Non-destructive headspace moisture detection for lyo cycle optimization and 100% inspection of the finished product

LIGHTHOUSE
The Science of Pharmaceutical Manufacturing

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Introduction

This poster describes the application of Frequency Modulation Spectroscopy (FMS) for optimization of a commercial freeze-drying cycle and for 100% moisture inspection of the finished lyo product. Standard moisture analysis methods used in the industry, Karl Fischer (KF) titration and thermo-gravimetric analysis (TGA), do not distinguish between active water that is detrimental to product stability and bound water that can not chemically interact with the active ingredient. From a practical point of view, the KF and TGA methods are time consuming, sometimes unreliable, and end up destroying the sample. Consequently, fast feedback on drying efficiency is not possible and quality control of finished product is limited to off-line analysis of a small sample set. The FMS headspace moisture inspection method is rapid and non-destructive and overcomes these issues. The measurement is accomplished by sending laser light at an absorption wavelength of the water molecule through the empty headspace to measure water vapor concentration in the vial. It has been demonstrated that headspace moisture correlates to KF measurements (see Figure 1) and can be used to directly predict product stability. Water vapor in the headspace is a measure of the 'active' water available to chemically interact with the active ingredient.

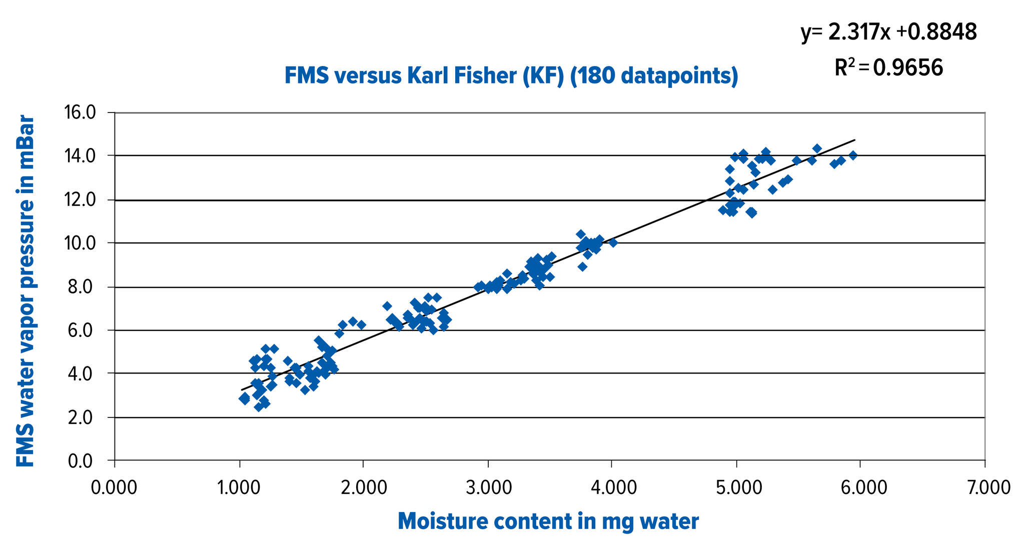

Figure 1
Correlation of headspace moisture levels to residual product moisture content as measured by Karl Fischer is plotted here. The product samples consisted of a 200 mg cake packaged in a clear tubing 10cc vial under one atmosphere of nitrogen. Similar correlations were seen using NIR moisture analysis methods.

Method

Three thousand two hundred (3200) lyophilized product vials, stoppered and crimped in 10 ml clear tubing glass vials under 800 mbar of nitrogen, were prepared using two different commercial freeze drying cycles. A LIGHTHOUSE FMS-1400 Headspace Moisture/Vacuum Analyzer performed rapid, non-destructive headspace inspection of the manufactured product. The FMS-1400 simultaneously measures water concentration and vacuum levels in the vial headspace. Using the headspace moisture results from the initial batch, the lyo cycle was further optimized with the aim of achieving more consistent and homogenous drying with the second batch. Product from the optimized freeze drying cycle was then analyzed with the FMS-1400 with three objectives: 1) compare efficiencies of the initial and optimized lyo cycles, 2) identify out-of-specification samples that were not sufficiently dried, and 3) identify vials that had lost closure resulting in loss of vacuum.

