

Basis for Using Moisture Vapor Transmission Rate Per Unit Product in The Evaluation of Moisture-Barrier Equivalence of Primary Packages for Solid Oral Dosage Forms

By

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Introduction

For pharmaceutical solid oral dosage forms, it is well recognized that the most common cause for a packaged product failing to meet its specification is its instability, as a result of “moisture uptake”¹⁻³. The failure is usually related to out-of-specification or out-of-range values in any or combination of the following quality attributes: assay, product degradants, dissolution rate, and other physical properties.

Pharmaceutical solid oral dosage forms are typically packaged in plastic bottles, thermoformed plastic blisters, or cold-formed aluminum blisters. These container closure systems are sealed either by compression-fit between a hard surface and a soft surface or by application of heat to an adhesive layer of polymers. These container closure systems are considered semi-permeable packages and therefore the moisture barrier properties need to be characterized.

For the purposes of this discussion, it is assumed that manufacturers have procedures in place to demonstrate that container closure systems are free from pinholes and channels. Therefore, packages with pinholes or channels that allow convective mass transfer are excluded.

Change from the use of one container closure system to another requires demonstrating that the container closure system affords equivalent or better protection. This can be achieved in one of two ways, either by generating formal stability data, or by providing performance-based data for the container closure system being compared. We will show that the relationship of a container closure system's Moisture Vapor Transmission Rate (MVTR), and the number of units contained in the system can be used to demonstrate moisture-barrier equivalence. Specifically, it will be shown that MVTR/Unit Product is the critical parameter for demonstrating this equivalence.

Ingress of Moisture to Container Closure Systems

Moisture ingress into the well-sealed primary packages occurs via two major routes, permeation through the container wall and the seal layer, and diffusion through narrow

imperfection channels in the seal or the container wall. Note that other than imperfections introduced in the forming and sealing operations, the container wall is either a nonporous “dense” polymer or a multi-layer polymer/aluminum foil composite.

Gas-permeation through polymers has long been recognized to follow a solution-diffusion mechanism^a and can be quantitatively described by the Fick’s Law. When the moisture partial pressures on both sides of the barrier are held constant, steady-state permeation will be reached in due time^b. At steady-state, the following relationship holds for a flat film:

Steady-state moisture permeation rate, mpr = (permeability coefficient, P_p) x (surface area for permeation, A_p) x (moisture partial pressure difference across the polymer per unit film thickness, $\frac{\Delta p}{\ell}$)

or, expressed mathematically,

$$mpr = P_p \times A_p \times \frac{\Delta p}{\ell} \quad \text{Eq(1)}$$

The moisture permeability coefficient, P_p , of a moisture-barrier or seal polymer (such as HDPE^c, PVC, PVDC, PCTFE, LDPE, PP, polycycloolefins, PET, and various copolymers, is a characteristic property of the individual barrier material. It is practically a constant for a given material at a given temperature, essentially independent of the driving force, Δp .

For a specified commercial container, Equation (1) has to be integrated over the whole effective permeation area where the thickness may be variable, in order to determine the overall steady-state moisture permeation rate, MPR, into the container:

$$MPR = (P_p \times \oint \frac{dA_p}{\ell}) \times \Delta p \quad \text{Eq(2)}$$

Note that the term in the parenthesis in Equation (2), $(P_p \times \oint \frac{dA_p}{\ell})$, is a property of the specific container of interest.

^a The gas molecules are first “absorbed” into one face of the polymer barrier, then move through the bulk of the polymer by molecular diffusion, and finally are “desorbed” from the other face of the polymer barrier. Polymers with low affinity for water molecules, and/or with low free-volume and/or strong chain-chain attraction, are therefore high water barriers.

^b The time to reach steady-state depends primarily on the diffusion coefficient and the thickness of the barrier. (See for example, J Crank and G.S. Park “Diffusion in polymers”, Academic Press, New York 1968)

^c See attached Glossary for Acronyms

Diffusion of gases through micro-channels is non-convective and is also well described by the Fick's law, and can be described by an expression similar to Equation (1). For a given sealed container, the following equation applies:

Steady-State Moisture Diffusion Rate, $MDR = (\text{effective permeability coefficient, } P_d) \times (\text{effective surface area for diffusion, } A_d) \times (\text{moisture partial pressure difference across the container, } \Delta p) \div (\text{effective diffusion length, } \ell_d)$

or, expressed mathematically,

$$MDR = (P_d \times \frac{A_d}{\ell_d}) \times \Delta p \quad \text{Eq(3)}$$

Note that the term $(P_d \times \frac{A_d}{\ell_d})$ is also a property of the specific sealed container of interest.

