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A new model for predicting moisture uptake by packaged solid pharmaceuticals

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Abstract

A novel mathematical model has been developed for predicting moisture uptake by packaged solid pharmaceutical products during storage. High density polyethylene (HDPE) bottles containing the tablet products of two new chemical entities and desiccants are investigated. Permeability of the bottles is determined at different temperatures using steady-state data. Moisture sorption isotherms of the two model drug products and desiccants at the same temperatures are determined and expressed in polynomial equations. The isotherms are used for modeling the time–humidity profile in the container, which enables the prediction of the moisture content of individual component during storage. Predicted moisture contents agree well with real time stability data. The current model could serve as a guide during packaging selection for moisture protection, so as to reduce the cost and cycle time of screening study.

Keywords: Prediction; Moisture content; Packaging; Moisture permeability; HDPE bottle

1. Introduction

Many solid pharmaceutical products may sorb moisture during long-term storage as the commonly used packaging materials are permeable to moisture. Moisture content can be used as the critical criteria for judging the quality of products that are degraded by moisture. However, the determination of moisture content of packaged products, in real life, is expensive and extremely time consuming. Hence the ability to predict the moisture content during storage under a variety of conditions is very important for reducing the cost and the cycle time of product development.

Container moisture permeability is a commonly used criteria for container ranking (USP 25, 2002). However, permeability alone is not sufficient for predicting the rate of moisture uptake as the rate is governed by the environmental conditions and the water activity in the container as well as container permeability. The rate of moisture permeation through a container usually decreases over time as the humidity in the container increases due to the accumulation of moisture in the container. The effect of all these factors must be considered in order to predict the rate of moisture uptake in real life situations.

A basic model has been reported by Labuza et al. to calculate the moisture uptake by a single component (Labuza et al., 1972). But, iterative approximation procedures have to be carried out when the product isotherm is not linear. Since most pharmaceutical products do not have a linear moisture isotherm and

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products may consist of multiple components, more simplification and approximations have to be made in order to apply this basic model.

An iterative approximation method has been used to estimate the moisture uptake and the quality of some packaged products (Nakabayashi et al., 1980). In this method, a sophisticated computation procedure has to be carried out for each time interval of several days during the product's shelf life.

A sorption–desorption moisture transfer (SDMT) model has been developed by Zografi et al. to predict the moisture transfer among various solid pharmaceutical excipients via the vapor phase in a closed system (Zografi et al., 1988). In this model, the Guggenheim–Anderson-de Boer (GAB) equation (Van den Berg, 1981) is shown suitable for representing the isotherms of a variety of pharmaceutical excipients and products. This model has been used to balance the moisture content and the brittleness of capsule products (Kontny and Mulski, 1989; Chang et al., 1998). It has also been applied to simulate the humidity and product moisture contents in packages as a function of time (Kontny et al., 1992; Badawy et al., 2001). To date, there is no exact mathematical solution available for predicting the moisture uptake by packaged products.

In this paper, we describe a new mathematical tool using polynomial equations for predicting the moisture content of packaged products during storage. The use of polynomial equations allows a simple operation for differentiation and the subsequent integration in model application. The predicted moisture contents of products and desiccants agree well with real life stability data gathered under ICH conditions. Our model could be used to guide packaging selection so as to reduce the cost and cycle time of product development.

2. Theoretical modeling

The model is developed based on the following assumptions:

1. Moisture content of a product is a function of the equilibrium humidity.
2. Moisture permeation through the container is the rate-limiting step.
3. Lag time for moisture diffusion through the container is negligible compared to the shelf life of the product.
4. Moisture permeability of the container is constant at a given temperature.

Under constant temperature and external humidity, the rate of moisture permeation through a container at quasi-steady state can be expressed as

$$\frac{\mathrm{d}_w}{\mathrm{d}_t} = k(\mathrm{RH}_{\mathrm{out}} - \mathrm{RH}) \qquad (1)$$

where $\mathrm{d}_w/\mathrm{d}_t$ is the rate of moisture permeation through the container, k represents the apparent moisture permeability of the container, $\mathrm{RH}_{\mathrm{out}}$ and RH represent the % relative humidity outside and inside the container, respectively.

