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Controlling water content in oral solid dosage (OSD) products, and dry pharmaceutical products in general, is essential to maintaining efficacy and safety. Water activity ($A_w$) is a measurement of the free or loosely bound water available to participate in unwanted chemical, physical, and biological reactions. Measuring the water activity at multiple time points during the product life-cycle will correlate to changes in critical quality attributes such as degradation of the active ingredient, changes in the dissolution or disintegration rate, and changes in physical properties such as hardness or friability.
The Lighthouse Instruments FMS-Water Activity Analyzer is a non-destructive headspace gas analyzer used to monitor the headspace water partial pressure in sealed, optically transparent containers. This analyzer employs a near infrared (NIR) laser that is tuned to match the specific transition frequency of the water molecule (~1400 nm). During a measurement session, the laser is passed through the headspace region (i.e. the region located above the product) and the laser frequency is repeatedly scanned over the absorption feature (Figure 1). Successive scans are averaged to improve the signal to noise ratio and the resulting amount of light absorbed after exiting the container is detected by a photodetector. The absorption of the light is proportional to the water vapor partial pressure in the headspace of the product-package system [1]. The water activity associated with the headspace of a sealed product-package system is then determined by taking the ratio between the water partial pressure measured in the container headspace and the water partial pressure observed above pure water at the same temperature; therefore, a direct measurement of water activity can be made using the FMS-Water Activity Analyzer. Finally, because the water activity of a sample is highly dependent on temperature, the FMS-Water Activity Analyzer is equipped with a temperature-controlled sample chamber. Measurements can be acquired at temperatures ranging from 19°C to 45°C.

Figure 1. Schematic overview of the measurement technique. The area and width of the Frequency Modulation Spectroscopy (FMS) absorption signal can be used to determine physical parameters of the headspace of a container, including the water vapor partial pressure.
Table 1 displays example system performance data acquired on an FMS-Water Activity Headspace Analyzer. Each measurement session begins with calibration using a saturated solution of sodium chloride (NaCl), which has a known water activity of ~0.75 at room temperature. A linearity check is then performed using additional saturated salt standards and a desiccant standard, all of which have known water activities at the specified measurement temperature [2]. The linear fit coefficient greater than 0.999 of the system performance check data displayed in Figure 2 indicates a strong correlation between the measured and expected water activity values.

<table>
<thead>
<tr>
<th>Saturated Salt</th>
<th>Headspace Expected Value</th>
<th>Mean Measured Value</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>KNO₃</td>
<td>0.94</td>
<td>0.94</td>
<td>3.56E-03</td>
</tr>
<tr>
<td>NaCl</td>
<td>0.75</td>
<td>0.75</td>
<td>-3.80E-04</td>
</tr>
<tr>
<td>NaBr</td>
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<td>0.59</td>
<td>1.27E-02</td>
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<tr>
<td>NaI</td>
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<td>4.34E-02</td>
</tr>
<tr>
<td>MgCl₂</td>
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<td>3.55E-03</td>
</tr>
<tr>
<td>LiCl</td>
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<td>0.11</td>
<td>1.29E-03</td>
</tr>
<tr>
<td>LiBr</td>
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<td>0.07</td>
<td>7.64E-03</td>
</tr>
<tr>
<td>Des</td>
<td>0.00</td>
<td>0.01</td>
<td>7.10E-03</td>
</tr>
</tbody>
</table>

Table 1. FMS-Water Activity performance data on 6R clear tubing vial saturated salt standards at 24.2°C. Each standard was measured five times. The error is calculated as the mean measured value minus the expected value.

