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How water activity can affect the stability of compounded non-sterile preparations

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There is more than meets the eye when it comes to the stability of a compounded non-sterile preparation. Observing physical change over time can provide an initial assessment of stability; however there are other factors to consider, such as drug potency and potential for microbial contamination. Overall stability is an important factor in ensuring the identity, strength, quality, and purity of drug substances.[1] The United States Pharmacopeia (USP) defines stability as "the extent to which a product retains, within specified limits, and throughout its period of storage and use (i.e., its shelf-life or Beyond-use Date), the same properties and characteristics that it possessed at the time of its manufacture".[2]

There are five general types of stability outlined in USP Chapter <1191>.[3]

1. **Physical:** The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained.
2. **Chemical:** Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
3. **Microbiological:** Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.
4. **Therapeutic:** The therapeutic effect remains unchanged.
5. **Toxicological:** No significant increase in toxicity occurs.

A good knowledge of the types of stability is essential for preparing safe compounded formulations.[4]

There are several approaches that can help stabilize pharmaceutical preparations containing drugs prone to degradation by common pathways, such as hydrolysis, oxidation and microbiological contamination. An example of this is to minimize or eliminate water from the pharmaceutical system. Water catalyzes degradation reactions such as hydrolysis and oxidation (dependent on pH) and promotes microbial growth, which can be harmful when used by the patient.[5] Therefore, a water-free vehicle (anhydrous base) may be an excellent option for active pharmaceutical ingredients (APIs) known to be unstable in water.

Beyond-use Date (BUD) is defined by USP Chapter <795> as the date after which a compounded preparation must not be used and it is assigned from the date the preparation is compounded.[6] Until recently, default BUDs were based on generalized properties of stability, which may not have been suitable for all formulations.[5] Consequently, there have been many discussions over several years on identifying alternative parameters to more accurately determine safe and reliable BUDs. In these discussions, water activity became a focal point, guiding a new method for determining default BUDs.

Understanding the part water activity (a_w) plays in compounded dosage forms (solid, semi-solid, and liquid) is helpful to obtain a formulation with optimal chemical, physical, and antimicrobial properties. Water activity influences the chemical stability, microbial stability, and dissolution rate of pharmaceutical dosage forms. The importance of water activity has been recognized by USP and is now captured in the new General Chapter <795> Pharmaceutical Compounding - Non-Sterile Preparations (to be official on November 1, 2023), as part of the scientific rationale for applying default BUDs.

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Table 1. Beyond-use Date for Compounded Non-Sterile Preparations According to USP <795>

General Chapter USP <795> Official 2020

Type of Preparation	Beyond-use Date
Water-containing oral formulation	14 days (refrigerated)
Water-containing topical/ dermal and mucosal liquid and semisolid formulation	30 days
Non-aqueous formulation	6 months

General Chapter USP <795> to be Official Nov 2023

Type of Preparation	Beyond-use Date
Non-preserved aqueous dosage form ($a_w \geq 0.60$)	14 days (refrigerated)
Preserved aqueous dosage form ($a_w \geq 0.60$)	35 days
Non-aqueous oral liquids ($a_w < 0.60$)	90 days
Other non-aqueous dosage forms ($a_w < 0.60$)	180 days

Water activity defines the amount of free, unbound, or available water in a formulation and is different from total moisture content, which is a measure of both free and bound water. The amount of water that is in free form is available to microorganisms for their proliferation and survival as well as available for degradation reactions with the API. Water activity is determined by the ratio of the vapor pressure of a test material to the vapor pressure of pure water at an ambient temperature.

$$\textit{Water Activity } (a_w) = \frac{\textit{Vapor Pressure of the Product } (P)}{\textit{Vapor Pressure of Pure Water } (P_0)}$$

The water activity of pure water is 1.00, therefore, the lower the water activity of a product, the lower the amount of free or available water. A low water activity value means that a portion of the total water content of a formulation is tightly bound to other ingredient molecules contained in the product, making it unavailable to foster microbial growth or degradation reactions. In other words, since microbial proliferation and hydrolysis reactions require water, the water activity of a product is directly proportional to the rate of microbial proliferation and API degradation. The potential for microbial contamination of a formulation can be reduced by lowering its water activity. In general, growth of most bacteria is inhibited if the water activity is < 0.90. Similarly, the growth of yeasts and molds, with the exception of osmotolerant species, is hindered if the water activity is < 0.70 and virtually no microorganisms can grow when the water activity reaches a value below 0.60.[7]

According to USP Chapter <1112> the application of water activity determination to nonsterile pharmaceutical products aids in the decisions relating to the following:[8]

- Optimizing product formulations to improve antimicrobial effectiveness of preservative systems.
- Reducing the degradation of active pharmaceutical ingredients within product formulations susceptible to chemical hydrolysis.
- Reducing the susceptibility of formulations (especially liquids, ointments, lotions, and creams) to microbial contamination, and.
- Providing a tool for the rationale for reducing the frequency of microbial limit testing and screening for objectionable microorganisms for product release and stability testing methods contained in the general test chapter Microbial Enumeration Tests <61> and Tests for Specified Microorganisms <62>.

The above in consideration, the water activity measurement of pharmaceutical preparations is crucial for predicting the type and number of microorganism that can be responsible for product degradation, chemical stability, non-enzymatic reactions and lipid peroxidation, and assessing physical properties such as moisture migration and dating of the preparations.

In conclusion, water activity is a useful tool in assessing potential physical, chemical, and microbiological stability and can be referenced to determine suitable BUDs as per the new USP <795> for compounded non-sterile preparations. Compounders are not required to measure water activity of compounded non-sterile preparations. They may refer to examples provided within the chapter as well as available water activity data. Based on reliable scientific information and development of new vehicles using high quality ingredients, pharmacists are capable of using pre-made bases that allow them to achieve the desired BUD for their compounded formulations based on water activity reported.