Assuming that the water content of any unit component in the container, w_i, is a function of the equilibrium humidity

$$w_i = f_i(\mathrm{RH}) \qquad (2)$$

The total quantity of water of n components in the container, w, can be expressed as

$$w = \sum_{i=1}^{i=n} q_i f_i(\mathrm{RH}) \qquad (3)$$

where q_i is the quantity of the ith component in the container.

Differentiation of Eq. (3) with respect to relative humidity leads to

$$\frac{\mathrm{d}_w}{\mathrm{d}_{\mathrm{RH}}} = \frac{\mathrm{d}}{\mathrm{d}_{\mathrm{RH}}}\left[\sum_{i=1}^{i=n} q_i f_i(\mathrm{RH})\right] \qquad (4)$$

Rearranging and substituting Eq. (1) into (4), the rate of moisture permeation through the container can be related to the quantities and the moisture isotherms of all components in the containers, as described by Eq. (5):

$$k(\mathrm{RH}_{\mathrm{out}} - \mathrm{RH})\, \mathrm{d}_t = \frac{\mathrm{d}}{\mathrm{d}_{\mathrm{RH}}}\left[\sum_{i=1}^{i=n} q_i f_i(\mathrm{RH})\right] \mathrm{d}_{\mathrm{RH}} \qquad (5)$$

Rearranging Eq. (5) results in

$$\mathrm{d}_t = \frac{\dfrac{d}{d_{\mathrm{RH}}}\left[\displaystyle\sum_{i=1}^{i=n} q_i f_i(\mathrm{RH})\right]}{k(\mathrm{RH}_{\mathrm{out}} - \mathrm{RH})}\, \mathrm{d}_{\mathrm{RH}} \qquad (6)$$

The t–RH profile inside the container can be calculated by integrating Eq. (6). This leads to

$$\int_0^t \mathrm{d}_t = \int_{\mathrm{RH}_0}^{\mathrm{RH}} \frac{\dfrac{d}{d_{\mathrm{RH}}}\left[\sum_{i=1}^{i=n} q_i f_i(\mathrm{RH})\right]}{k(\mathrm{RH}_{\mathrm{out}} - \mathrm{RH})}\,\mathrm{d}_{\mathrm{RH}} \tag{7}$$

The water content of each individual component, as a function of time, can be estimated by substituting the RH at time t into the corresponding moisture isotherm of the component, on the availability of the t–RH profile.

3. Materials and methods

3.1. Materials

Two new products in development, A and B (tablets A and B), were used as the model products in the current study. The products were color-coated immediate release tablet formulations. Each product contained a new chemical entity and some commonly used pharmaceutical excipients including lactose, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose, silicon dioxide and magnesium stearate. The products were manufactured using traditional methods employing wet granulation, drying, compression and coating processes. Bentonite DesiCan (Clay, 1 g, U.D. Belen) was used as the desiccant in the packaging of product A. Dry calcium chloride (Anhydrous, lot# T22609, VWR), and glass beads (0.75–1 mm ∅) were used for determining the moisture permeability of two sizes of high density polyethylene (HDPE) bottles (Marlex 5502BN, 1.5 oz with 24 mm induction seal cap, and 3 oz with 38 mm induction seal cap).

3.2. Equipment

Humidity and temperature control chambers (SB11^{160}, Weiss) were used as the storage chambers for measuring the moisture permeability of HDPE bottles and the moisture uptake by packaged products. Calibrated temperature and humidity chart recorders (Omega Engineering Inc.) were used to monitor the humidity and temperature of the Weiss chambers. In addition, stability stations that complied with ICH guidelines (ICH, 2000) at 25 °C/60%RH and 40 °C/75%RH were used to conduct the stability study for the model drug products in HDPE bottles. 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 700A-0205, Uson) were used to seal and test the bottles for potential leaking. An oven (Model DKN600, Yamato) and a balance (Model AG245, Mettler Toledo) with 0.1 mg precision were used to conduct the loss on drying (LOD) of tablets and desiccants.

