ARTICLE

Water Activity and Primary Packaging Selection for Oral Solid Dosage Products.

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The recently published general chapter USP<922> states that water activity determination can be used to assess the level of protection provided by primary packaging for an oral solid dosage (OSD) product over its entire shelf life [1]. Primary packaging must maintain a low relative humidity for as long as necessary to ensure the pharmaceutical product maintains its key quality attributes including potency, purity, dissolution rate, tablet hardness, and capsule swelling, up to its expiration date. During the development phase, data must be acquired to determine if an existing package can provide adequate protection, or if new technologies are required for new formulations. For commercial products, a replacement package must be assessed to determine if it has equivalent, inferior, or superior performance. Water activity (a_w) measurements provide unique information, and therefore expand and complement the data collected from USP<670> Auxiliary Packing Components and USP<671> Containers - Performance Testing.

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WATER ACTIVITY BACKGROUND

Water activity is the partial vapor pressure of water in a substance divided by the partial water vapor pressure of pure water at the same temperature. It is a direct indication of the amount of loosely bound or free water within an OSD drug product that is available to participate in chemical, biochemical, or physical reactions. The water activity of a pharmaceutical product changes over time, from when it is first placed in its primary packaging and throughout its exposure to varying relative humidity and temperature conditions. As the humidity inside the primary package increases, the water activity of the product increases. In fact, the a_w of the product has a direct relation to the equilibrium relative humidity (%ERH) inside the package:

$$a_w * 100 \equiv \% \ ERH$$

The packaging development team and the QC testing team will need to determine:

1. What is the initial relative humidity (RH) inside the package when first manufactured (RH_0)?
2. How does RH inside the package change over time (RH_t)?

WHAT IS THE STARTING POINT (RH_0)?

Every stability study has a starting time and an initial RH inside the package. This critical value can vary from as little as 10% up to as high as 60%. The starting RH cannot be accurately estimated or calculated, but it can be easily measured by testing 1 tablet from each package 1-2 days after sealing. Table 1 displays the RH_0 and a_w of common over-the-counter medications.

Table 1. Measured RH and corresponding a_w of common over-the-counter medications.

Active Ingredient	Physical Form	Packaging	RH_o (%) and a_w
Aspirin	Tablet, enteric coated	30mL HDPE bottle, heat induction seal, 1-gram desiccant	$\%RH_0$= 17 a_w = 0.17
Ibuprofen	Tablet, uncoated	60mL HDPE bottle, heat induction seal	$\%RH_0$ = 52 a_w = 0.52
Naproxen	Tablet, coated	Blister pack	$\%RH_0$ = 37 a_w = 0.37
Ibuprofen	Capsule, liquid gel	Blister pack	$\%RH_0$ = 57 a_w = 0.57

HOW DO DESICCANTS CHANGE THE INITIAL CONDITIONS?

When desiccants are added to the primary packaging, water moves from the product formulation to the desiccant. This process continues until the water activity of the desiccant and the water activity of the product are equal. The process can be monitored by measuring the RH of the headspace in the package. Figure 1 shows the headspace RH of samples originally stored at 25°C with an RH of 60% after sealing them with desiccants in a glass vial. The RH decreases from 60% to 8% after approximately 14 hours [2].

In this study the impact of changing the type of desiccant, amount of desiccant, or the tablet count on the initial RH was assessed quickly and accurately.

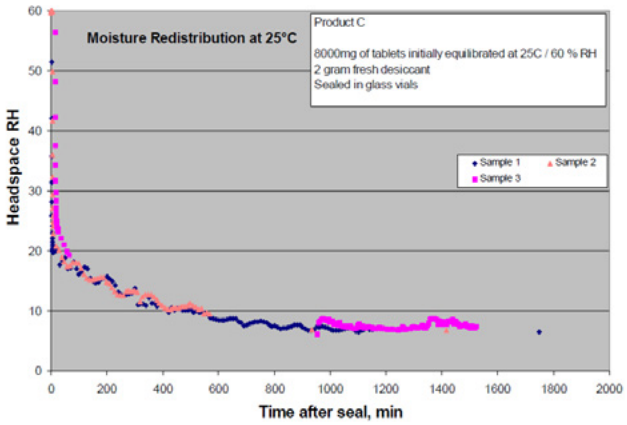

Figure 1. RH (%) versus time as tablets reach equilibrium with desiccant inside package.

