Water Activity

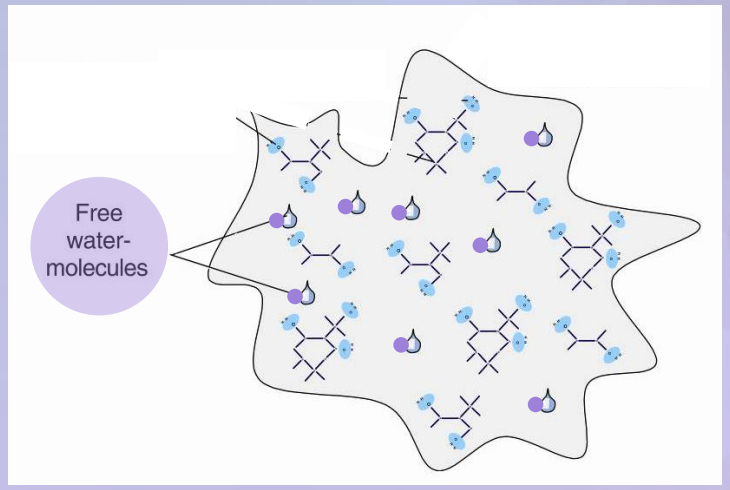
Driving Product Quality and Safety in Pharma Applications

May 2025

Water activity represents the energy level of water in a sample and gives insight into so much more than just the share of water in the sample

WATER ACTIVITY VS. MOISTURE CONTENT

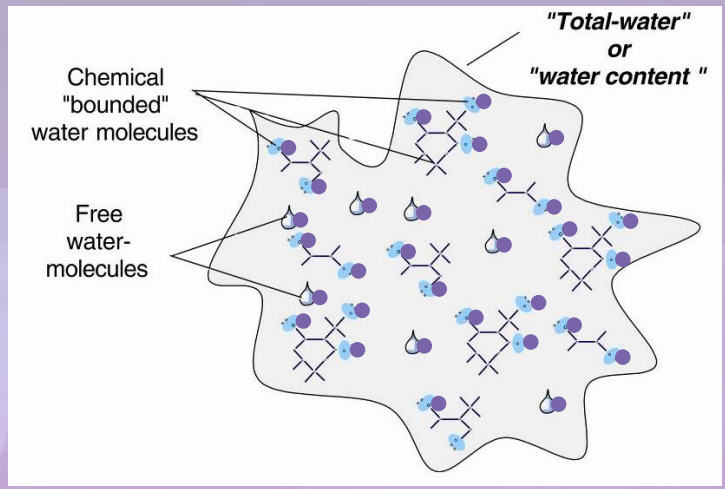
Water Activity (aw)



- Qualitative
- Referenced to scientific report (Greenspan report)
- Microbial growth
- Physical, chemical stability

Aw is **the energy status of the water in a system**

Moisture Content



- Purely quantitative
- Not standardized

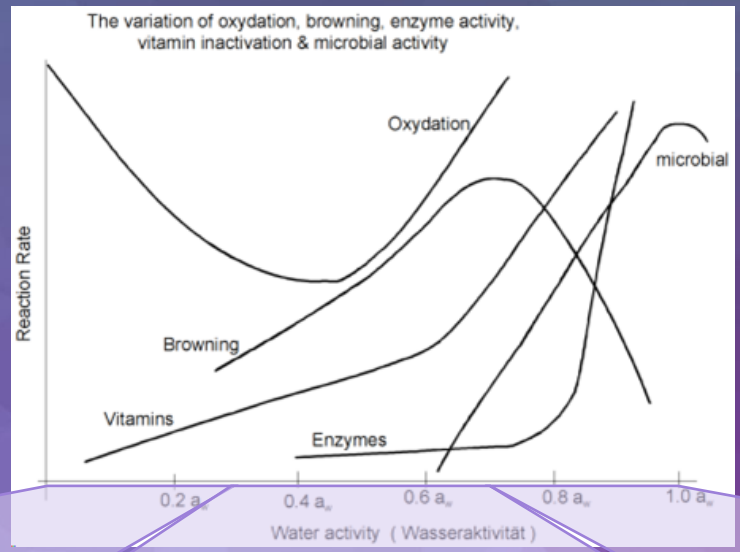
Total water in the sample

Factors that control Water Activity:

