

Implementation of Water Activity Testing to Replace Karl Fischer Water Testing for Solid Oral-Dosage Forms

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For solid oral-dosage forms, water testing usually is performed to control the chemical, physical, or microbiological properties of the drug product.

Measurements of total water as made with Karl Fischer (KF) techniques is not needed and water-activity often will provide a better correlation with changes in chemical, physical, or microbiological properties than KF techniques. In these cases, water activity testing can easily replace KF testing. Water-activity measurements are nondestructive, require little labor, and the equipment required is generally inexpensive. Only a few simple checks are needed to ensure the validity of measurements. Strategies for implementing water activity testing are described.

ost pharmacopeial monographs that have procedures for the measurement of water are based on the measurement of total water either by the Karl

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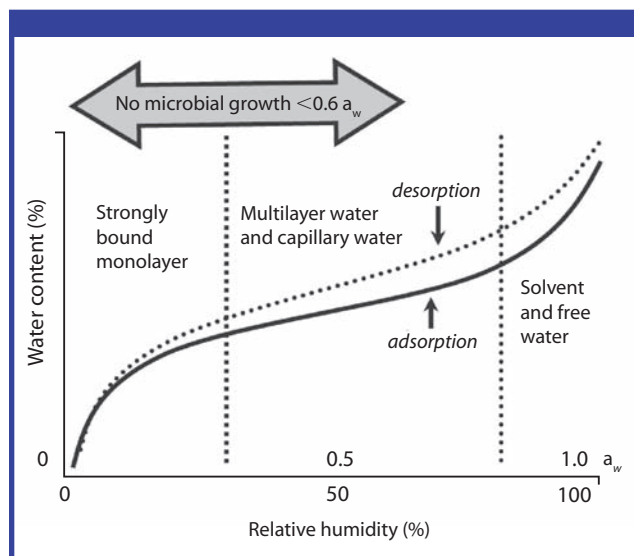


Figure 1: Water sorption isotherm.

indicates the total absence of water molecules. Water activity is the effective mole fraction of water, defined as:

$$a_w = \lambda_w x_w = p/p_0$$

in which λ_w is the activity coefficient of water, x_w is the mole fraction of water in the aqueous fraction, p is the partial pressure of water above the material, and p_0 is the partial pressure of pure water at the same temperature (*i.e.*, the water activity is equal to the equilibrium relative humidity [ERH]), expressed as a fraction. The relationship between water activity and weight percent water is shown in a sorption isotherm (see Figure 1). Figure 1 also shows the hysteresis observed when the sorption isotherm depends on whether the water is added to the dry material or removed from the wet material. This hysteresis is caused by nonreversible structural changes and/or kinetic effects.

The sorption isotherm for a formulated drug product is the result of the combination of the individual-component sorption isotherms. Sorption isotherms for excipients and the drug substance may be used to model the sorption isotherm of the finished dosage form (5). Figure 2 shows an example of an adsorption isotherm for a typical oral formulation. Two recently published studies present adsorption and desorption isotherms for several common excipients (5–6).

Materials of differing water activity exhibit time- and temperature-dependent water migration from areas with high to low a_w . For example, a gelatin capsule filled with a powder that has a different water activity will undergo water migration and, at equilibrium, the capsule shell and powder contents have the same a_w . For packaged products, the moisture-vapor barrier properties of the packaging become crucial in the rate of moisture loss or gain. In addition, desiccants inside a package change the initial water activity as well as the subsequent rate of water activity change. Because

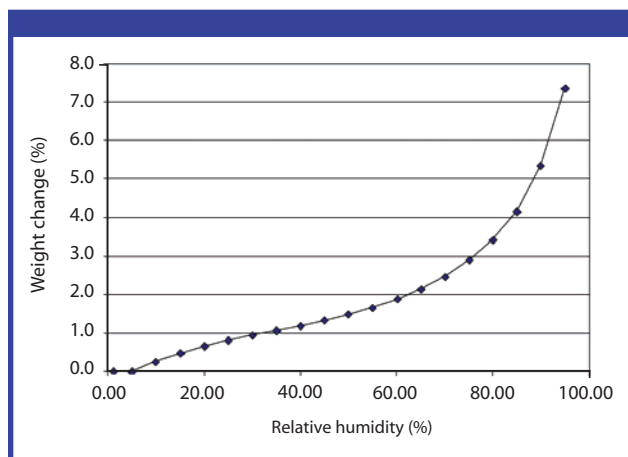


Figure 2: Typical adsorption isotherm for tablet formulation.

