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Incorrect Water Measurements Costly

Water activity is key to pharmaceutical safety and quality

WATER ACTIVITY

Water is critical to the chemical, physical, and microbiological stability of most pharmaceuticals. They are formulated, manufactured, and packaged carefully to avoid spoilage and preserve correct dosage, both chemically and physically. Traditionally, this led formulators and manufacturers into monitoring water content. Water activity measurements are a powerful tool in formulating, manufacturing, packaging, and storing non-sterile, over-the-counter drugs and cosmetics.

Food scientists now understand how to quantify the effects of these preservative methods. They measure not how much water a food contained, but rather how much of that water is "available." This measurement — water activity —determines how much water is free from physical and chemical bonds and thus available for migration, chemical reaction, use by microorganisms, or other activity.

Water activity is measured by placing a sample in a closed chamber and allowing it to come to equilibrium. The water vapor pressure of the air over the sample is then measured, and water activity is expressed as the ratio of this sample vapor pressure to the vapor pressure of pure water at the same temperature. A sample with water activity of 0 is completely dry, while 1.0 is the water activity of pure water. By measuring and controlling the water activity of a formulation, scientists can increase its stability and reduce or eliminate the risk of microbial growth. The growth of specific microorganisms is limited below certain specific water activities (Table 1). These limits are well defined in scientific literature. For example, below 0.6 a_w, water is so tightly bound that it is unavailable to even the most xerophytic fungi. That boundary applies to every product, ingredient, and substance.

Makers routinely manipulate the water activity of pharmaceuticals without realizing it. Through drying, adding humectants, using natural and chemical preservatives, and trying to stabilize water activity via moisture-barrier packaging — all of these alter water activity.

Unfortunately, they try to qualify microbial safety using expensive, time-consuming microbial testing — or by measuring water content — when they could be using a quick and easy water activity test to demonstrate microbial safety. As proposed by United States Pharmacopoeia (USP) Method <1112> Microbiological Attributes of Nonsterile Pharmaceutical Products — Application of Water Activity Determination, measurements of water activity may provide a faster and more accurate window into the microbial effects of these methods of preservation.

Content vs. Activity

The water content measurements more traditionally used in formulating drugs and cosmetics are not as useful as water activity measurements. The water content of a safe product varies from product to product and from formulation to formulation. One safe, stable product might contain 12.5 percent water while containing just 7.5 percent water is susceptible to microbial growth. If the water in the wetter product is chemically bound, it is unavailable to microbes. Even though the wetter product contains proportionally more water, its water activity may be lower than that of the drier product. Using only water content values, it's impossible to predict which of these products is properly preserved.

For example, a lip balm manufacturer's product contained so little moisture — only 1 to 2 percent — that he didn't think there was any question of spoilage. When he measured the water activity, however, he discovered that it was 0.8 — well into the range where microbes will grow. By adding ingredients to the aqueous phase during formulation, he reduced water activity dramatically and made the product naturally preserving. Before measuring water activity, he didn't even know he had a potential problem. Some products are not sufficiently preserved. Others are over-preserved. Without testing water activity, it's difficult to tell one from the other.

Manufacturers would like to err on the side of over-preserving. For the same reason, they tend to over-test their ingredients and products. But more than just being another test, water activity can provide a much clearer picture. Knowing water activity, for example, can help manufacturers decide which raw ingredients are relatively safe and which need careful treatment. In certain cases, especially for raw ingredients with very low water activities, a history of testing combined with water activity measurements can provide justification for eliminating routine microbial testing. A manufacturer of cough syrups used high fructose corn syrup as a principal ingredient. The syrup arrived in huge tankers, making it difficult and expensive to test before pumping it into the tank farm and scheduling it for