- Colligative effects or solute interactions (e.g. salt or sugar)
- Matrix effects or surface interactions (e.g. H2O binds to proteins)
- Capillary effects (e.g. H2O gets trapped in tiny pores of a powder or gel)

Understanding how water activity influences oxidation, browning, enzyme reactions, vitamin loss, and microbial growth helps us control product stability and spoilage risks

WATER ACTIVITY



0 – 0.3 aw

- Oxidation is high – fats and oils can go rancid quickly
  → leads to off-flavors and reduced shelf life
- Browning reactions start happening
  → color and flavor changes over time
- Microbial growth is not active – too dry for microorg.
  → good microbial stability
- Vitamin loss is slow
  → nutritional quality remains stable
- Enzyme activity is almost zero
  → no texture or enzymatic spoilage risks

0.3 – 0.7 aw

- Oxidation decreases (less oxygen available)
  → better fat stability
- Browning increases
  → more noticeable color and taste changes.
- Microbial growth still low, but starts to increase
  → shelf life is limited depending on product type
- Vitamin loss increases slowly
  → gradual nutrient degradation
- Enzyme activity starts to rise
  → risk of enzymatic texture/flavor changes begins

0.7 – 1.0aw

- Oxidation and browning reactions strongly decrease
  → less color change, but other degradation dominates
- Fast Microbial growth – this is the danger zone!
  → high risk of spoilage and food safety issues
- Vitamin loss continues to rise
  → reduced nutritional value
- Enzymes work very actively
  → breakdown of texture, flavor, and nutrients

Especially in Pharma, water activity enables a data-driven, science-based approach to quality control

WHY IS WATER ACTIVITY CRITICAL IN PHARMA

Water activity in pharmaceutical applications can help to…

1) …**reduce the need for frequent microbial testing**

2) …**stabilize APIs** by slowing down degradation, **ensuring safety and effectiveness**

3) …optimize dissolution rates **to improve bioavailability and performance**

1. Incorporating water activity measurements into your QC process helps reduce the need for frequent microbial testing, as low aw prevents microbial growth

WATER ACTIVITY APPLICATIONS

Lowering water activity limits microbial growth by making less water available. Microbes can only grow above a certain aw level — below that, they stop.
→ **Controlling aw helps predict microbial risk and reduces the need for frequent testing.**

Bacteria

Microorganism	Minimum a_w
Clostridium botulinum E	0.97
Pseudomonas fluorescens	0.97
Escherichia coli	0.95
Clostridium perfringens	0.95
Clostridium botulinum A, B	0.94
Salmonella spp.	0.95
Vibrio parahaemoliticus	0.94
Bacillus cereus	0.93
Listeria monocytogenes	0.92
Bacillus subtilis	0.91
Staphylococcus aureus (anaerobic)	0.90
Staphylococcus aureus (aerobic)	0.86

Mold

Microorganism	Minimum a_w
Rhizopus nigricans	0.93
Penicillum expansum	0.83
Penicillum islandicum	0.83
Aspergillus fumigatus	0.82
Penicillum cyclopium	0.81
Penicillum martensii Penicillum chrysogenum	0.79
Aspergillus niger	0.77
Aspergillus ochraceous	0.77
Aspergillus restrictus	0.75
Aspergillus candidus	0.75
Eurotium chevalieri	0.71
Eurotium amstelodami	0.70
Monascus bisporus	0.61

Yeast

Microorganism	Minimum a_w
Saccharomyces cerevisiae	0.90
Candida	0.88
Debarymoces hansenii	0.83
Saccharomyces bailii	0.80
Zygosaccharomyces rouxii	0.62

Cut Microbial Testing Time from Days to Minutes!

