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The Art of Precision Measurement

APPLICATION NOTE

PHARMACEUTICAL TRENDS: WATER ACTIVITY MEASUREMENT

Water activity has been broadly used in the pharmaceutical industry since the publication in 2006 of USP <1112>, an informational chapter on the application of water activity in pharma. While <1112> provided guidance for the utilization of water activity, it was not an official method.

Now USP has developed USP <922> Water Activity as an official method which will hopefully further facilitate its implementation as an integral part of a pharmaceutical quality program.

Potential applications for water activity in pharmaceuticals include stability control, microbial risk prevention, optimized formulation, reduced caking and clumping, and moisture migration control. The resulting key benefits of these applications are higher quality production output, greater consumer satisfaction and confidence, and less product waste and recalls. Clearly, water activity is a powerful and often essential quality parameter for pharmaceutical products.

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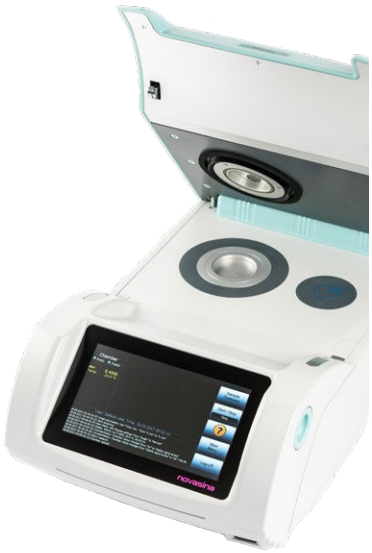
WHAT IS WATER ACTIVITY?

Water activity is defined as the energy status of water in a system and is rooted in the fundamental laws of thermodynamics through the Gibbs free energy equation (1). It represents the relative chemical potential energy of water as dictated by the surface, colligative, and capillary interactions in a matrix. Practically, it is measured as the partial vapor pressure of water (P) in a headspace that is at equilibrium with the sample, divided by the saturated vapor pressure (P0) of water at the same temperature (T). Water activity is equal to the Equilibrium Relative Humidity (ERH) divided by 100:

$$a_w = \left(\frac{P}{P_0}\right)_T = \frac{\%ERH}{100}$$

This water activity index covers a range from 0 for bone-dry conditions up to 1.00 for pure water. Water activity is often incorrectly referred to as “free water,” which is misleading because “free” is not scientifically defined and is interpreted differently depending on the context. As a result, the concept of free water can cause confusion between the physical binding of water, a quantitative measurement, and the chemical binding of water to lower energy, a qualitative measurement. Rather than a water activity of 0.50, indicating 50% free water, it more correctly indicates that the water in the product has 50% of the energy that pure water would have in the same situation. The lower the water activity, the less the water in the system behaves like pure water.

Water activity is an intensive property that describes the energy of the water in a system, whereas moisture content is an extensive property that determines the amount of moisture in a product. Although related, water activity and moisture content are not the same. Moisture content is typically determined through loss-on-drying or chemical titration and though useful as a measurement of purity and a standard of identity, moisture content does not correlate as well as water activity with microbial growth, chemical stability, or physical stability. Water activity and moisture content are related through the moisture sorption isotherm.



LabMaster aw-neo
Most reliable water activity meter on the market

USP <922> WATER ACTIVITY METHOD

Recommendations for the determination of water activity are outlined in USP <922> Water Activity. This method becomes official in May 2021 and provides guidance for water activity measurement. It includes a brief theoretical background explanation and discusses some factors that influence water activity including solute concentration and temperature.

Sensor types and calibration: USP <922> also provides a short review of the various sensor types available for measuring water activity and highlights the strengths of each. It provides guidance on the qualification of instruments with water activity instruments classified as Group B instruments. It highlights that water activity meters should be calibrated using standard solutions and this should be done at a minimum yearly or whenever a calibration check fails. Calibration verification checks should be conducted daily based on the instructions from the instrument manufacturer and using a minimum of two standards that book-end the typical water activity range. The number of replicates used for a calibration check should match the number of replicates used for sample testing.

Sampling: For sampling, guidance is given to limit exposure of the sample to ambient conditions by using sealed containers with limited headspace. The transfer of samples from extreme temperatures is discouraged due to the potential for condensation to form inside the containers. Water activity measurements should be conducted according to the manufacturer's instructions and reported along with the temperature.