In the absence of gross defects, overall (steady-state) moisture vapor transmission rate, MVTR, into a given sealed container is thus the combined contribution of the two moisture ingress routes:

$$\begin{aligned} MVTR &= MPR + MDR \\ &= (P_p \times \oint \frac{dA_p}{\ell}) \times \Delta p + (P_d \times \frac{A_d}{\ell_d}) \times \Delta p \\ &= K \times \Delta p \end{aligned} \quad \text{Eq(4)}$$

where K is a characteristic property of the specific container closure system of interest. The unit for MVTR is typically expressed in mg/day/container; the water partial pressure is often expressed in mmHg.

Equation (4) embodies the theoretical basis for quantifying the moisture-barrier property of a given container at a given temperature. It also provides the foundation for experimental determination of this intrinsic property of a given container closure system.

Experimentally, a sufficient amount of high-capacity desiccant is placed in the empty container. The container is sealed with the selected closure, placed in an environmental chamber at fixed temperature and relative humidity, and the weight gain is monitored with time. If the amount and type of desiccant is chosen correctly, the internal water partial pressure will remain low (e.g. <5 mmHg at 40C) throughout the measurement run; as a result, the Δp in Equation (4) remains essentially constant during the course of the MVTR measurement.

MVTR is, therefore, interchangeable with K, the characteristic moisture-barrier of a given container closure system via the rearranged Equation (4):

$$K = \frac{MVTR}{(\Delta p)_{test}} \quad \text{Eq(4a)}$$

where $(\Delta p)_{test}$ is a constant depending only on the test condition.

In the following discussion, mass-balance considerations together with Equation (4a) will be used to establish the equation that governs the moisture-time profile inside any container closure system for solid oral dosage forms. The governing equation (see below) unequivocally describes the time-profile of the moisture content or relative humidity inside the container for a given set of external test conditions (e.g. ICH 40C/75%RH, or 30C/65%RH, or 25C/60%RH). Using the governing equation, we will proceed to demonstrate that

equivalent value of (MVTR/unit product) corresponds to equivalent moisture protection.

Governing Equation

Consider the mass-balance for water within a sealed container. Assuming negligible chemical consumption of water, we can write the following mass-balance equation with the help of Equation (4) for a sealed package^d:

$$\frac{dn}{dt} = MVTR = K \times (p_{ex} - p) \quad \text{Eq (5)}$$

where n is the total mass of water inside the container, in the headspace and solid (mg)
 t is time (day)
 p is the (internal) headspace partial pressure of water vapor (mmHg)
 p_{ex} is the external partial pressure of water vapor (mmHg)

The total mass of water inside the container, n , comprises the moisture in the headspace and in the solids. The solid could be the product, the desiccant, or fillers such as cotton.

Let the total headspace volume inside the container be V (ml), then the rate of change of water mass in the headspace, according to the ideal-gas law will be

^d For a vast majority of oral solid dosage forms, the amount of water consumed by chemical reaction is negligibly small or non-existent. The impact of the small induction period on this mass-balance equation is negligible because of the long time scale of shelf-life stability studies (2 years for most oral solid products).

$$\frac{dn_{(headspace)}}{dt} = 18 \frac{V}{RT} \frac{dp}{dt} \quad \text{Eq(5a)}^e$$

If there are N solid components that absorb water vapor reversibly inside the container, the rate of change of water mass in the solids will be

$$\frac{dn_{(solids)}}{dt} = \sum_1^N m_i \frac{dC_i}{dt} \quad \text{Eq(5b)}$$

where m_i is the dry mass of component i inside the container (g)

C_i is the equilibrium concentration of water in component i (mg/g dry-basis), when the water partial pressure inside the container is p (mmHg)

R is the gas constant (62.36 mmHg-ml/m mole-°K)