the humidity of the air is defined as 60% ($a_w = 0.6$) by the International Conference on Harmonization under Climatic Zones II, materials with lower a_w tend to gain water and those with higher a_w tend to lose water. Most solid oral-dosage forms are produced with water activities of 0.3 to 0.5 and thus gain water in stability studies.

Use of water activity. The food industry has long used water activity to control microbial growth and chemical stability. Consistent with the US Food and Drug Administration's use of water activity in controlling the microbial attributes of food (7), water activity also is being used to control the microbiological properties of pharmaceutical products (8, 9). The growth of most bacteria is inhibited below approximately $a_w = 0.91$. Similarly, most yeasts cease growing below $a_w = 0.87$, and most molds stop growing below $a_w = 0.80$. The absolute limit of microbial growth is approximately $a_w = 0.6$.

The importance of water activity in controlling the microbial properties of pharmaceutical products was added to *US Pharmacopeia (USP) Chapter <2023>*, "Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements," and a new *USP* chapter was written: <1113> "Application of Water Activity Determination to Nonsterile Pharmaceutical Products." *USP Chapter <1113>* primarily describes the application of water-activity measurement for the control of a nonsterile formulation's microbial attributes, but also mentions the control of chemical degradation. The correlation of water activity and chemical changes in food also has been investigated extensively (10). A correspondingly common practice in pharmaceutical development is to equilibrate products at different humidities (water activities) and study their degradation rates. Water activity also correlates with changes in chemical and physical stability (11, 12). The degradation rate of several pharmaceutical products is well modeled by water activity using the BET function (rate is proportional to $1/[1 - a_w]$) (11) as well as other approaches (12–15).

Measurement of water activity. Water activity is determined by the measurement of water in the gas phase immediately sur-

Table I: Examples of required changes in water activity to double degradation rate.

Example	Change in a_w to double degradation rate	Change in water content to double degradation rate
Cephalosporin degradation (19)	0.2	0.3–0.5%
N-oxide formation (20)	0.2	4.1–5.7%
Waterman aspirin degradation (21)	0.2–0.3 (estimated)	Not available
Hydrolysis of nitrazepam (22)	0.1–0.2	Not available
Asparatamine degradation (23)	0.1–0.2	Not available

rounding the sample. The measurement of water activity in foods is described by AOAC's *Official Methods of Analysis*, No. 978.18, "Water Activity of Canned Vegetables" (16). The principal techniques are changes in electrical capacitance or resistance of polymer thin films and dew point by chilled mirror. Newer techniques include the measurement of water in the headspace either spectroscopically (17) or chromatographically (18).

Method Number 978.18 also compares various types of instruments. For sensor-type instruments, a typical instrument chamber would have a depth of approximately 1.3 cm and a diameter of 4.2 cm. Sufficient sample is needed to fill the chamber to the appropriate level (one-half to two-thirds full). Probes also are available for insertion into bulk materials or possibly through product packaging. Measurement time is controlled by sensor measurement time (usually a few minutes) and time for the headspace to equilibrate (the time for water activity in the headspace to come into equilibrium with the material being tested). Typical equilibration times vary from 5 to 30 minutes.

The rate of equilibration of the dosage form with the chamber's headspace depends on several factors, including:

- the difference in water activity between the dosage form and the air in the chamber's headspace immediately following the sample-transfer process;
- the headspace volume of the measuring chamber containing the sample;
- the transfer rates of water within the sample and between the sample and the gas phase;
- the gas-phase diffusion rate for water in the headspace.