3.3. Procedure

3.3.1. Determination of moisture sorption isotherms

Tablets and desiccant canisters were equilibrated at different humidities in desiccators containing saturated salt solutions (Nyqvist, 1983; Greenspan, 1977). The desiccators were stored in a controlled temperature chamber at 25 or 40 °C for 2 weeks. At the end of 2 weeks, samples were removed from the desiccators. The equilibrium moisture content of the samples was measured using a gravimetric method for LOD by heating the intact tablets and desiccant canisters at 110 °C for 7 h. The desiccant canister, including the plastic container and the desiccant content, was treated as one single component in this study. Moisture sorption isotherms of the samples were obtained by fitting the equilibrium moisture contents into polynomial equations with respect to humidity using a SigmaPlot® software (Version 7, SPSS Inc.).

3.3.2. Determination of moisture permeability of HDPE bottles

HDPE bottles were filled with anhydrous $CaCl_2$ or glass beads according to the USP method (USP 25, 2002). The bottles were sealed using heat induction sealer and vacuum tested to ensure the integrity of the sealing. The bottles were stored in the Weiss humidity chamber at 40 °C/75%RH. The weight gain of the bottles was determined every 2–4 weeks up to 3 months. The experiment was also conducted at 25 °C/60%RH and 30 °C/60%RH for the bottles. The profiles of weight gain versus time were constructed. Rate of moisture permeation into the bottles was determined by linear regression using the data from the linear portion of the weight gain profile. An Excel spreadsheet (Version 9, Microsoft Corp.) was used for the linear regression analysis. Apparent permeability of the bottles, k, was calculated using Eq. (8):

$$k = \frac{\text{Rate}}{\text{RH}_{\text{out}}} \tag{8}$$

The unit of k is mg/(day bottle %RH).

For comparison, the apparent moisture permeability of the bottles was also calculated according to the USP method (USP 25, 2002) using Eq. (9). However, the volume of the bottle was not included in the calculation:

$$\text{Rate} = \frac{(M_{\text{f}} - M_{\text{i}}) - (C_{\text{f}} - C_{\text{i}})}{14} \tag{9}$$

where $(M_{\text{f}} - M_{\text{i}})$ is the difference between the final and the initial weight of the test bottles, $(C_{\text{f}} - C_{\text{i}})$ is the difference of the average weight of the control bottles containing glass beads, and the number 14 is the duration of days for testing.

3.3.3. Moisture uptake by tablets and desiccant in HDPE bottles

Ten tablets were placed in 1.5 oz and 20 tablets in 3 oz bottles. One desiccant canister was also included in each bottle for product A. All the bottles were induction sealed. The bottles were stored in the Weiss humidity chamber at 40 °C/75%RH. Three bottles of each configuration were sampled at each time points. The moisture contents of tablets and desiccants were determined by the LOD method. Samples were discarded after each measurement.

4. Results and discussion

4.1. Moisture permeability of HDPE bottles

The weight gain profiles of the HDPE bottles filled with calcium chloride and stored under different conditions are shown in Fig. 1. The weight gain includes the moisture retained within and permeated through the bottle wall. It is observed that the rate of weight increase is substantially faster at the beginning than the later intervals. This initial surge has resulted from the absorption of moisture by the bottle materials in addition to the migration of moisture through the bottle. The rate of weight gain at the beginning depends on the initial condition of the bottles. Theoretically, the total weight gain will be faster at the beginning if the wall is dry, or slower if it is saturated with water. At the steady state when a linear concentration gradient is established in the wall, the effect of the initial wall condition is eliminated. Based on the above analysis, permeability of HDPE bottles has been determined