T is the temperature (°K)

t is time (days)

Equation (5) can now be re-written as

$$18 \frac{V}{RT} \frac{dp}{dt} + \sum_1^N m_i \frac{dC_i}{dt} = K \times (p_{ext} - p) \quad \text{Eq (6)}$$

Integration of Equation (6) gives^f:

$$\left[\frac{18V}{RT} \int_{p_0}^{p_f} \frac{dp}{p_{ext} - p} + \sum_1^N m_i \int_{C_i^0}^{C_i^f} \frac{dC_i}{p_{ext} - p} \right] \times \frac{1}{K} = t \quad \text{Eq (7)}$$

where p_0 is the initial water partial pressure inside the container

p_f is the water partial pressure at time t

C_i^0 is the initial equilibrium water content of component i

C_i^f is the equilibrium water content of component i at time t

^e The numerical number 18, the molecular mass of water, was included to ensure dimensional consistency.

^f Implicit in this mathematical operation is the assumption that the headspace and the various solid contents in the container are at thermodynamic equilibrium at any given instant. This turns out to be a very good approximation as demonstrated by the data shown in Appendix A. In those examples, three different products were pre-equilibrated at pre-selected conditions, and were sealed with desiccant in glass vials separately. The headspace relative humidity was then monitored over time to determine how fast the system reached equilibrium. The data clearly demonstrated that it took no more than one day which is negligible compared with the typical expectation of 2-yr shelf life. The equilibrium approximation is thus well justified.

The first term in Equation (7), $\frac{18V}{RT} \int_{p_0}^{p_f} \frac{dp}{p_{ext} - p}$, corresponds to the total change in water content of the headspace, and the second term, $\sum_1^N m_i \int_{C_i^0}^{C_i^f} \frac{dC_i}{p_{ext} - p}$ corresponds to total change in water content of the various solids in the container.

For the vast majority of packages for solid dosage forms, the first term is negligibly small relative to the second term. This can be demonstrated by simply considering the amount of water that can be held in the (gaseous) container headspace and in the solids.

For example, consider the change in the amount of water in one ml of headspace gas (air) at 40C^g when the RH increases from 15% to 75%, an extreme change for a primary package. This corresponds to a change of 0.031 mg water per ml of headspace. For a 100 mg tablet packaged in a unit-dose blister, the typical headspace is no more than 1.0 ml. Thus, even if the headspace has increased from 15% to 75%, the amount of water in the headspace will increase by 0.03 mg, which corresponds to a mere 0.03% of the mass of the 100 mg tablet.

For a multiple-unit container such as a 75 ml bottle containing 30x100 mg tablets, the above extreme change of headspace humidity of 60% corresponds to 2.32 mg water. This amounts to only 0.08% of the total mass of the tablet, near or below the accuracy of the current methods used for water content determination.

Equation (7) can therefore be simplified to the following expression with negligible loss in accuracy^h:

$$\sum_1^N m_i \int_{C_i^0}^{C_i^f} \frac{dC_i}{p_{ext} - p} = K \times t = \frac{MVTR}{(\Delta p)_{test}} \times t \quad \text{Eq(8)}$$

This expression is the governing equation that describes the water content of component i as a function of time under any of the ICH stability testing conditions. The relationship between C_i and p is an intrinsic material property, typically expressed in terms of “moisture sorption isotherm” that can be determined experimentally and independently for each solid.

The definitions for the symbols in Equation (8) are presented below again for clarity:

t is the duration of the test time

m_i is the dry mass of component i in the container

^g The water “vapor pressure” at 40C is 55.3 mmHg.

^h The conclusion drawn from this simplification is not changed even if the headspace contribution is not negligible. This simplification is made here mainly to make the mathematical presentation as simple as possible. See Appendix B for details.

p is the water partial pressure inside the container
 p_{ext} is the constant external water partial pressure (e.g. 55.3 mmHg \times 75% at 40C, corresponding to the 40C/75%RH test condition)
 C_i^0 is the initial equilibrium water content of component i
 C_i^f is the equilibrium water content of component i at time t
 $(\Delta p)_{test}$ is a constant depending only on the test condition used in determining MVTR at the temperature of interest
 MVTR is the steady-state moisture transmission rate into the container/closure at the temperature of interest and the relative humidity in the testing chamber