Figure 2. Plot of measured headspace water activity versus expected water activity at 24.2°C for the Lighthouse saturated salt standards listed in Table 1. Linear fits of the headspace water activity data confirm the linearity of the system response over water activities ranging from 0.00 to 1.00 (linear fit coefficient $R^2 > 0.999$).
CASE STUDY:
As previously mentioned, monitoring changes in water activity can be correlated to changes in critical quality attributes. The objective of the following case study was to determine if a change in water activity from a “fresh” sample (i.e. directly out of the primary packaging bottle) to a pre-conditioned sample could be observed when the conditioned sample was stored in an environment having a relative humidity of ~75% at room temperature. It should be noted that water activity is related to relative humidity (RH) via the following relationship:

\[
\text{Water Activity} = \frac{\% \text{ Relative Humidity}}{100}
\]

Relative humidity ranges from 0 to 100% while water activity ranges from 0 to 1.

Three uncoated acetaminophen tablets were placed in one of five vials after removal from their primary HDPE packaging. The initial water activity was determined by stoppering and crimping one of the five vials, and allowing it to come to equilibrium at ambient conditions overnight, before being measured the following day.

The remaining four vials were partially stoppered with a lyophilization stopper which allowed for the headspace of the vials to be exposed to their storage environment. They were then placed in one of four sample conditioning chambers, each of which had previously been conditioned with a saturated NaCl solution to a RH of 75%. Vials were conditioned for 24hrs, 72hrs ~1week, or ~2 weeks, with one sample conditioning chamber belonging to one of the four tested time points. After the storage period was complete, the sample conditioning chamber was opened, the stopper was fully inserted, and the vial was capped/crimped and left at ambient conditions overnight. The following day the sample was measured on the FMS-Water Activity Analyzer. The results, presented in Figure 3, demonstrate that tablets came to equilibrium with the saturated NaCl environment (~75% RH or 0.75 \(A_w\)) between 24 and 72 hrs of storage.

Figure 3. Headspace water activity measurements on uncoated tablets in a 6R vial at five different timepoints: A baseline measurement prior to storage, after 24hrs of storage, after 72 hrs of storage, after ~1 week of storage, and after 2 weeks of storage. The black dotted line represents the approximate expected water activity based on the storage conditions (~0.75).
An additional experiment was conducted to monitor the equilibration time of a “fresh” sample. While the previously described fresh sample equilibrated with the vial headspace overnight before being measured, the following fresh sample was reiteratively measured as soon as it was removed from its primary packaging. To do this, three aspirin tablets were placed in a 6R glass vial. The vial was stoppered, and multiple consecutive measurements were immediately acquired. The results are presented in Figure 4.

These results indicate that it takes more than 5 minutes for the sample to come to equilibrium in the sealed vial container and this equilibration period can be monitored in real time.

![Figure 4. Headspace water activity measurements on fresh aspirin tablets immediately after being removed from their primary packaging.](image)

The above results show the FMS-Water Activity Analyzer can be used to monitor the water activity of OSD products including samples that were preconditioned at known relative humidity values. Additionally, it can successfully be used to monitor the real time equilibration of samples after removing them from their primary packaging and placing them in a different environment. The Lighthouse Instruments FMS-Water Activity Analyzer uses frequency modulation spectroscopy to determine the water activity of pharmaceutical products. This approach for water activity determination has advantages over traditional methods including:

- Measurement of saturated salt standards demonstrates that the system meets USP <922> requirements for accuracy, precision, and linearity.
- Sample preparation is simple and robust so materials that either change rapidly or equilibrate slowly can be measured accurately.
- The spectroscopy measurement is specific to water vapor, so volatile organic molecules do not interfere.
- It is a non-destructive technique; the same sample can be measured at multiple timepoints.
- Measurements can be acquired in five seconds.
- Measuring samples of differing water activities back to back is not an issue (i.e. a moist sample will not impact the measurement of a dry sample).
- A built-in temperature controller allows the water activity to be measured at the same temperatures used in stability protocols.

The FMS-Water Activity Analyzer can be used to not only make water activity measurements, but to also quantify relative humidity conditions inside containers. The ability to generate robust data in these areas with one instrument is a big advantage for combining a variety of formulation and packaging studies in all stages of the product life cycle.
REFERENCES