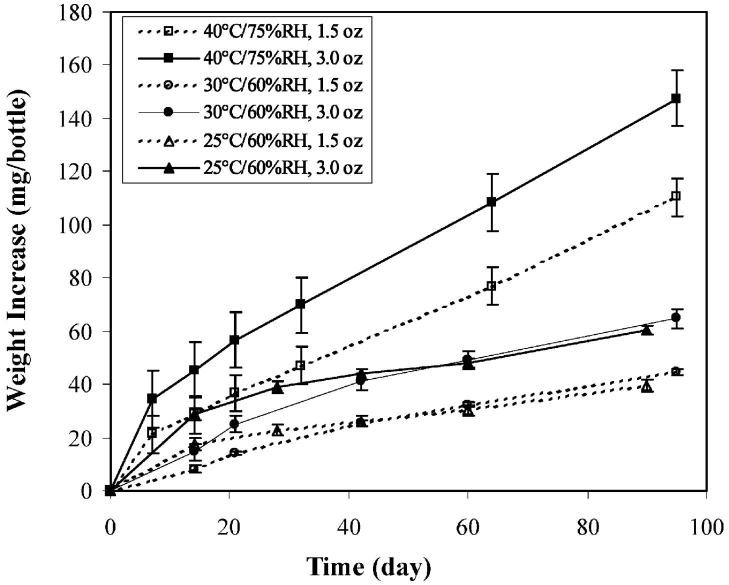

Fig. 1. Weight gain of HDPE bottles containing anhydrous $CaCl_2$ at 25 °C/60%RH, 30 °C/60%RH, and 40 °C/75%RH.

Table 1
Moisture permeability of HDPE bottles

Temperature (°C)	$k \times 10^3$ (mg/(day bottle %RH), Mean (S.D.)			
	1.5 oz		3.0 oz	
	USP	Current	USP	Current
40	24.9 (6.5)	13.5 (0.4)	37.5 (10.0)	17.1 (0.3)
30	5.5 (1.7)	8.7 (0.4)	9.2 (3.5)	13.0 (0.9)
25	2.1 (2.5)	4.7 (0.1)	6.3 (2.8)	5.7 (0.2)

using the data from the linear weight–time profile after the initial surge. The results of the current method are listed in Table 1 along with those calculated using the USP method. The two methods result in different values without a specific trend, and there are significant differences in the standard deviation of the two methods. The variation is 26–119% for the USP method, and less than 10% for the current method. A small variation indicates that the permeability determined using the steady-state data is highly reproducible for the present method.

The permeability of the 1.5 oz bottle (total volume of the bottle is 52.7 ml) at 40 °C/75%RH is 0.0135 mg/(day bottle %RH). This value can be expressed as 1.02 mg/day/bottle, which is similar to the reported result although the bottle size is not exactly the same. Badawy (Badawy et al., 2001) reported a value of 0.975, 0.88 and 0.776 mg/day/bottle for the 60, 30, and 40 ml HDPE bottles, respectively, measured at 40 °C/75%RH using a different method. Further study has shown that the permeability determined by the current method provides accurate results for predicting the moisture uptake by packaged products. Therefore, it can be concluded that the permeability of bottles measured using steady-state data is accurate and reliable.

4.2. Moisture sorption isotherms of tablets and desiccants

Preliminary study indicated that moisture equilibrium is reached in 2 days after the tablets and desiccants are placed in desiccators with different humidities. This indicates the time of 14 days used in this study is sufficient to ensure the equilibrium of moisture sorption by the products. The equilibrium water contents of the model tablets and desiccants at 25 and 40 °C are shown in Fig. 2. The moisture isotherms obtained by curve fitting using polynomial equations are listed in Eqs. (10)–(15). In addition, the gas law, Eq. (16), is used to represent the moisture isotherm in the headspace.