LASER-BASED HEADSPACE ANALYSIS FOR WATER ACTIVITY DETERMINATION

The data in Figure 1 was collected using the reiterative test mode of the Lighthouse Instruments FMS-Water Activity Analyzer, which uses a tunable diode laser absorption spectroscopy technique called frequency modulation spectroscopy. This technique is described in USP <922>, and is recommended as the only method to reliably and accurately measure water activity when the sample contains other volatile compounds. The ease-of-use and rapid measurement time enables straightforward generation of robust water activity and relative humidity data. This laser-based headspace analysis approach includes using closed sample containers which avoids cross-contamination issues resulting in very accurate water activity determination.

HOW RAPIDLY DOES MOISTURE PERMEATE INTO THE PACKAGE?

OSD products can be stored in multi-dose plastic bottles, or as single doses in plastic blisters or compression-sealed aluminum foil. Each of these primary containers allow moisture permeation, however the rate of moisture permeation differs widely based on the specific package design and the quality of the seal.

Packaging Engineering groups have used USP Chapter <671>, Containers Performance Testing (updated in USP41-NF36, 2018) to measure the performance of different primary packaging products. USP<671> defines methods for determining the moisture vapor transmission rate (MVTR) by measuring the weight of water absorbed by a specified weight of desiccant placed inside the package at a specified temperature and humidity (T=30°C/RH=65% or 40°C/75%). MVTR is the change in total water content of the desiccant per day at the specified temperature and humidity, expressed as mg per day per package volume (mg/day/liter).

In the example displayed in Figure 2, blisters were filled with water and placed into a sealed glass vial. The amount of water that permeated out of the blisters into the vial headspace was measured each day for 2-weeks using the Lighthouse Instruments laser-based headspace analysis approach. Results suggest that the moisture permeation process is not linear, but exponential, as shown in Figure 2. Laser-based headspace analysis provides a fast and accurate method to evaluate different blister films and different blister sizes, and the data can be collected at 25°C, 30°C and 40°C as needed.

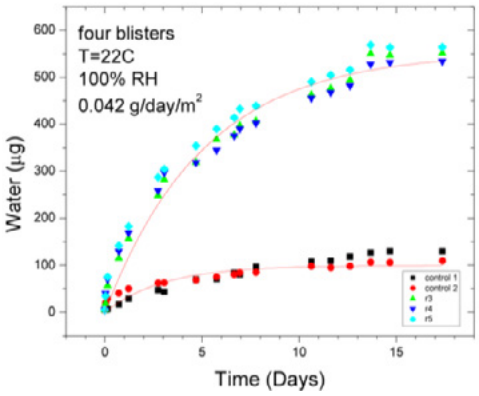

Figure 2. Mass of water permeating from 4-blisters versus time.

HOW DOES THE INTERNAL RH CHANGE OVER TIME?

The primary packaging is selected to protect the OSD by slowing the rate that the humidity inside the package changes. The RH inside the package when it is manufactured and sealed is equal to the specific water activity associated with the OSD. The RH will continue to change over time until the RH inside the package reaches the RH of its exterior storage environment. When the interior and exterior RH are equal, the system is at equilibrium with its environment.

In the example displayed in Figure 3, the tablet product was stored in four different primary package configurations. HDPE bottles were heat induction sealed with either 7-tablets or 30-tablets to show the impact of tablet count. Individual tablets were placed into blisters thermoformed with a low MVTR and a high MVTR plastic film. The packages were stored in an environment at ICH Q1A accelerated conditions of 40°C/75%RH. Tablets were tested for initial water activity, and then new packages were opened after 60, 90, and 180-days to measure water activity changes versus time (see Figure 3).