Applications: In terms of suggested uses for water activity, USP <922> extends beyond the usage suggestions of USP <1112> to include:

Selecting ingredient isolation and product manufacturing process conditions in terms of maintaining a_w below the critical threshold to obtain thermodynamic control of the desired solid form (e.g., hydrate versus anhydrate)

- Selecting excipients for which a_w may impact their material flow, compression characteristics, hardness, and performance characteristics (e.g., disintegration and dissolution) of dosage forms
- Optimizing fluidized bed drying processes
- Reducing the degradation of active ingredients within product formulations (e.g., those susceptible to chemical hydrolysis)
- Establishing the level of protection to product formulations to moisture by primary packaging materials during their shelf life
- Optimizing the shelf-life stability of probiotics
- Providing a complementary method for monitoring changes in water content
- Controlling and monitoring physical, chemical, and microbial product stability
- Optimizing formulations to improve the antimicrobial effectiveness of preservative systems
- Reducing the susceptibility of formulations to microbial contamination
- Providing a tool to justify the reduction of microbial testing of nonsterile drug and dietary supplements formulations (see Application of Water Activity Determination to Nonsterile Pharmaceutical Products 1112)

Let's take a look at each of these applications in turn.

CRITICAL WATER ACTIVITY FOR CRYSTALLINE EXCIPIENTS

Excipients, among many functions, act as bulking agents and protect Active Pharmaceutical Ingredients (API) in pharmaceutical solid dosage products. Typically, the matrix of these excipients is either crystalline or amorphous.

For crystalline excipients, the addition or loss of waters of hydration or deliquescence can result in undesirable changes in product quality such as modification of dissolution properties or reduction in the efficacy of the API. These change processes are thermodynamically controlled and, therefore, are related to water activity.

The moisture sorption isotherm, which describes the relationship of moisture content to water activity, will clearly show the deliquescence of the crystalline material by a sharp 90 degree turn in the isotherm (Figure 1) (2). The water activity where these changes occur is called "critical water activity." The key to avoiding problems with a crystalline excipient is to specify that the water activity be in a safe range based on the critical water activities identified through the moisture sorption isotherm. Any incoming excipient supplies should then be monitored for water activity to ensure that this specification is being met.

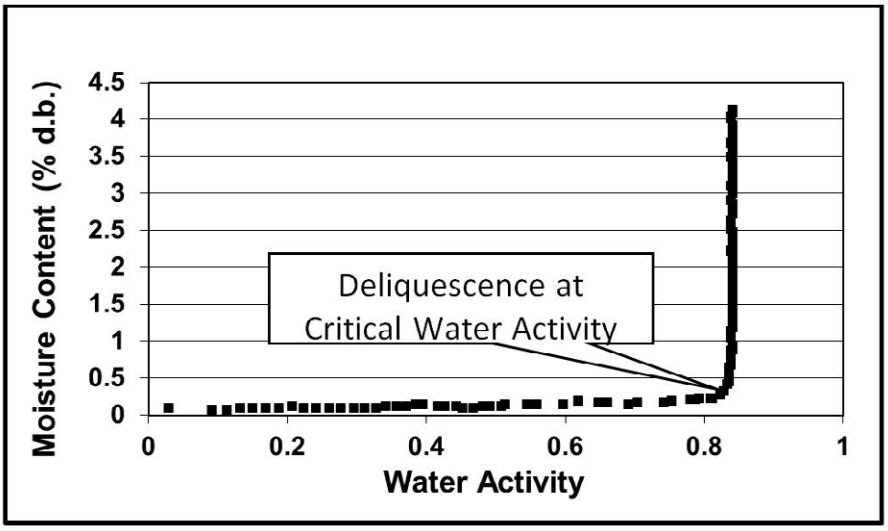


Figure 1. Moisture sorption isotherm showing the deliquescence of a crystalline material. (3)