The gas-phase diffusion rate of water is not a significant factor based on the configuration of typical sensor cells. The gas-phase diffusion rate is approximately 0.1 cm²/s and the largest distance in the chamber is approximately 4 cm. Because the sample occupies most of the chamber, the largest distance is actually closer to 0.5 cm (from the top of the sample to the top of the chamber). The transfer rate of water between the sample and the gas phase is related to the specific sample for evaluation. Depending on the sample, the transfer rates within the sample and between the sample and the gas phase can vary significantly. Heterogeneous samples such as intact capsules or coated tablets may have longer equilibration times than uniform powder samples.

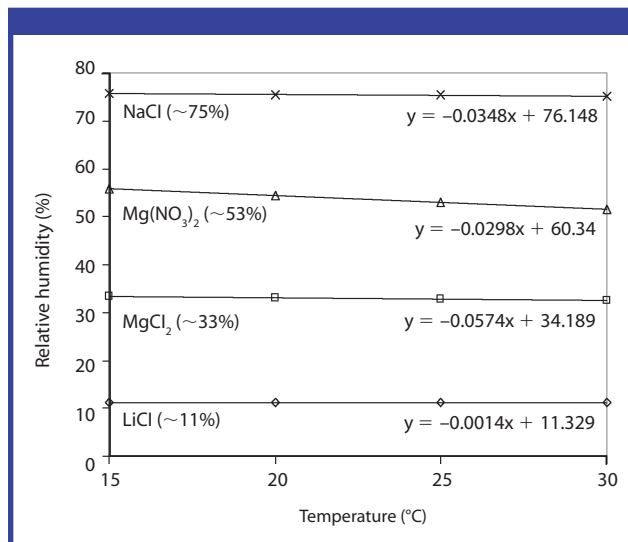


Figure 3: Relative humidity as a function of temperature for saturated salt solutions used for calibration (only the magnesium nitrate standard is sensitive to temperature).

Although sample transfer can be performed rapidly to minimize changes to the sample moisture content, moisture still must be absorbed or desorbed from the sample to equilibrate the measuring chamber's headspace. For a typical sample, the change in the sample's moisture content during this equilibration process will not have a significant effect on the accuracy of the sample's final a_w reading. Air at a temperature of 25 °C contains approximately 0.023 mg/mL of water at 100% RH. For a sample at 75% RH, with the external environment at 0% RH and a sample chamber headspace of 6 mL, the sample must replace only approximately 6 mL × 0.023 mg/mL × (0.75 – 0.10) or 0.01 mg of water. With a sample weight of 2 g in the chamber and a water content of 2%, the total amount of water in the sample is 40 mg. In this case, only a very small fraction of the total water is removed from the dosage form to equilibrate the humidity in the headspace (the water content of the sample would drop by less than 0.01%).

Samples that contain very little water or have a very shallow slope for the sorption isotherm in the region of interest will be problematic with regards to bias during equilibration in the chamber. The use of laser-absorption spectroscopy (which can determine the water activity in the headspace of a sample vial without breaching the seal) would be beneficial for these types of samples. An example of a product that could be difficult is a lyophilized cake with very low water content. Nonetheless, the typical capsule or tablet product generally contains a large amount of water and is an excellent candidate for water-activity testing.

For most solid oral-dosage forms, the range of interest for water activity is 0.30–0.75. Water-activity measurements are generally precise and accurate to 0.01–0.02 units. Thus, water activity should be capable of providing 23 levels ((0.75 – 0.30)/0.02) of distinction over this measurement range. Sev-

Table II: Protective filters used with water-activity instruments from Novasina for Capsule B measurements.