Implication of The Governing Equation

The utility of Equation (8) in establishing moisture-barrier equivalence can be illustrated by considering a simple case where no other moisture-absorbing solid is present other than the drug product itself. This simplified case corresponds to, for example, single-unit blister packages or multiple-unit bottle packages without desiccant; the equation simplifies to:

$$\int_{C_1^0}^{C_1^f} \frac{dC_1}{p_{ext} - p} = \frac{MVTR}{m_1} \times \frac{1}{(\Delta p)_{test}} \times t \quad \text{Eq(9)}$$

where m_1 is the mass of the drug product itself.

Note that the only unknown in Equation (9) is (C_1^f) , the final moisture content of the drug product at time t for a packaged product under stability testing.

Thus, for a given drug product of the same initial moisture content, as long as the value $(MVTR/m_1)$ is kept constant, the moisture content of the drug product will be the same at any specified time point during the stability test, regardless of the primary container.

In other words, two container closure systems that exhibit the same (MVTR/unit product) are equivalent as far as moisture-protection is concerned.

An example is given in Appendix C to illustrate and support this conclusion.

Another example is given in Appendix D to illustrate the effectiveness of the approach for differentiating the degree of moisture-protection offered by different container-closure systems.

Conclusion and Recommendations

In this paper, we have presented a step-by-step derivation of the equation that governs the time-profile of the moisture content inside any container closure system for solid oral dosage forms. The physical phenomena involved are straightforward and can be reduced to rigorous mathematical treatment with high degree of accuracy. As clearly illustrated in the discussion associated with Equation (9), (MVTR/unit product) is indeed the critical container closure parameter that allows one to establish the “moisture barrier” equivalence.

On the practical side, the MVTR determination is subject to experimental errors as well as small variations in the properties of the container closure such as wall thickness and closure sealing. In practice, an equivalent (MVTR/unit product) “range” will have to be demonstrated via stability studies or other scientific means for a given drug product during pharmaceutical development. Once this range is established, post approval changes made to the container closure system will be assured of moisture-barrier equivalence as long as the (MVTR/unit product) of the modified or new system falls in the qualified range.

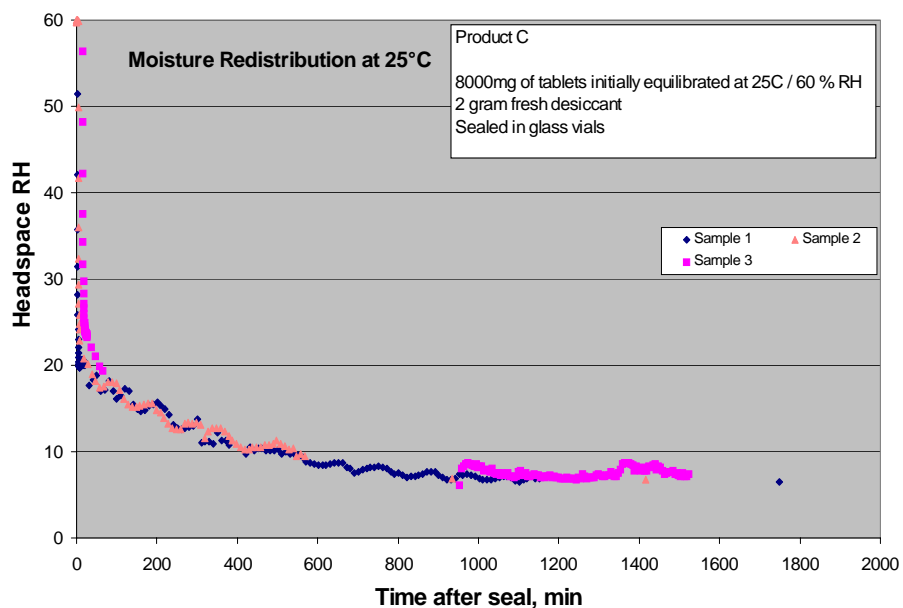
Current methods for determination of MVTR may not be sensitive enough for high barrier materials required for the packaging of moisture sensitive products. In order to apply the MVTR/unit product concept to high barrier materials, a method with increased sensitivity is required. An improved test method will thus be investigated as part of the proposed project

