What is Water Activity?

In the most recent USP General Chapter <795>, titled "Pharmaceutical Compounding-Nonsterile Preparations", released on June 1, 2019, we see references to water activity in Section 10.0 "Establishing Beyond Use Dates". In fact, the beyond use dating (BUD) is primarily based upon the water activity of a preparation. According to <795>, a preparation with a water activity below 0.6 is considered to be non-aqueous and can have BUD of 90 days. Solid dosage form preparations such as capsules, tablets, and powders, will have essentially zero water activity and can have BUDs of 180 days. (There are certain caveats, of course, such as shorter expiration dates of the active(s) or stability of the APIs used in making the preparations which could limit these dates). On the other hand, preserved aqueous dosage forms having water activity greater than 0.6 will have BUDs limited to 35 days, and non-preserved aqueous dosage forms must be stored in the refrigerator and can have only 14 day BUDs.

To have BUDs longer than these dates is possible (up to 180 days), but there must be stability indicating test data to support this. Our laboratory routinely performs such stability testing. Please contact us if you are interested in having your formulations tested to be able to extend your BUDs.

So, what is water activity and why is it important?

What is water activity? Is it the amount of water in the product, similar to the number we often see on the certificate of analysis for an active ingredient? Is it the same as loss on drying (LOD)? The answer is "No" to both of these questions.

Water activity (A_w) is the ratio of the vapor pressure of water in a preparation vs. the vapor pressure of pure water at the same temperature, in a closed system. Or for a simpler way of thinking about it, we can refer to it as being related to a measurement of the humidity within a container of product. Water activity can be measured using specialized equipment and the number generated will relate to humidity within the preparation. Typically, water activity values will range from 1.0 on the high end, to near zero on the low end. These numbers would be examples of a totally aqueous solution, and a dry powder, respectively.

The higher the A_w value, the greater the opportunity for microbial growth and the greater the opportunity for some active ingredients to breakdown due to hydrolysis. So, if water activity can be reduced, the BUD may be able to be extended. In addition, with lower A_w values, antimicrobial effectiveness of preservatives is improved. Susceptibility to microbial contamination of multiuse products which might be contaminated by the user, such as topical creams, is reduced with lower A_w values. Also, the life of many active ingredients is extended. Beyond these, the frequency to perform Microbial Enumeration Tests <61> and Tests for Specified Microorganisms <62> can be reduced.

To understand the importance of water activity values, it is important to understand that many bacteria will not survive in products having water activity below 0.86. Most molds and yeast will not grow if water activity is below 0.77 although some can grow with A_w down to 0.60. Therefore, a good target for water activity which will optimize shelf life insofar as microbial growth, is to achieve A_w values of 0.60 or lower. This number means the vapor pressure is 60% of that of pure water.

How can water activity be reduced?

Certainly non-aqueous preparations or dry solid dosage forms will not support microbial growth or spore germination because of their inherent low water activity. For dosage forms containing water, one way to reduce water activity, of course, is to reduce the amount of water in the formulation. This might not always be practical however. Consider an aqueous oral solution or suspension which must contain a considerable amount of water in its formulation. Consider also, some topical products which need a certain quantity of water to formulate properly or to provide needed characteristics. So we might ask, in what way can these be reformulated to reduce the A_w value? It turns out that small changes in the concentration of alcohol, glycerin, or propylene glycol can reduce water activity by linking to water molecules by means of hydrogen bonding. Likewise, the addition of sucrose or sodium chloride can reduce water activity and make preparations self-preserving. Possible, also, is the addition of solids in a formulation, especially those which absorb or bind water, such as methylcellulose, will reduce the A_w value. In your formulations, consider if these or similar substances would be appropriate and if so, it just might make a significant difference in its BUD.

Final comments.

If you would like to determine the A_w value of any of your preparations so you will know what BUD you can use, please send us a sample for testing. We have the specialized instrumentation to perform this test for any dosage form. If you have a desire to modify a formulation in an effort to reduce its A_w value and thus extend its BUD, this test result will establish its baseline value before any formulation changes are made. Then consider the suggestions for reducing the A_w value provided above, reformulate, and have us retest to identify the effectiveness of your modification(s).