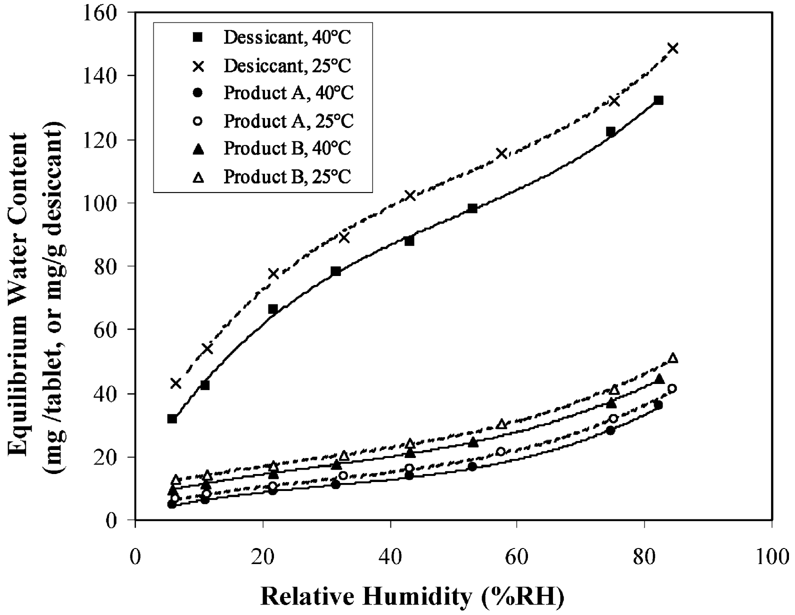

Fig. 2. Moisture sorption isotherms of Bentonite DesiCan, tablet products A and B at 25 and 40 °C. Lines are fitted curves.

Tablet product A:

$$w_{25^\circ\mathrm{C}}\ (\mathrm{mg/tablet}) = 3.8542 + 0.4573\mathrm{RH} - 8.209 \times 10^{-3}\mathrm{RH}^2 + 9.4533 \times 10^{-5}\mathrm{RH}^3 \quad (10)$$

$$w_{40\,^\circ\mathrm{C}}\ (\mathrm{mg/tablet}) = 1.7969 + 0.5085\mathrm{RH} - 0.01036\mathrm{RH}^2 + 1.112 \times 10^{-4}\mathrm{RH}^3 \quad (11)$$

Tablet product B:

$$w_{25\,^\circ\mathrm{C}}\ (\mathrm{mg/tablet}) = 9.8682 + 0.4565\mathrm{RH} - 6.603 \times 10^{-3}\mathrm{RH}^2 + 8.2161 \times 10^{-5}\mathrm{RH}^3 \quad (12)$$

$$w_{40\,^\circ\mathrm{C}}\ (\mathrm{mg/tablet}) = 6.8914 + 0.4892\mathrm{RH} - 7.532 \times 10^{-3}\mathrm{RH}^2 + 8.6047 \times 10^{-5}\mathrm{RH}^3 \quad (13)$$

Bentonite DesiCan:

$$w_{25\,^\circ\mathrm{C}}(\mathrm{mg/g}) = 23.3389 + 3.3083\mathrm{RH} - 0.04803\mathrm{RH}^2 + 3.125 \times 10^{-4}\mathrm{RH}^3 \quad (14)$$

$$w_{40\,^\circ\mathrm{C}}\ (\mathrm{mg/g}) = 13.9438 + 3.1910\mathrm{RH} - 0.04686\mathrm{RH}^2 + 3.117 \times 10^{-4}\mathrm{RH}^3 \quad (15)$$

Headspace:

$$w\ (\mathrm{mg}) = \frac{18,000 V P_\mathrm{s} \mathrm{RH}}{100RT} \quad (16)$$

where V is the headspace volume in the container in ml, P_s is the saturated water vapor pressure at temperature T (Kelvin), R is the gas constant, 18,000 is the molecular weight of water (mg/mole), and 100 is the correcting factor for % relative humidity. All the coefficients in Eqs. (10)–(15) are found significant by *t*-test.

An example of detailed application of polynomial isotherms for modeling the moisture uptake by a product is listed in Appendix A.