References

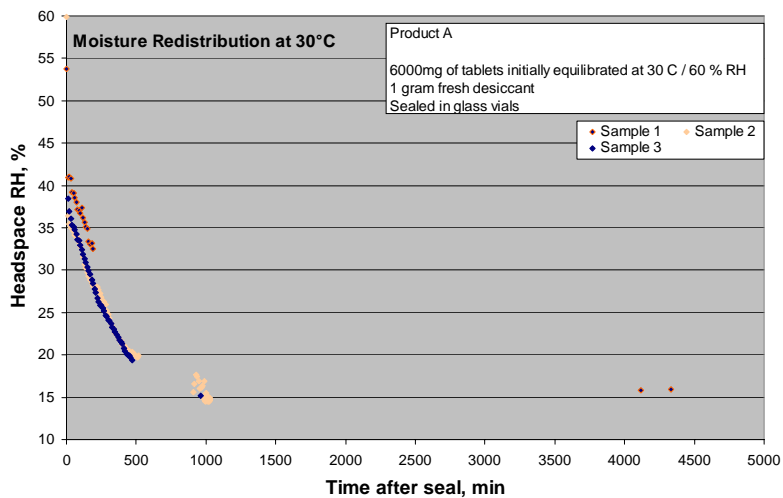
1. FDA Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, Section III G "Solid Oral Dosage Forms and Powders for Reconstitution" page 33, May 1999.
2. "Application of sorption-desorption moisture transfer modeling to the study of chemical stability of a moisture sensitive drug product in different packaging configurations", S.I.F. Badawy, A.J. Gawronski, F.J. Alvarez, *Int. J. Pharm.*, 223, 1-13(2001).
3. "The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state", C. Ahlneck, and G. Zografi, *Int. J. Pharm.*, 62, 87-95(1990).

Appendix A

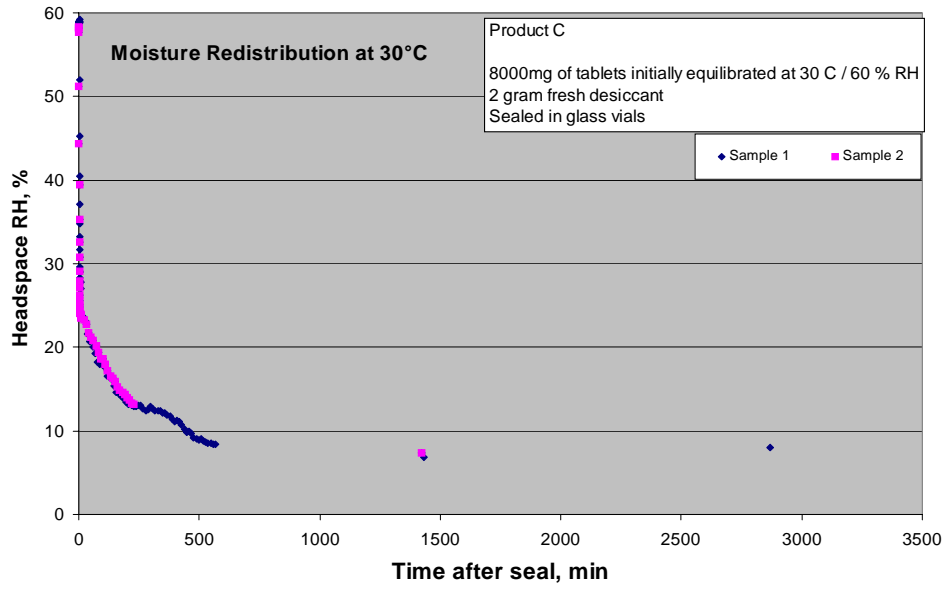
Rate of Moisture Exchange



Rate of Moisture Exchange



Rate of Moisture Exchange



Appendix B

Moisture-Barrier Equivalence When Headspace Contribution Is Not Negligible

In instances where one packages a small quantity of product in an oversized container, for example, one tablet in an 80 ml bottle, Equation (7) is simplified to:

$$\frac{18}{RT} \times \frac{V}{m_1} \int_{p_0}^{p_f} \frac{dp}{p_{ext} - p} + \int_{C_1^0}^{C_1^f} \frac{dC_1}{p_{ext} - p} = \frac{MVTR}{m_1} \times \frac{1}{(\Delta p)_{test}} \times t \quad \text{Eq(10)}$$