Commercial description	Function
Mechanical prefilter/ eVMT-2	Protects sensor from particles of sample
EVC-21	Protects sensor from acidic compounds
EVC-26	General chemical filter
EVALC-1	Protects sensors from alcohol
REDOX	Oxidizes, reduces interfering compounds

eral examples of degradation as a function of water activity are shown in Table I, and water activity changes of about 0.1–0.2 are needed to double the degradation rate. In a case for which a 0.1 change in water activity is critical, tighter controls of calibration may be needed. In general, the water activity would be controlled at a level well below when significant degradation occurs. Thus, the examples in Table I represent mostly the worst cases in terms of required accuracy. Compared with Karl Fischer water testing, water activity has particular advantages when:

- the sample is hygroscopic;
- the sorption isotherm is relatively flat over the region where increased degradation rates are noted (*i.e.*, little change in water content);
- the amount of total water is high (*e.g.*, hydrates) and variability in the measurement makes discriminating changes in water content difficult.

Calibration. Calibration is accomplished with the use of either saturated salt solutions or solutions with well-characterized water activities. Saturated salt solutions that have reference values traceable to National Institute of Standards and Technology standards (24) are available. Figure 3 shows the effect of temperature on some typical water-activity standards.

Experiment

Over-the-counter tablets of ibuprofen, naproxen, and enteric-coated aspirin were obtained from a local retail establishment for evaluation. Two developmental capsule formulations also were evaluated. Capsule A was a starch-based formulation and Capsule B contained enteric-coated beads. The water-activity instruments used were from the same manufacturer (Novasina, Pfäffikon, Switzerland) but obtained from Omnimark Instrument Corp. (Tempe, AZ). The names of the two models are the Ms1 and the AW Lab.

Both instruments use the same measuring cell and sensor. The AW Lab model has an additional capability of determining whether the measurement has reached equilibrium by establishing a limit of the change in water activity with time. All measurements were made using the mechanical prefilter, except for those made for Capsule B. For the Capsule B measurements, all of the protective filters listed in Table II were evaluated.

Water-activity standards (saturated salt solutions) were obtained from the instrument supplier. Both Novasina instruments take into account temperature during calibration as long as the temperature is between 15 °C and 30 °C.

The Novasina instruments do not allow for temperature control. To obtain temperature-effect data, the measuring chamber was placed in a plastic bag and immersed in a water bath. Measurements were only recorded after the sensor temperature reading agreed with the external water-bath temperature.

Because it is not easy to predict the effect of test samples on the instrument sensor, bracketing readings of water activity standards were performed regularly (one low and one high standard reading during each period of use, typically 24 hours).

The equilibration of dosage forms to different water activities were performed to ensure the validity of the water-activity measurement. In general, the same type of salt solutions used in sealed desiccators also were used for calibration. Intact tablets or capsules were

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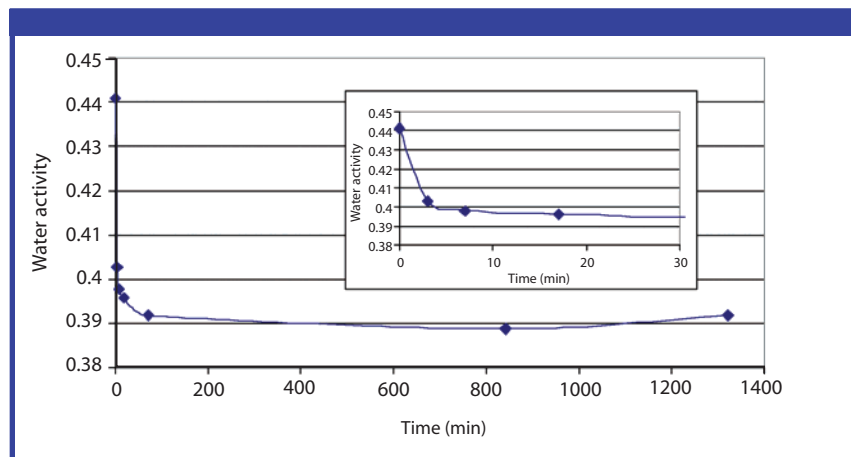


Figure 4: Rate of equilibration of Capsule A.