An example - Validating Water Activity (aw) for Microbial Risk Assessment

Why Validate?

- Supports risk-based approach to microbial testing
- Aligns with principles such as USP <922>
- Provides documented evidence for reducing microbial testing frequency

How to Validate aw in QC Processes?

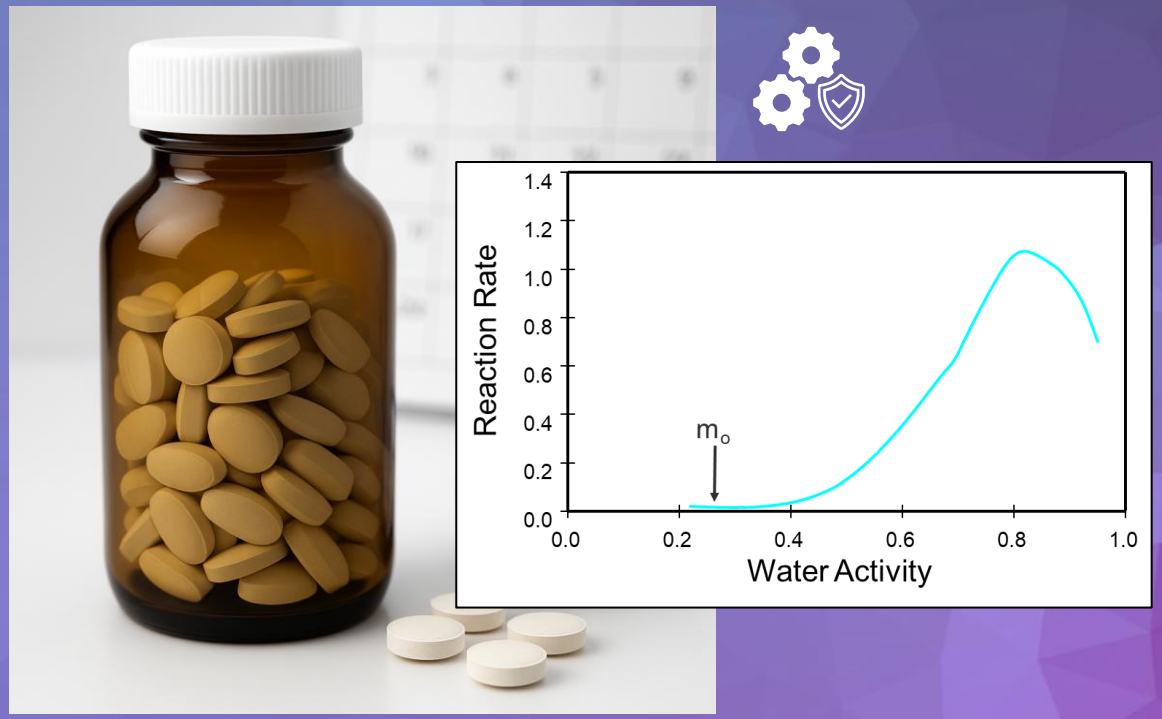
- **Parallel Testing**
  - Measure both water activity (aw) and microbial counts on the same sample batches
  - Conduct over a defined qualification period
- **Correlation Analysis**
  - Compare aw values with microbial results
  - Identify trends and establish threshold values for low-risk classification
- **Documentation**
  - Record all results in a validation protocol
  - Use findings to justify reduced microbial testing where appropriate

Outcome

- ✓ Improved efficiency through resource allocation in microbial testing
- ✓ Science-based justification for aw as a predictive tool
- ✓ Strengthened compliance through risk-driven decision-making
- ✓ Harmonized and standardized QC to scale across additional QC sites

2. Control API degradation to guarantee effectiveness and safety, because chemical reaction rates increase with water activity level

WATER ACTIVITY APPLICATIONS



- In general, reaction rates increase as water activity increases, meaning faster degradation of APIs, which lowers API efficacy (e.g. enzymatic and other reactions can degrade active ingredients, e.g. API efficacy)
- Peak reaction rates occur at a higher aw
- Relationship between degradation and water activity can be modeled with temperature. As temperature increases, the degradation rate increases exponentially!