CRITICAL WATER ACTIVITY FOR CRYSTALLINE EXCIPIENTS

Amorphous excipients are typically low-moisture and are in a meta-stable glassy state. Their ability to provide protection to the API depends on them remaining in the glassy state throughout the life of the product. A transition of the excipient matrix from the glassy state to the rubbery state, called a "glass transition," will result in structural collapse, increased mobility, changes in dissolution, and increased susceptibility to caking and crystallization (4). Consequently, the product will not flow, compress, or tablet properly, and dissolution may occur prematurely. A glass transition can be induced through either a change in temperature or a change in water activity. The water activity where a glass transition occurs for a product is called the "critical water activity" and can be identified as a sharp inflection in the moisture sorption isotherm (Figure 2) (5). To maintain the functionality of amorphous excipients, it is important to determine its critical water activity and take measures to ensure that the water activity of the product remains below that critical water activity throughout the life of the product.

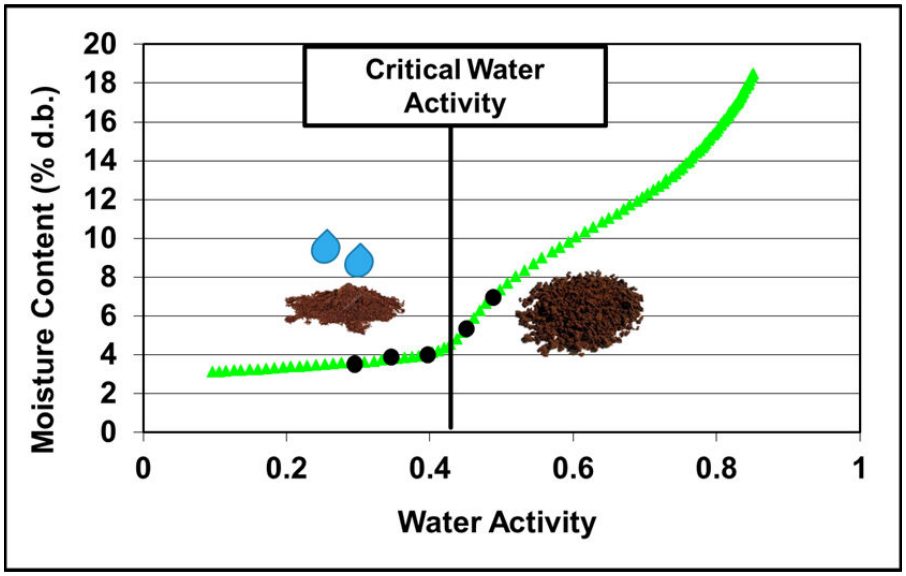


Figure 2. Moisture sorption isotherm indicating the critical water activity for a glass transition. Below the critical water activity, the product remains stable. Above the critical water activity, the product becomes unstable and shelf life is reduced (5).

WATER ACTIVITY AND MICROBIAL SAFETY

Microorganisms require access to water of a sufficient energy to allow for movement of water into the cell. This water is critical for maintaining turgor pressure and normal metabolic activity. The energy of the water surrounding the microorganism is described by the water activity and for water to move into the microbe, the interior water activity of the organism must be lower than the water activity of its surroundings. In other words, water activity is not the water available to microorganisms to grow; it is the energy of the water and that determines if water can move into or out of the cell. When a microorganism encounters an environment with lower water activity than its internal water activity, it experiences osmotic stress and water leaves the cell, thereby lowering the turgor pressure and causing metabolic activity to cease (Figure 3). In response, the organism will try to control its internal water activity through the concentration of solutes. This ability to lower the internal water activity is unique to each organism, which is why different microorganisms have different water activity minimum growth limits (Table 1) (7).

Notice that moisture content has not been mentioned as having an impact on microbial growth because it is not the amount of water that determines if a microorganism can access it but the water activity (energy) compared to the internal water activity of the organism. Consequently, any efforts to provide control limits for the risk of microbial contamination, and an accompanying reduction in microbial limits testing, must be based on water activity measurements and not moisture content.