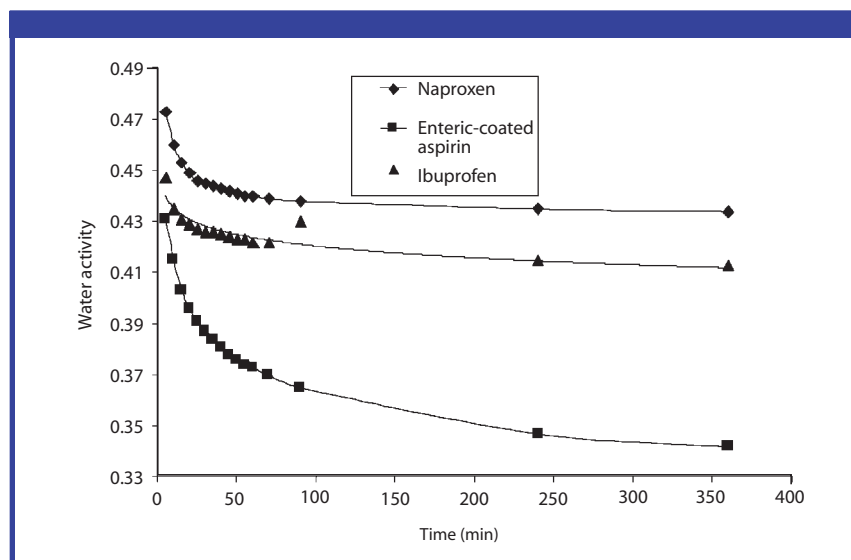


Figure 5: Rate of equilibration of several solid oral-dosage forms.

equilibrated for 7–14 days. Crushed or composited dosages were equilibrated for 24 hours.

Studies requiring RH control were performed with a humidity-controlled glove box (Coy Laboratory Products, Grass Lake, MI).

Results and discussion

Key operating conditions that were investigated include the effects of sample temperature, equilibration time, and sample handling (in particular, the humidity of the environment in which samples are transferred). In addition, the factors affecting the specificity of the sensor must be considered to support the validation of the technique. Based on an earlier discussion, changes

in a_w of >0.01 to 0.02 were not considered significant.

Sample temperature. If the sample and the equilibration chamber are at the same temperature, then temperature has a small effect on water activity within the temperature range of most laboratories. The authors previously discussed the effects of temperature on the water activity of the saturated salt standard solutions used for calibration. Those effects are generally small and taken into account by the instrument. The effect of temperature on solid oral-dosage forms was studied for two samples: Capsule A and naproxen. The observed effects of temperature changes on water activity were 0.003 and $0.004 a_w / ^\circ\text{C}$ and were similar to those reported by a man-

ufacturer (25). The small effect of temperature is explained by the fact that the change in the partial pressure of water vapor (p) with temperature for the sample is similar (but not equal) to the magnitude of the change of the saturation pressure (p_0) above pure water. Any change in the temperature of a hygroscopic product automatically causes the product to exchange moisture with the air (or gas) that surrounds it. Moisture is exchanged until the partial water-vapor pressure at the product's surface and in the air is equal. For this reason, a constant temperature is important when measuring a_w .

Equilibration time. To understand the time required for the headspace to come into equilibrium with the sample, water activity was measured as a function of time for the products shown in Figures 4 and 5. The results for Capsule A indicated that equilibration occurred within 10 minutes and no significant changes occurred over the subsequent 12 hours (see Figure 4). Figure 5, which includes two typical tablet formulations and an enteric-coated aspirin tablet, shows that a 30-minute equilibration time was appropriate for the tablet formulations. A longer equilibration time would be needed with the enteric-coated formulation for the same degree of accuracy. In general, the authors have used an accuracy of $\pm 0.02 a_w$ as being acceptable. Another alternative would be to crush the enteric-coated tablet, but this procedure needs special precautions.

For some instruments, the equilibration time is not a concern. These instruments measure the rate of change of a_w with time and will indicate a stable reading only when the rate of change is below a selected threshold. Other instruments use a mathematical function to estimate the final equilibrium value. The advantage of measuring water activity on intact tablets is shown in Table III, in which the water activity of intact tablets is compared with that of crushed tablets under 10% and 80% RH. The total exposure time to the ambient RH was approximately 2 min (including the time to crush the tablets with a mortar and pestle). This time was used to sim-

Table III: Effect of sample grinding on measured water activity.