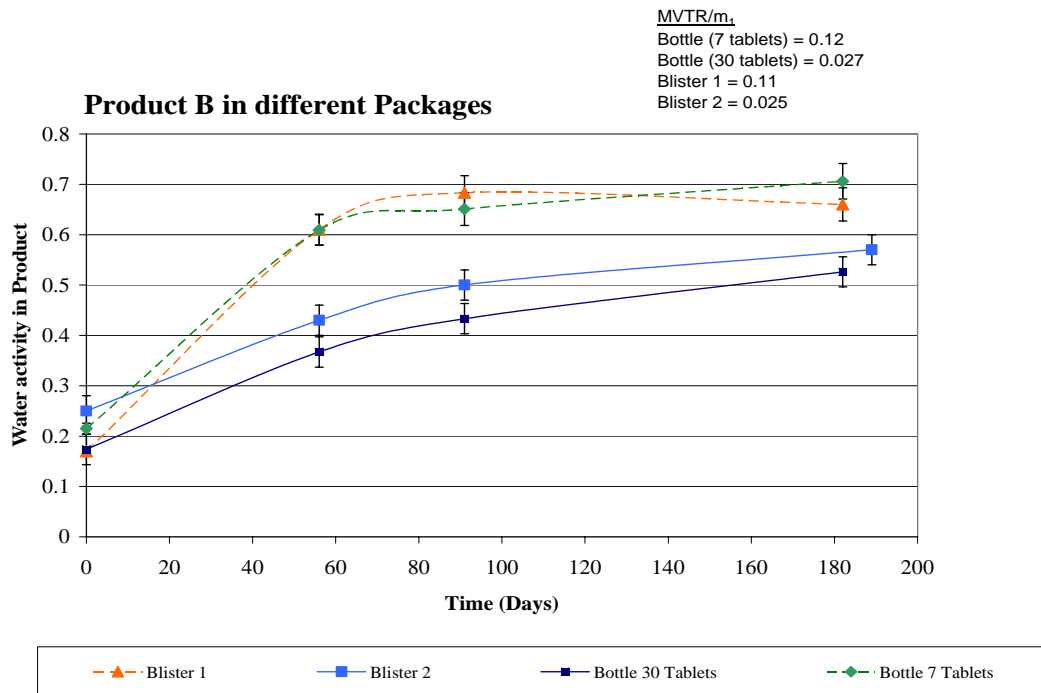
Equation (10) is the governing equation for a container closure system without desiccant when the water content in the headspace is of the same order-of-magnitude as that in the product. [See the examples preceding Equation (8) for this estimation.]

In this case, two container closure systems are equivalent as long as $(MVTR/m_1)$ and (V/m_1) are the same. In other words, when the headspace contribution is not negligible, the “headspace volume per product mass” together with “MVTR per product mass” can be used to establish moisture-barrier equivalence between container systems. The validity of “MVTR/Unit Product” thus holds.

Appendix C Examples of moisture-barrier equivalency for container-closure systems that exhibit the same (MVTR/unit product)

In this example, Product B was packaged in two different blister types and two different bottle configurations. The packages were chosen so that the (MVTR/ m_1) values for Bottle (7 tablets) and Blister 1 are similar. Same situation holds for Bottle (30 tablets) and Blister 2. The packages were stored in an ICH 40C/75%RH chamber for 180 days. At different times in the test period, individual packages were taken from the chamber and water activity in the product was determinedⁱ.

The data clearly demonstrate that the water activity profile (vs. time) of the product indeed is the same when the (MVTR/ m_1) value of the container closure system is adjusted to the same level^j. In other words, Bottle (7 tablets) and Blister 1, and Bottle (30 tablets) and Blister 2, respectively, are equivalent as far as moisture-barrier is concerned.



ⁱ Because the packages were not prepared under exactly the same environment and at exactly the same time, the initial water activity did vary somewhat; nevertheless, they are in the same range at around 0.23. A variety of instruments commonly used in the industry (such as food industry), based on principles of dew-point, or capacitance could be used for the water-activity measurement.