4.3. Prediction of moisture uptake by packaged products

Several assumptions have been made for the development of the current model. These assumptions describe the characteristics of the commonly used packaging systems and therefore are not difficult to satisfy. But, the model is not applicable if product moisture content does not change with humidity, or if the moisture permeation through container is not the rate-limiting step. Pinhole leaks are also not accounted for by the current model. Similar to any existing methods for quantitative prediction, the application of the current model involves a computational process. The commonly available software, such as SigmaPlot® and Excel spreadsheet, are suitable for curve fitting and the subsequent computation.

Table 2
Experimental and predicted water content of product A and desiccant in HDPE bottles at 40 °C/75%RH

Time (days)	10 tablets, 1 DesiCan in 1.5 oz bottle				20 tablets, 1 DesiCan in 3 oz bottle			
	Water content of tablets (%)		Water content of DesiCan (%)		Water content of tablets (%)		Water content of DesiCan (%)	
	Experimental	Predicted	Experimental	Predicted	Experimental	Predicted	Experimental	Predicted
7	1.2	1.5	3.3	4.0	1.5	1.7	4.3	4.5
14	1.4	1.6	3.6	4.1	1.8	1.8	4.6	4.7
21	1.4	1.7	3.9	4.3	1.8	1.9	4.8	4.8
32	1.6	1.8	4.3	4.6	1.9	2.0	5.2	5.1
64	2.0	2.1	5.3	5.4	2.2	2.2	6.1	5.8
95	2.1	2.3	6.1	6.2	2.4	2.4	6.7	6.4
150	2.6	2.8	7.3	7.3	2.9	2.8	7.6	7.4
186	3.0	3.0	8.1	8.0	3.2	3.0	8.2	8.0

Table 3
Experimental and predicted water content of products in 3 oz HDPE bottles at ICH conditions

Time (days)	Water content of tablets (%)							
	30 tablets of product A/bottle				20 tablets of product B/bottle			
	25 °C/60%RH		40 °C/75%RH		25 °C/60%RH		40 °C/75%RH	
	Experimental	Predicted	Experimental	Predicted	Experimental	Predicted	Experimental	Predicted
0	2.1	2.1	2.1	2.1	3.5	3.5	3.5	3.5
14	2.1	2.1	ND[a]	ND	ND	ND	ND	ND
42	2.3	2.2	2.3	2.4	ND	ND	3.9	4.2
90	2.3	2.4	2.7	2.8	3.7	4.0	4.3	4.7
126	ND	ND	ND	ND	3.7	4.1	4.6	5.1
180	2.9	2.6	3.2	3.3	4.2	4.3	5.3	5.4
270	2.6	2.8	ND	ND	ND	ND	ND	ND
365	2.5	3.0	ND	ND	ND	ND	ND	ND

[a] No data.

The significant advantage of our model over the existing methods is that our model does not require any simplification in application. Modeling of moisture uptake by products can be carried out using the standard differentiation and integration procedures upon the availability of the polynomial isotherms and the initial moisture contents of the products. On the other hand, complicated theoretical isotherms, such as the GAB equation in the SDMT model, are not directly integratable and require tedious stepwise approximations for the application of predicting moisture uptake.

The predicted water contents using our model for different packaging configurations and conditions are listed in Tables 2 and 3 along with the experimental stability data. The stability data are from three different test locations within Abbott and represent the inter-laboratory variation. The predicted results agree very well with the real life stability data for both the tablets and the desiccants. These results show that our model can be used for predicting a priori, the moisture uptake by packaged solid pharmaceutical products, so as to evaluate the selection of packaging materials, design configurations, and the use of desiccants for product protection.

5. Conclusions

A mathematical model has been developed to predict the moisture uptake by packaged solid pharmaceutical products during storage. The model accounts for the effects of container moisture permeability, environmental conditions, product quantities, moisture isotherms, and the initial moisture contents of products on the subsequent moisture uptake. The predicted moisture content, as a function of time, agrees well with real time stability data gathered under ICH conditions. It has been demonstrated that reliable container permeability is important to ensure the accuracy of prediction. It has been shown that polynomial equations can provide a good fit for nonlinear isotherms, and are critical for the successful development and application of the current model. Our model is very easy to use, and enables a development scientist to predict *a priori*, the moisture uptake by packaged solid pharmaceuticals under various conditions. Therefore, it can be used as a tool to guide packaging selection.