Table 1. Water Activity Limits for Growth of Microorganisms

WATER ACTIVITY	MICROORGANISM
0.97	*Pseudomonas aeruginosa*
0.95	*Bacillus cereus, Clostridium botulinum,* Type A, *Escherichia coli, Clostridium perfringens, Lacto bacillus viridescens, Salmonella spp.*
0.94	*Enterobacter aerogenes*
0.93	*Micrococcus lysodekticus, Rhyzopus nigricans*
0.92	*Mucor plumbeus, Rhodotorula mucilaginosa*
0.90	*Bacillus subtilis, Saccharomyces cerevisiae*
0.86	*Staphylococcus aureus*
0.84 – 0.81	*Paecilomyces variotti, Penicillium chrysogenum, Aspergillus fumigatus, Penicillium glabrum*
0.78 – 0.75	*Aspergillus flavus, Aspergillus niger, Halobacterium halobium*
0.62	*Zygosachharomyces rouxii* (osmophilic yeast)
0.61	*Xeromyces bisporus* (xerophilic fungi)
<0.60	No microbial proliferation

use. The maker wondered if it was really necessary to test every batch of syrup coming in. Testing the water activity of the high fructose corn syrup and finding it very low, the company found further microbial testing unnecessary.

A manufacturer of liquid-filled capsules also discovered the benefits of measuring water activity. This company was doing lengthy and expensive microbial testing on every batch of product. A long and problem-free testing record supported reducing the frequency of tests. When this manufacturer measured the water activity of the product, they discovered that it was not susceptible to microbial growth. That test was a key element in eliminating routine testing, saving $200,000 a year while maintaining the assurance that the product was safe.

Knowing water activity values can also help predict moisture migration and shelf stability, especially of moisture-sensitive substances. Imagine that a manufacturer wants to predict conditions over time in a gel capsule. He makes sure that the water content of the capsule is equal to that of the drug formulation it will contain. It may seem to him that this combination would be stable — that water would only migrate from a wetter ingredient to a drier one. But of course if one of these components has a higher water activity (meaning that the water it contains is not chemically or physically bound), that water will migrate until the water activities of the two components come to equilibrium, making the capsules either swollen and sticky or dried and cracked, and potentially altering the properties of the drug formulation. Water activity, not water content, is the actual predictor of water migration within a product. The gel capsule manufacturer can measure the water activity of the internal drug dosage formulation and pair it with a gel capsule formulated to the same water activity to ensure a safe, stable product. If the water activities of the two components are the same, there will be no moisture migration.

Effective packaging can also benefit from understanding and measuring water activity. A manufacturer of an enzyme system for topical application discovered that the water activity of the cream they were manufacturing was too high, causing the active ingredient to lose its catalytic properties while on the shelf. In order to formulate an effective version of the product, they considered microencapsulating the dried enzyme. But microencapsulation is both expensive and tricky. Using water activity measurements and creative packaging, they discovered that they could ensure longer shelf stability by packaging the dried powder and the cream separately in a plunger. When the consumer dispenses the plunger, the powder mixes with the cream, rapidly raising the water activity of the powder and activating the enzyme as the cream is applied. A nutraceutical manufacturer similarly uses creative packaging to keep a dried acidophilus formulation stable at a low water activity while the product is on the shelf. This maker puts the powder in a straw together with a container of yogurt. The consumer gets the dose of acidophilus by putting the straw into the yogurt and taking a sip.

Pharmaceutical manufacturers tend to be obsessed with quality and safety. They are highly risk-averse, and understandably so. Water activity measurements represent a great opportunity for them to get clearer and more detailed information about their formulation, manufacturing, packaging, and storage practices. By measuring the quality of the water in a product — how much is free from physical and chemical bonds — as opposed to the quantity, they can determine the effectiveness of various preservative methods, ensure quality of raw materials, monitor and prevent changes and spoilage during storage, and test and improve packaging. Water activity tests may also be helpful in validating product expiration dates, monitoring physical, chemical, and microbial stability of drugs under use conditions, and as a screening method to trigger more extensive microbiological tests for contamination and impurities. ■

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