Hygrothermal Time Model

$$\text{Rate} = r_o \exp(Ba_w - E_a/RT)$$

Where r_o, B, and Ea/R are derived empirically through modeling

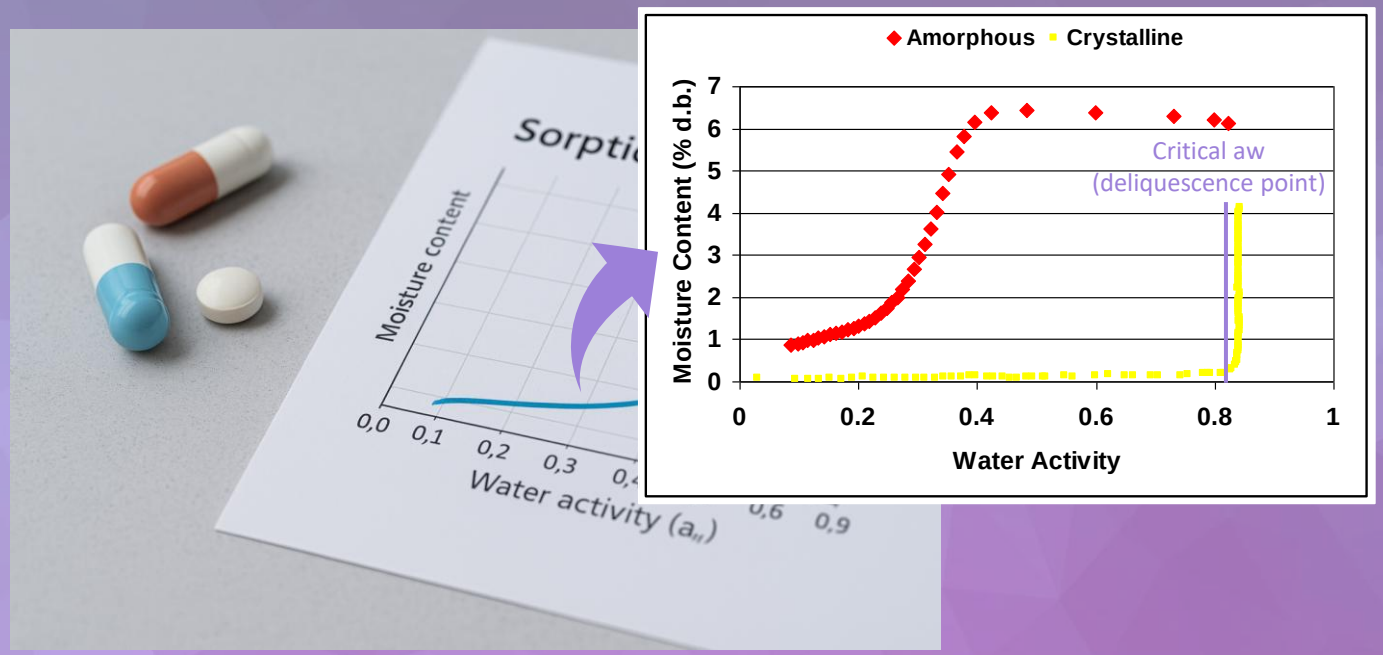
Controlling aw preserves API stability and shelf-life!