Although only bottle systems are verified with experimental data in the current study, the model has been developed based on the diffusion theory and mass balance principle. We believe it should be applicable to other packaging systems such as blisters or bags, as long as they satisfy the initial assumptions listed in this paper.

The effect of moisture uptake on the quality of products depends on the specific products, and must be studied separately.

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Appendix A

This appendix describes the application of polynomial isotherms determined in Section 4.2 and the application of the current model for predicting the moisture uptake by packaged solid pharmaceutical products. Product A and desiccants are packaged in HDPE bottles with the following quantities

Bottle: 1.5 oz HDPE, headspace: 48.25 ml
Product: 10 tablets of product A with initial moisture content of 8.9 mg/tablet.
Desiccant: 1 desiccant canister, 1.863 g with initial moisture content of 31 mg/canister.

The quantity of water in the headspace is calculated using the ideal gas law at the experimental condition at 25 °C/34%RH. The initial total amount of water in the bottle is determined to be 120.8 mg.

When the components are closed in the bottle and placed at 40 °C (313.2 K)/75%RH, moisture will transfer among components in the bottle. Assuming the quantity of incoming moisture in a short period of time is negligible, the total quantity of water in the bottle is the total of the initial water content of all components. Therefore, the initial relative humidity RH_0 in the container can be calculated by substituting the moisture sorption isotherms and the amounts of desiccant and tablet A, and the ideal gas law into Eq. (3), as described by Eq. (A.1).

$$\begin{aligned} w = {} & 1.863(13.9438 + 3.1910\mathrm{RH} - 0.04686\mathrm{RH}^2 \\ & + 0.0003117\mathrm{RH}^3) + 10(1.7969 + 0.5085\mathrm{RH} \\ & - 0.01036\mathrm{RH}^2 + 0.0001112\mathrm{RH}^3) \\ & + \frac{18,000 \times 10^{-6} \times 48.25 P_\mathrm{S}\,\mathrm{RH}}{8.314 \times 313.2 \times 100} \end{aligned} \tag{A.1}$$

where P_S is the saturated water vapor pressure at 40 °C, which is 7381.4 Pa

Using the initial total water of 120.8 mg for the w in Eq. (A.1), it was calculated that an initial humidity RH_0 of 8.4% will satisfy the equation.

Differentiation of Eq. (A.1) with respect to the percent relative humidity leads to

$$\begin{aligned} \frac{\mathrm{d_w}}{\mathrm{d_{RH}}} = {} & 1.863(3.1910 - 2 \times 0.04686\mathrm{RH} \\ & + 3 \times 0.0003117\mathrm{RH}^2) + 10(0.5085 \\ & - 2 \times 0.01036\mathrm{RH} + 3 \times 0.0001112\mathrm{RH}^2) \\ & + \frac{18,000 \times 10^{-6} \times 48.25 P_\mathrm{s}}{8.314 \times 313.2 \times 100} \end{aligned} \tag{A.2}$$

Substituting Eq. (A.2) into Eq. (7), the t–RH profile in the bottle during storage can be calculated using Eqs. (A.3)–(A.5), with the apparent moisture permeability of the 1.5 oz HDPE bottle at 40 °C being 0.01354 mg/(day bottle %RH)

$$\int_0^t \mathrm{d}_t = \int_{\mathrm{RH}_0}^{\mathrm{RH}_t} \left(\frac{\begin{array}{l} 1.863(3.1910 - 2 \times 0.04686\mathrm{RH} + 3 \times 0.0003117\mathrm{RH}^2) \\ +10(0.5085 - 2 \times 0.01036\mathrm{RH} + 3 \times 0.0001112\mathrm{RH}^2) \\ +(18,000 \times 10^{-6} \times 48.25 \times 7381.4)/(8.314 \times 313.2 \times 100) \end{array}}{0.01354 \times (\mathrm{RH_{out}} - \mathrm{RH})} \right) \mathrm{d_{RH}} \tag{A.3}$$