Experiment	Water activity	Error compared with intact
Intact ibuprofen tablets (different lot than in Figure 5)	0.345	—
Ibuprofen tablets crushed in a 80% relative humidity environment (2 min exposure)	0.530	+53%
Ibuprofen tablets crushed in a 10% relative humidity environment (2 min exposure)	0.321	-7%

ulate rapidly crushing, weighing, and transferring tablets in alternative methods such as Karl Fischer. Whereas the low humidity only created a small bias, the high humidity created a large error. There was a larger difference between the sample water activity and the ambient conditions for the high humidity (45% RH higher) *versus* the low humidity (22% RH lower). The rate of water uptake *versus* loss is not expected to be the same. A technique for reducing water changes during crushing is to use a device sold to home customers that sandwiches the sample between two holders, thus reducing contact with the ambient atmosphere.

Sample handling. The effect of ambient humidity on sample handling was assessed by transferring Capsule A in environments of 10% and 80% RH. As shown in Figure 6, the effect of high or low humidity is to increase the equilibra-

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ated with an enteric-coated aspirin tablet and two other tablet formulations as shown in Table IV with a general accuracy of 0.01–0.02 a_w . The same approach was taken by Mahajan *et al.*, with a similar degree of accuracy (17). As previously mentioned, a 30-minute equilibration time generally has been adequate for capsules and tablets.

Precision. Replicate measurements were made for two tablet formulations and one capsule formulation (see Table V). The relative standard deviations for replicate measurements were 1–3%.

Instrument qualification of maintenance (Novasina Instrument). Using the guidelines published in a recent white paper (27), water-activity instruments would be Class B, principally re-
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- validating methods once they are being used for lot-release purposes.

Table VI describes some differences in the types of instruments. Only representative manufacturers are included.

The approach used by all of the instruments is nondestructive. The instruments vary in the cutoff at low RH, the control of temperature, and the detection of the equilibration end-point. Measurement time is faster for the laser absorption and the instruments that extrapolate the detection of the end-point; but, temperature control generally lengthens the measurement time to 10–30-minutes for all the instruments. The Lighthouse instrument would be especially useful for lyophilized formulations because the measurement can be made on the headspace of the product vial. Reference 16 has more details about differences in cost and applicability.

The control strategy also must be consistent with the regulatory strategy. Table VII summarizes options relative to the product registration status.

Routine control of instrumentation. For the instruments that have sample contact with the sensor, bracketing readings of the standard solutions should be used to ensure that the sensor is providing accurate results and that the samples did not contaminate the sensor. The use of a protective filter should be tracked such that the filter is replaced at least as frequently as the manufacturer suggests. Standards that are saturated

Table VII: Options for implementing water-activity testing as a function of registration status.

Product registration status	Options
Marketed product with Karl Fischer water test	<p>Establish water activity as an alternate procedure with a limit based on sorption isotherm.</p> <p>If actual water levels are close to registration limit, then variations in isotherms should be considered.</p>
Marketed product with no registered Karl Fischer water test	Follow normal practices for changing analytical procedures.
Product starting registration stability or earlier	<ol style="list-style-type: none"> 1. Implement with the intent to use water activity as an internal GMP test (<i>e.g.</i>, not registered). 2. Correlate Karl Fischer and water activity tests to keep options open, but use water activity as the principal test.

salt suspensions also require some maintenance to replace lost water from evaporation. These standards should be checked each time they are used.

Conclusions

Water activity is a valid alternative to total water measurements (KF) in assessing the potential for water to adversely affect the formulation's microbial or chemical quality. Water activity has been accepted in the food industry and widely discussed in the pharmaceutical industry as an appropriate measurement for water to prevent microbial growth. Likewise, water activity also can be used to evaluate the potential effect of water on chemical and physical changes in the formulation. The Novasina ms1 and AW instruments in particular have proven to be sufficiently precise and accurate to measure the water activity of typical solid oral-dosage forms.

Acknowledgments

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