3. Optimize dissolution rates to improve bioavailability, product performance, and guide the selection of suitable excipients

WATER ACTIVITY APPLICATIONS

Water activity effects dissolution rates. Sorption isotherms show how different materials absorb moisture, helping choose the right excipient for specific humidity conditions. The effect of moisture sorption on disintegration time depends on whether the material is crystalline or polymeric:

- **Crystalline excipients** are less hygroscopic but can undergo **phase transitions** at higher water activity levels (aw), becoming **sticky or dissolving**, which may affect processing or stability
- **Amorphous excipients**, on the other hand, tend to **absorb moisture more quickly** due to their open structure, leading to **instability or clumping** if not properly controlled



Select the right excipient for your formulation and improve bioavailability and performance

Due to its benefits to control product safety, regulation around water activity is picking up globally

REGULATION OF WATER ACTIVITY

Regulation/Method	Description	What It Means for Pharma
ICH Q1A(R2)	Stability Testing of New Drug Substances and Products	Ensures stability by evaluating how water activity affects product shelf-life and degradation.
ICH Q6A	Defines the inherent dryness referenced in decision tree #6 and #8	
QbD ICH Q8-Q10	Pharmaceutical Development, Risk Management, and Quality Assurance	Encourages control of critical quality attributes (CQAs), including water activity, during product development.
USP <922>	**Standardized method for how to measure water activity**	**Provides methods for accurate water activity measurement and its implications for stability and microbial control.**
USP <1112>	**How to apply aw data in microbial control of nonsterile pharma products**	**Discusses the role of water activity in microbial prevention and control.**
USP <1111>	Microbiological Examination of Nonsterile Products	Sets microbial limits where controlling water activity is critical to ensure microbial stability.
USP <51>	USP standard method for testing the effectiveness of antimicrobials	Determines if microbial challenge testing is needed based on water activity.
USP <795>	USP informational chapter on pharmaceutical compounding - nonsterile preparations	Uses water activity as part of the guidelines for setting beyond use dates.
Japanese Pharmacopeia	Japanese standard for drug stability and quality	Aligns with ICH guidelines, where water activity is monitored in stability studies.
China NMPA GMP (2020)	National Medical Products Administration's GMP regulations	Highlights environmental and water activity control for product safety and stability.
USP <797>	USP informational chapter on pharmaceutical compounding - sterile preparations	Uses water activity as part of the guidelines for setting beyond use dates.
European Pharmacopoeia Chapter 5.1.4	Microbiological Quality of Non-Sterile Pharmaceutical Preparations	Highlights water activity's role in ensuring microbiological quality in non-sterile products.
FDA cGMP Guidelines (21 CFR Part 211)	Current Good Manufacturing Practices for finished pharmaceuticals	Emphasizes water activity control under product stability and environmental monitoring.
WHO GMP Guidelines	Good Manufacturing Practices for Pharmaceuticals	Ensures quality through microbial control, where water activity levels are a key parameter.
ISO 29621	Guidelines for assessing microbiological safety of products	Specifies water activity <0.6 as a critical factor for microbial safety, which applies to pharmaceutical formulations.
PIC/S GMP Guidelines	Global standard for Good Manufacturing Practices	Aligns with WHO and EU GMP, emphasizing contamination prevention via water activity control.
EMA Quality Guidelines	European Medicines Agency guidelines for quality	Focuses on stability and safety, where water activity is monitored as part of risk management.