$$\begin{aligned} t = {} & \left(\frac{1.863 \times 3.1910}{0.01354} + \frac{10 \times 0.5085}{0.01354} + \frac{18,000 \times 10^{-8} \times 48.25 \times 7381.4}{0.01354 \times 8.314 \times 313.2} \right) [-\ln(\mathrm{RH_{out}} - \mathrm{RH})]_{\mathrm{RH}_0}^{\mathrm{RH}_t} \\ & - \left(\frac{1.863 \times 2 \times 0.04686}{0.01354} + \frac{10 \times 2 \times 0.01036}{0.01354} \right) [\mathrm{RH_{out}} - \mathrm{RH} - \mathrm{RH_{out}} \ln(\mathrm{RH_{out}} - \mathrm{RH})]_{\mathrm{RH}_0}^{\mathrm{RH}_t} \\ & + \left(\frac{1.863 \times 3 \times 0.0003117}{0.01354} + \frac{10 \times 3 \times 0.0001112}{0.01354} \right) \left[- \left(\begin{array}{l} 0.5(\mathrm{RH_{out}} - \mathrm{RH})^2 - 2\mathrm{RH_{out}}(\mathrm{RH_{out}} - \mathrm{RH}) \\ +\mathrm{RH_{out}^2} \ln(\mathrm{RH_{out}} - \mathrm{RH}) \end{array} \right) \right]_{\mathrm{RH}_0}^{\mathrm{RH}_t} \end{aligned} \tag{A.4}$$

$$
\begin{aligned}
t = {} & \left(\frac{1.863 \times 3.1910}{0.01354} + \frac{10 \times 0.5085}{0.01354} + \frac{18,000 \times 10^{-8} \times 48.25 \times 7381.4}{0.01354 \times 8.314 \times 313.2}\right) \left[\begin{array}{l} -\ln(\mathrm{RH_{out}} - \mathrm{RH}_t) \\ +\ln(\mathrm{RH_{out}} - \mathrm{RH_0}) \end{array}\right] \\
& - \left(\frac{1.863 \times 2 \times 0.04686}{0.01354} + \frac{10 \times 2 \times 0.01036}{0.01354}\right) \left[\begin{array}{l} \mathrm{RH_{out}} - \mathrm{RH}_t - \mathrm{RH_{out}} \ln(\mathrm{RH_{out}} - \mathrm{RH}_t) \\ -\mathrm{RH_{out}} + \mathrm{RH_0} + \mathrm{RH_{out}} \ln(\mathrm{RH_{out}} - \mathrm{RH_0}) \end{array}\right] \\
& + \left(\frac{1.863 \times 3 \times 0.0003117}{0.01354} + \frac{10 \times 3 \times 0.0001112}{0.01354}\right) \\
& \times \left[-\left(\begin{array}{c} 0.5(\mathrm{RH_{out}} - \mathrm{RH}_t)^2 - 2\mathrm{RH_{out}}(\mathrm{RH_{out}} - \mathrm{RH}_t) \\ +\mathrm{RH_{out}^2} \ln(\mathrm{RH_{out}} - \mathrm{RH}_t) \end{array}\right) + \left(\begin{array}{l} 0.5(\mathrm{RH_{out}} - \mathrm{RH_0})^2 - 2\mathrm{RH_{out}}(\mathrm{RH_{out}} - \mathrm{RH_0}) \\ +\mathrm{RH_{out}^2} \ln(\mathrm{RH_{out}} - \mathrm{RH_0}) \end{array}\right)\right]
\end{aligned}
\tag{A.5}
$$

Eq. (A.5) is useful for calculating the time (t) required for the bottle to reach a certain percent of relative humidity, RH_t. This can be used for estimating the water content, w_t, of each component at any given time.

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