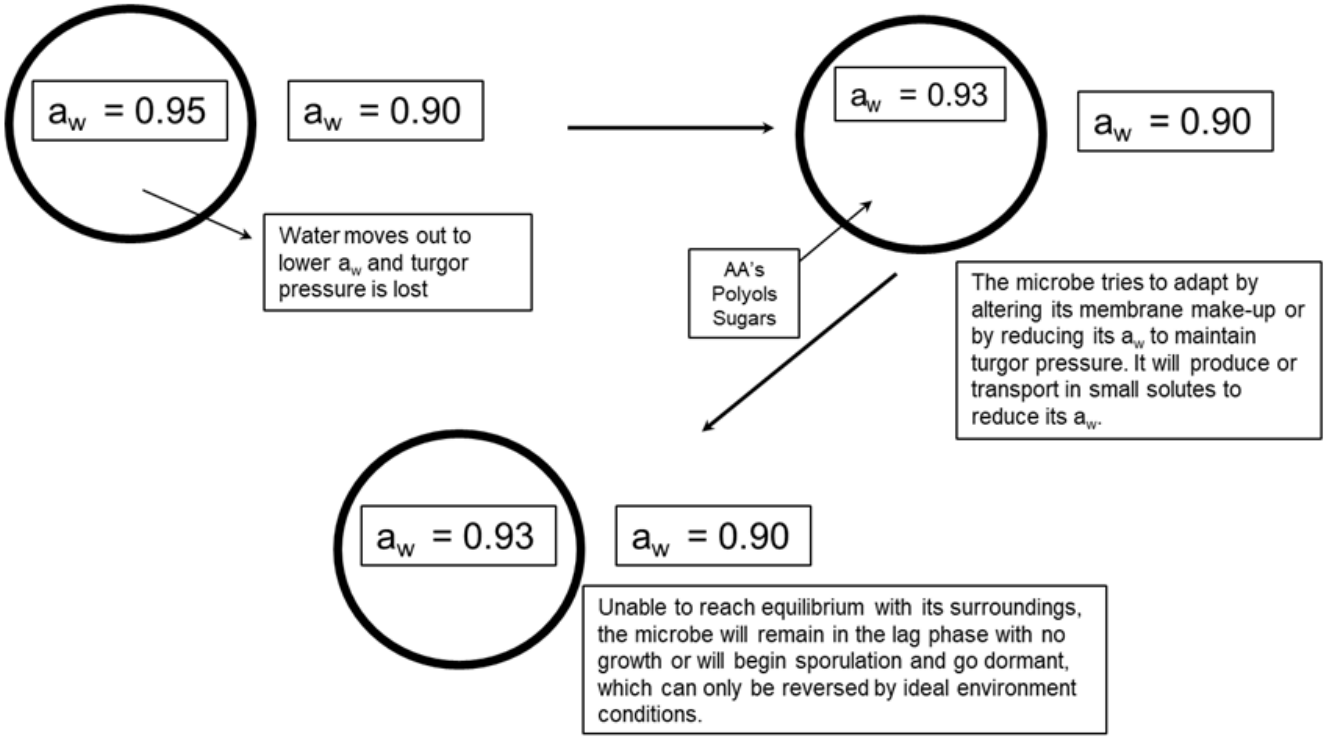


Figure 3. Mode of action for water activity control of microbial growth (6)

a_w limit	Microorganisms
0.91	Gram negative bacteria
0.86	Gram positive bacteria
0.88	Yeast (practical limit)
0.80	Production of mycotoxins
0.70	Molds (practical limit)
0.60	Absolute limit for all growth

Table 1. Minimum water activity levels required for the growth of various microorganisms

WATER ACTIVITY AND DEGRADATION OF ACTIVE INGREDIENTS

The water activity of solid dosage pharmaceuticals will typically be less than 0.70 a_w, indicating that microbial growth is not likely to occur. However, products in this range do not have an unlimited shelf life. For these products in the 0.40–0.70 a_w range, chemical degradation of the API is a strong candidate for the mode of failure because reaction rates are at a maximum. In general, as water activity increases so do reaction rates (8). The most common reaction that can result in the degradation of APIs is hydrolysis although lipid oxidation (rancidity) and enzymatic reactions may also play a role in the loss of active ingredients. The most effective way to prevent these reactions from resulting in significant loss of the API is to process them to a low water activity where reactions will be at a minimum and then choose the appropriate excipient that will do the best job of maintaining that water activity.