^j The slight difference between Blister 2 and Bottle(30 Tablets) is due to the small difference in the “initial” water activity.

Appendix D Evaluation of the moisture protection efficiency of packaging using (MVTR/unit product) for solid oral dosage forms

This example illustrates the use of (MVTR/unit product) to evaluate the protection efficiency of containers. The data are from an isolated study conducted by a participating company. A lower (MVTR/unit product) resulted in a lower product moisture content and hence a better protection of the product from moisture. Product X was sealed in HDPE bottles A and B and stored in at 25°C/60%RH. MVTR for the bottles was measured under the same conditions using steady state data. The MVTR values were 0.282 and 0.342 mg/day/bottle for Bottles A and B, respectively. The packaging configurations and the MVTR/m values (where m is the number of dose units in the bottles) were:

(1): 10 tablets of X in bottle A, $MVTR/m_1 = 0.0282$ mg/day/tablet

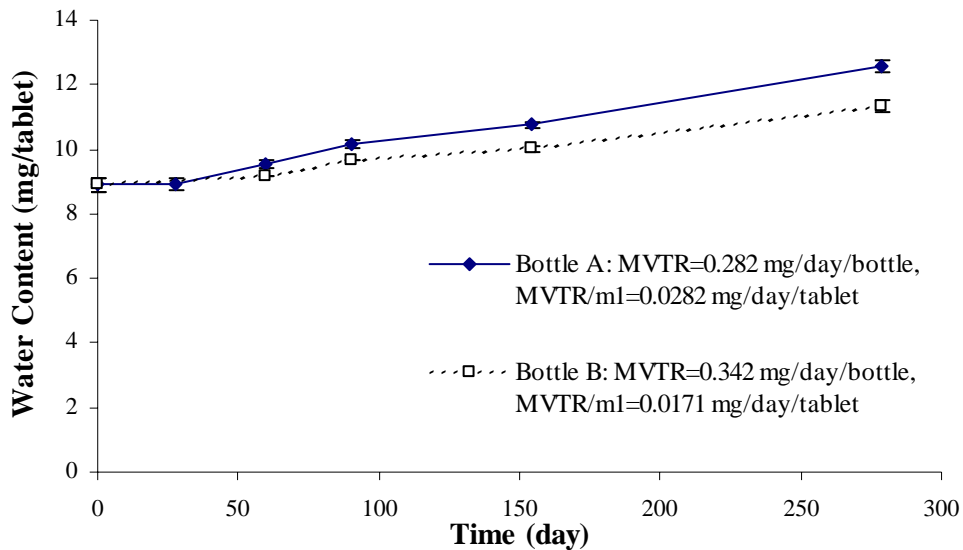
(2): 20 tablets of X in bottle B, $MVTR/m_1 = 0.0171$ mg/day/tablet

The increase in the rate of moisture uptake by tablets in bottle A using B as a reference was calculated to be: $R=0.0282/0.0171= 1.65$, and it was thus expected that bottle B would provide a better moisture protection for product X than bottle A.

At different times, samples were removed from the stability chamber, and the product water content was determined by a LOD method.

The observed rates of product water content increased in bottle A relative to bottle B were 1.60, 1.68, and 1.50 at the 3, 5, and 9 months, respectively. These results agree very well with the theoretical value of 1.65 for the two bottles, and thus show that the (MVTR/unit product) is an effective criterion for evaluating the moisture protection efficiency of primary packages, and that equivalent protection can be achieved by a proper design of the MVTR/m value using different containers for solid dosage forms.

MVTR/unit and water content of Product X in HDPE bottles at 25°C/60%RH



Glossary of Acronyms

HDPE	high density polyethylene
LDPE	low density polyethylene
MDR	overall steady-state moisture diffusion rate, Eq(3)
MPR	overall steady-state moisture permeation rate, Eq(2)
MVTR	overall moisture vapor transmission rate, Eq(4)
PET	poly(ethylene terephthalate)
PP	polypropylene
PVC	poly(vinyl chloride)
PVDC	poly(vinylidene chloride)
PCTFE	poly(chlorotrifluoro ethylene)