Results

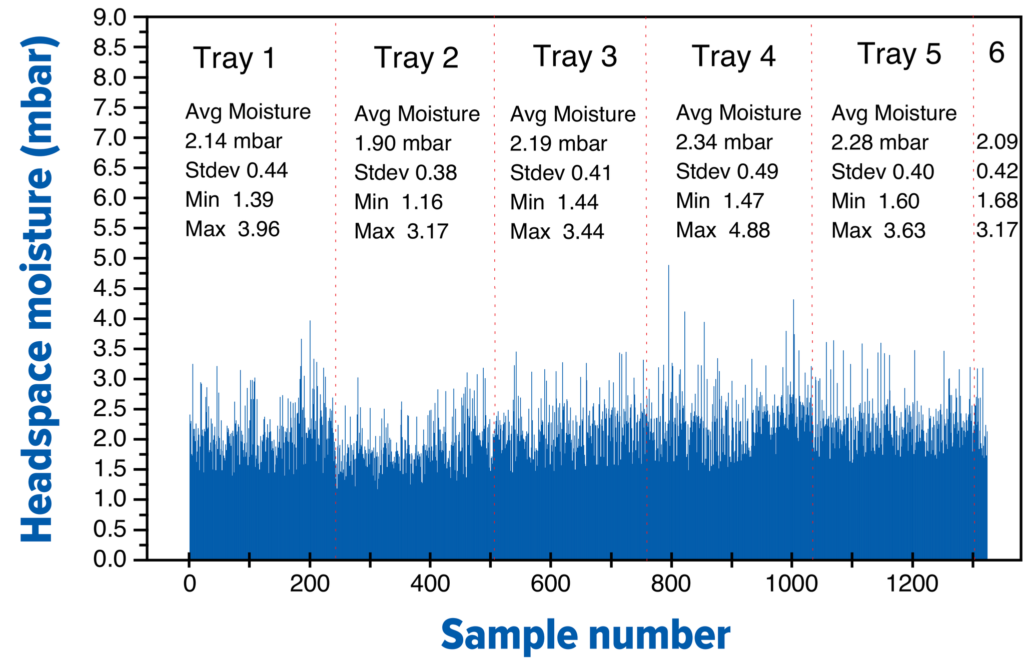

Figure 2
Headspace moisture values as a function of tray position are plotted for samples from the initial lyo cycle. It is clear that the drying efficiency for this lyo cycle depends on location within the freeze dryer. For example, average headspace moisture values and standard deviations across the tray show that samples in Tray 2 dried more efficiently than samples in Tray 4.