TRACKING MOISTURE CHANGE WITH WATER ACTIVITY

As shown by the moisture sorption isotherm, an increase in water activity is accompanied by a subsequent increase in moisture; however, the relationship is non-linear and unique to each product. An increase in the slope of the isotherm indicates an increase in hygroscopicity, which will limit the change in the water activity as moisture is absorbed. This is often a desirable characteristic in excipients because it allows the product to absorb moisture while still maintaining the water activity of the API at levels that limit the rate of degradative reactions as shown in the previous section.

Another way that the water activity of an API can increase to unsafe levels is through moisture migration in multiple component pharmaceuticals such as capsules. If the components are at different water activities, then water will move between the components regardless of their moisture content. Water moves from high water activity (energy) to low water activity (9). Moisture will continue to move between the components until an equilibrium water activity is achieved, which is dictated by the moisture sorption isotherms of each component and is not the midpoint between the initial water activities (Figure 4). If the water activity of the API increases, it could possibly be at high enough levels to speed up degradation. To avoid this problem, the components must be designed to have the same water activity.

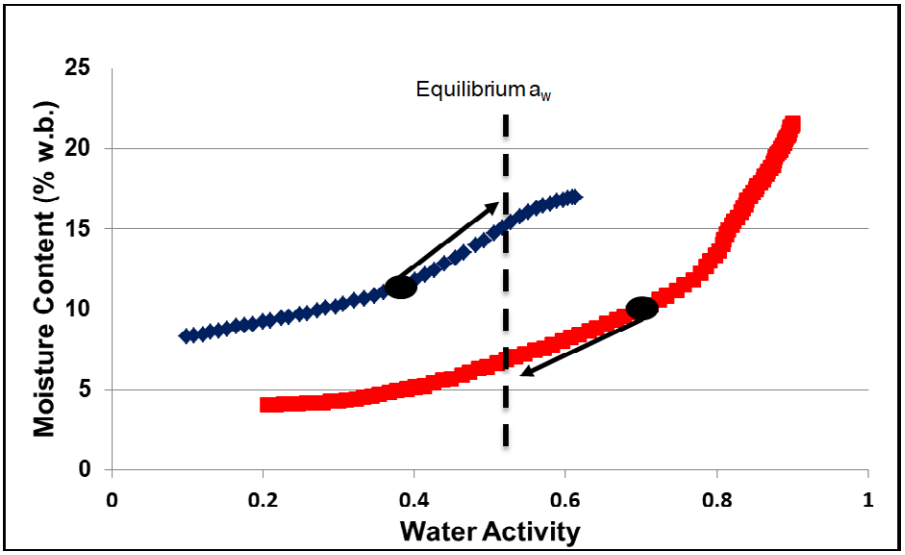


Figure 4. Moisture sorption isotherms for a product with two components at different initial water activities. The black dots indicate the initial water activity while the arrows indicate the direction of water movement for each component and the accompanying change in moisture content. The dotted vertical line indicates the water activity where the components will come into equilibrium and moisture movement will stop. The points where the isotherm curves cross the dotted vertical line indicate the moisture content of each component at the final water activity (9).

THE MOST IMPORTANT SPECIFICATION

Water activity is sometimes an overlooked and underestimated parameter in pharma quality and formulation. However, it offers critical information for optimizing product stability. Issues with deliquescence, caking and clumping, dissolution, microbial susceptibility, API degradation etc. can be resolved by identifying the ideal water activity range for the product and implementing water activity measurement as a routine parameter for batch release. With the water activity at this ideal range, most pharmaceutical products will also qualify for reduced microbial limits testing, resulting in time savings and reducing production costs.

THE AUTHOR

Dr. Brady Carter is a Senior Research Scientist with Carter Scientific Solutions. He specializes in Water Activity and Moisture Sorption applications. Dr. Carter earned his Ph.D. and M.S Degree in Food Engineering and Crop Science from Washington State University and a B.A. Degree in Botany from Weber State University. He has 20 years of experience in research and development and prior to starting his own company, he held positions at Decagon Devices and Washington State University. Dr. Carter currently provides contract scientific support to Novasina AG and Netuec Group. He has been the instructor for water activity seminars in over 23 different countries and has provided onsite water activity training for companies around the world. He has authored over 20 white papers on water activity, moisture sorption isotherms, and complete moisture analysis. He has participated in hundreds of extension presentations andhas given talks at numerous scientific conferences. He developed the shelflife simplified paradigm and hygrothermal time shelf life model.

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