Table 2. Medisca Anhydrous Bases with Low Water Activity (a_w <0.6)

Topical Bases

Anhydrous Bases	Water Activity (a_w)*	Description
AlpaWash®	0.155	• Occlusive vehicle containing natural ingredients intended for compounded wound preparations • *In vivo* study demonstrating wound-healing properties of AlpaWash™ • *In vitro* antimicrobial study on green propolis (cosmetic active ingredient in AlpaWash™) • Proven hypoallergenic through HRIPT
CopaSil®	0.559	• Occlusive vehicle with natural ingredients intended for compounded scar preparation • *In vitro* antimicrobial study on copaiba oil (cosmetic active ingredient in CopaSil™) • Proven hypoallergenic through HRIPT
Lipmax™	0.237	• Mixture of lecithin and isopropyl palmitate to be used as a standalone or in conjunction with Pluronic Gel 30% to form a PLO Gel
Oleabase™ Plasticized	0.173	• Topical vehicle for lipophilic and hydrophilic drugs • Occlusive base for anaesthetics • Ideal for dental applications and mucous membranes
Ointment Base (Emulsifying)	0.578	• Topical vehicle for lipophilic and hydrophilic drugs • May be used alone as a protectant or emollient
VersaPro™ Anhydrous Base	0.208	• Anhydrous versatile drug delivery vehicle for lipophilic and hydrophilic APIs • Contains synergistic combination of skin permeation enhancers and emollients to promote absorption of APIs • Formulated with film forming agents to promote long lasting delivery of APIs • Proven hypoallergenic through HRIPT

Suppository Bases

Anhydrous Bases	Water Activity (a_w)*	Description
PolyPeg Suppository Base	0.179	• Water-soluble and non-irritating suppository base • Blend of different molecular weights of Polyethylene Glycols (PEGs) with a small amount of oil for lubrication purposes
SPG Supposi Base™	0.499	• Amphiphilic fatty acid base intended for compounded rectal and vaginal suppositories • Enables solubilization and absorption enhancement of actives in rectal and vaginal suppositories without the need for mold lubrication • Exhibits excellent mold release characteristics
SPG™ Natural Supposi-Base	0.222	• All-natural, strictly from vegetable origin • Amphiphilic fatty acid base intended for compounded rectal and vaginal suppositories • Enables solubilization and absorption enhancement of actives in rectal and vaginal suppositories without the need for mold lubrication • Exhibits excellent mold release characteristics
Witepsol® H-15	0.577	• Consists of glycerol esters of vegetable saturated fatty acids • Intended for compounding rectal or vaginal suppositories

* Water activity (a_w) results are based on testing of the blank base. The addition of water-containing components during compounding can alter the water-activity of the final compounded preparation.

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Table 2. Medisca Anhydrous Bases with Low Water Activity (a_w <0.6) *(cont.)*

Oral Bases

Anhydrous Bases	Water Activity (a_w)*	Description
CapsuBlend®-H	0.282	• CapsuBlend®-H is a premixed excipient blend that resists moisture sorption and provides the stability needed for proper efficacy of hygroscopic drugs in capsules • Enhanced drug dissolution • Improved chemical stability • Lactose-Free • Increased efficiency
CapsuBlend®-P	0.302	• Based on the Biopharmaceutical Classification System (BCS), CapsuBlend®-P is a unique premixed excipient blend for poorly soluble drugs in capsules • Enhanced drug dissolution • Improved chemical stability • Lactose-Free • Increased efficiency
CapsuBlend®-S	0.293	• Based on the Biopharmaceutical Classification System (BCS), CapsuBlend®-S is a premixed excipient blend for soluble drugs in capsules • Enhanced drug dissolution • Improved chemical stability • Lactose-Free • Increased efficiency
Medi-RDT™ Base	0.323	• Sucrose-free, and finely granulated powder blend to compound rapid dissolve tablets that is compatible with a wide range of active ingredients • Provides significantly faster wetting (5 sec.) and disintegration (93 sec.) times compared to similar products on the market • Ease of administration and improves patient compliance
Medi X-Tabb™ Base	0.381	• Ready to use, powdered excipient blend for compounding oral disintegrating tablets • Sugar-free, naturally sweetened with Stevia and added Bitter-Bloc™ Technology • Lactose, Gluten, Preservative and Dye-free • May be used with Medi-RDT Mold, ProFiller RDT Mold or Medi X-tabb Mold System
NovaFilm™ Oral Transmucosal Films	0.344	• An innovative dosage form with excellent mucoadhesive properties • Compatible with a wide range of active ingredients • Faster wetting, disintegration, and dissolution • Suitable for both human and veterinary patients • Does not require water to swallow • Easy to compound and pack • Water activity result based on the preparation of a blank oral transmucosal film using NovaFilm™ Gel base (baked at 50 °C for 1 hour using a forced air convection oven)
Oral Mix Dry Alka, SF (Cherry Flavoured)	0.289	• Uniform powder blend buffered to an alkaline pH for drugs that require an alkaline medium for stability in aqueous oral vehicles (e.g. Omeprazole) • Sugar, preservative, and dye-free • Easily dispersible in water
Troche Base	0.273	• Sweetened blend of polyethylene glycol (PEGs) for compounding medicinal lozenges/troches • Easy to use and ready to add active ingredients, color and flavors
Troche Base NS	0.351	• Naturally sweetened blend of polyethylene glycol (PEGs) for compounding medicinal lozenges/troches • Easy to use and ready to add active ingredients, color and flavors

* Water activity (a_w) results are based on testing of the blank base. The addition of water-containing components during compounding can alter the water-activity of the final compounded preparation.

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