either by using a more sensitive balance to obtain more precise results, extending the test interval, using a more aggressive storage condition, or any combinations of the three. Note that balance readability or sensitivity is not the same as weighing precision. Readability is practically the minimum noise of weighing. In general, detection limit hence precision is approximately 3–5 times that of noise. Taking the readability of the commonly available balances into consideration, one will need to use a balance with a readability one magnitude smaller than the required precision for reliable weighing. Experience from our laboratory has demonstrated that using a balance with readability one tenth or one hundredth of the USP recording precision is very helpful in obtaining reproducible container WVTR results.

4.5. Effects of test conditions

Different test conditions, including three ICH stability conditions and other, non-conventional conditions were investigated in the current study. Tables 2 and 3 and Fig. 3 show that the rate of weight gain is higher at higher humidity and/or temperature. While WVTR can be determined at different conditions, the ICH stability conditions are preferred since data can be directly inferred as a moisture barrier property for product protection under the ICH conditions. When the weighing variability is controlled to a given precision, the use of an aggressive test condition will result in a higher rate and hence a smaller percent relative standard deviation (%R.S.D.) than using a mild condition, as listed in Table 4. A smaller %R.S.D. shows that the data is less scattered and hence the rate is more reproducible. ANOVA analysis using the data listed in Table 4 indicates that the %R.S.D. of WVTR determined at 40 °C/75%RH is significantly lower than the result from either the 25 °C/60%RH or the 30 °C/65%RH ($p < 0.01$). Based on these results, it can be concluded that the accelerated condition of 40 °C/75%RH is a preferred condition for measuring precise WVTR and moisture permeability for container comparison or ranking purpose. Of course, WVTR ought to be determined at the specific storage temperature such as

25 or 30 °C if the WVTR is intended for prediction of product quality under the same storage conditions.

5. Conclusions

The current study investigated the effects of desiccants and test conditions for determination of WVTR of HDPE bottles using a steady-state weight gain method. This method is justified based on diffusion theory and is supported by experimental data. Results of this study showed that the rate of initial bottle weight gain was substantially higher than that of the later steady-state phase, which agreed with diffusion theory. Steady-state was reached in a week or two after the initiation of the study for HDPE bottles. The moisture permeation rate obtained from the current study is similar to the reported value for HDPE material, indicating that the steady-state method is reliable for measuring WVTR of bottles.

The use of a sufficient amount of anhydrous calcium chloride for test bottles results in a negligibly low and constant humidity in the bottles. Drying of the desiccant at 210 °C prior to use is helpful to ensure that the desiccant is fully activated to assure a sink condition is achieved and maintained during study. Clay desiccant can be used in a smaller quantity than anhydrous calcium chloride because the former has a substantially higher moisture sorption capacity than the latter in the low humidity range, which is advantageous in maintaining a sink condition inside containers for WVTR measurement, particularly when containers have limited space for desiccants.

Most of the WVTR values from the current study were smaller than 1 mg/day per bottle at either 25 °C/60%RH or 30 °C/65%RH for all the HDPE bottles that are smaller than 200 ml. In order to obtain accurate and reproducible results for these sizes of bottles, weight gain data must be recorded with a precision that is not larger than 0.1 mg. Results from the current experiment showed that, when balance capacity permitted, the use of a balance with a precision of 0.01 mg was very helpful for obtaining precise results.

Any one of the three ICH conditions can be used for measuring container WVTR. However, if WVTR values are intended for predicting the moisture protection efficiency of containers for pharmaceutical products during stability study, WVTR ought to be determined under a specified ICH stability condition for the prod-

ucts. Due to the increase of both the moisture concentration in the air and the permeation coefficient of the plastic material at elevated temperature, WVTR results obtained at the 40 °C/75%RH condition is the highest, and the precision of the WVTR determination is the best among the three ICH conditions. Therefore, for the purpose of comparing the property of different containers, the 40 °C/75%RH conditions is a preferred condition for determination of WVTR of high barrier containers, such as HDPE bottles. The apparent moisture permeability of different sizes of HDPE bottles obeys the Arrhenius equation over the range of ICH conditions. Therefore, WVTR of HDPE bottles at one ICH condition can be used to calculate the WVTR at other ICH conditions upon the availability of the activation energy of water diffusion through the HDPE material.

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