When moisture permeates into the package, it is absorbed by the formulation. The consequence is an increase in the water activity of the tablet which will increase the chemical degradation rate, slow the dissolution rate, and cause other physical changes that may limit shelf life.

WHEN A BATCH FAILS ON STABILITY

If the stability protocol includes water activity testing at each sample pull point, a robust history of the humidity versus time profile for product batches will be quickly built. This database of product water activity values can be an invaluable tool for monitoring product batch quality. If an individual package fails to meet its critical quality, this might be detectable by increased levels of water activity compared to the historically acceptable batches. An analytical method that enables accurate and straightforward water activity determination is critical for building a historical database of batch quality data.

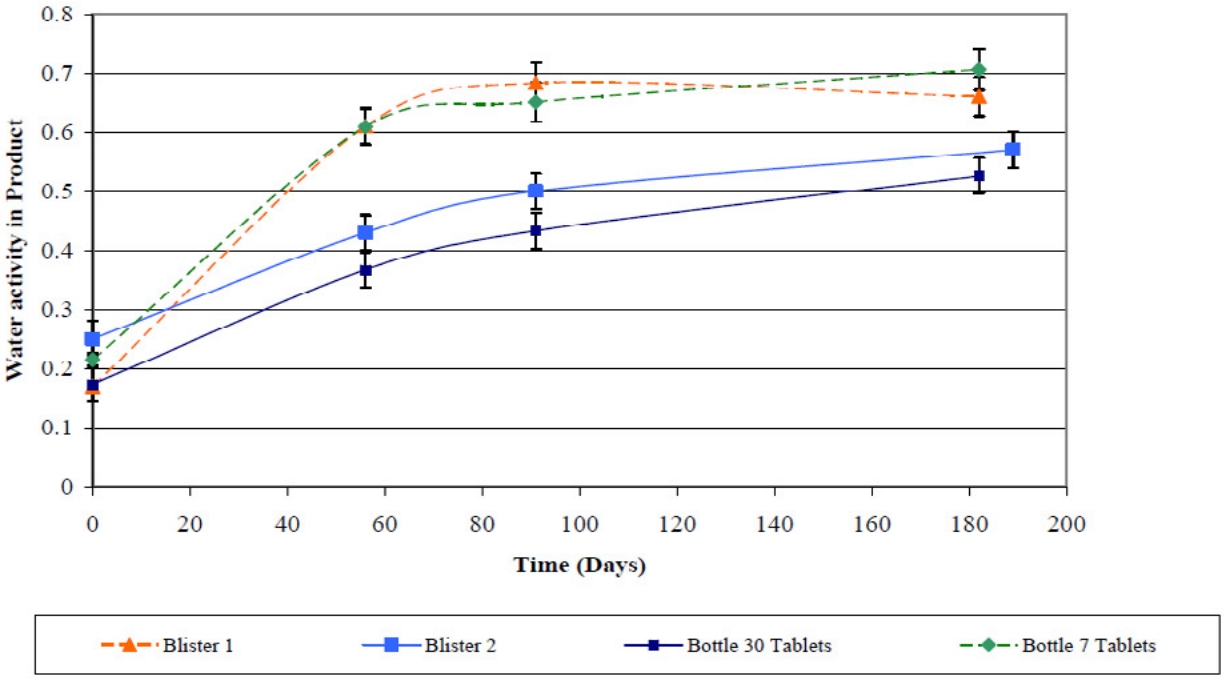

Figure 3: Water activity versus time for a single tablet formulation in 4-different package configurations.

REFERENCES

1. USP General Chapter <922>
   https://online.usppf.com/usppf/document/GUID-B5DDDC52-0DC8-4603-B81B-03EA4FB025B8_10101_en-US

2. 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, PQRI Container Closure Working Group (2004).

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