Novasina‘s LabMaster neo was developed for the pharma industry; it is a state-of-the-art benchtop headspace analyzer that allows you to gain insights into water activity

HOW NOVASINA CAN HELP: THE LABMASTER NEO

Novasina is **your trusted, science-driven partner for water activity measurement**, offering **superior quality, service and expertise**:

Industry-Leading Accuracy	±0.003 aW
Wide Measurement Range	0.0 – 1.0 aw
Temperature Control	from 0°C to +60°C
Stable and Reliable Performance	No hysteresis
Optimized for **Volatile Samples**	Protective filters
Low Cost Calibration	Reusable salt standards
User-Friendly Design	Easy and simple operation
Seamless **Data Integration**	Compatible with software and LIMS
Regulatory Compliance	Meets USP guidelines, 21 CFR part 11 and ISO standards

We provide full compliance with pharmaceutical‘s requirements on 21CFR11 part 11

HOW NOVASINA CAN HELP: FULL 21CFR11 COMPLIANCE

Audit Trails for Full Traceability

What’s Logged?
- All user actions, system events, technical incidents
- Time-stamped and digitally signed
- Cannot be changed or deleted, even with full rights

Export Options:
- XML format with digital signature
- Viewable with audit trail software

User Access and Permissions

Access Limited To Authorized Users
- Login required with identifier & password
- Permission profiles cannot be edited or deleted
- Auto-logoff feature configurable

Electronic Signatures:
- Linked to user ID and timestamp
- Cannot be reused or reassigned
- Stored securely in the system

Electronic Records and Signatures

- All data stored with integrity controls
- One-year audit trail stored locally, backup via USB
- Records available in human- and machine-readable format
- Record protection throughout retention period

The LabMaster-aw NEO fully meets 21 CFR Part 11

- ✓ Tamper-proof audit trail
- ✓ User-level access control
- ✓ Secure digital signatures
- ✓ Export & traceability
- ✓ Long-term record protection

FAQ

Topic	FAQ	Suggested Response
Validation	*How do we validate water activity as part of our QA process?*	You can run a **parallel study**: measure both **aw and microbial counts** for the same samples over a qualification period. Document **correlation trends** and establish **threshold values** that align with your internal specifications or risk levels. This supports a **science-based justification** for reduced microbial testing frequency.
Regulatory	*Is this method officially accepted?*	Yes. **USP <922>** outlines water activity as a recognized method for microbial risk assessment. It's also referenced in **ICH Q6A** for solid dosage forms, making it acceptable for pharmaceutical applications. Some pharmacopeias even recommend it in stability testing guidelines.
Microbial Limit Testing (MLT)	*Can aw replace our MLT for finished products?*	Not completely. Water activity is **not a replacement** for microbial limit tests, but it helps you **identify low-risk products**. This supports a **risk-based testing strategy**—e.g., less frequent MLT for low-aw products like tablets or capsules.
Samples	*For what sample types can aw be used?*	Especially effective for **solids and semi-solids** like tablets, powders, and capsules. For **suppositories and syrups**, applicability depends on the **matrix consistency** and how water is bound. Testing is still possible but may require **sample preparation or interpretation adjustments**.
Implementation	*What's the workflow? Do we need extra resources?*	The workflow is **fast and simple**: place sample in the cup, close the lid, and get results within minutes. No sample destruction, no reagents. Instruments are intuitive and can be handled by **QC or micro lab staff** with **minimal training**.
Limits	*What aw value should we consider safe?*	Generally, **<0.70 aw** is accepted as the limit below which **no pathogenic microbial growth** occurs. For more conservative thresholds or specific organisms (e.g., *Xerophilic molds*), **<0.60** may be relevant. You can define your own **internal cut-offs** based on product type and regulatory expectations.
Moisture Content	*Is water activity the same as moisture content?*	No — water activity measures the **availability of water**, not the total amount. Two samples can have the same moisture content but very different aw values. Water activity is a **more relevant parameter** for microbial risk and chemical stability.
Stability/Shelf Life	*Can water activity help in predicting product stability?*	Yes — aw is a key parameter in shelf life modeling. It allows you to predict risks of microbial growth, API degradation, and physical changes (e.g., caking or deliquescence), especially in combination with temperature data.
CPR	*Is an application for a new CPR needed?*	No new CPR application is required, but the safety plan in the registration must be updated with the regulatory authority; USP provides scientific methods to support this process, but does not issue regulatory guidance or approvals

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