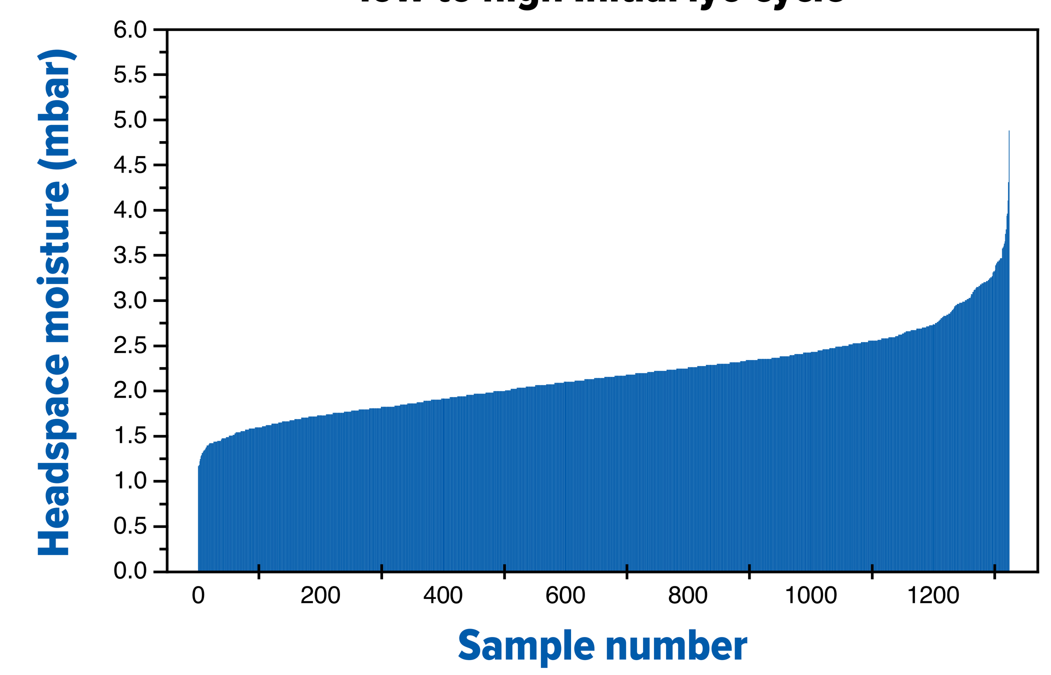

Figure 3
The headspace moisture distribution for all samples in the initial lyo cycle is plotted from low to high values. The high moisture tail in this distribution indicates a significant portion of samples that have not dried efficiently and contain elevated levels of water. Visual inspection verified that some samples in the high moisture tail also had a defective cake appearance. The moisture distribution has a significant slope from low to high values indicating non-homogenous drying.

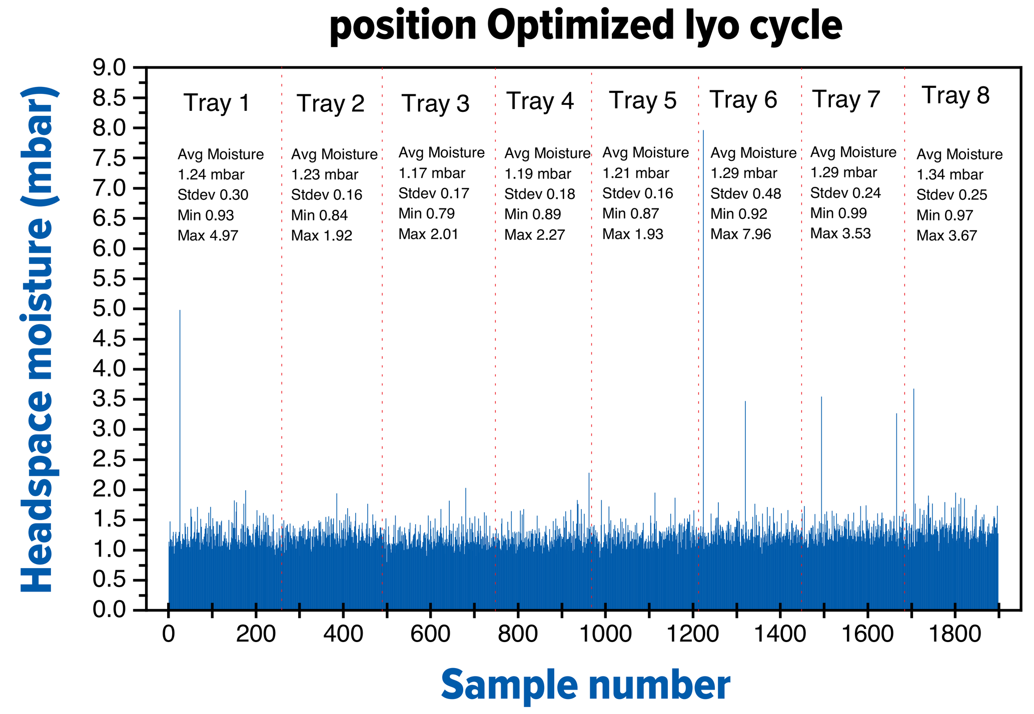

Figure 4
Headspace moisture as a function of tray position for the optimized lyo cycle shows more consistent drying across the freeze dryer shelf. Average headspace moisture values are also lower indicating better drying. It should be noted that even for this improved lyo cycle there are a number of vials (6 out of 1898) that have elevated levels of moisture content. The trays containing these 'wet' samples can easily be identified from the higher standard deviations measured across those trays (Trays 1, 6, 7, and 8).

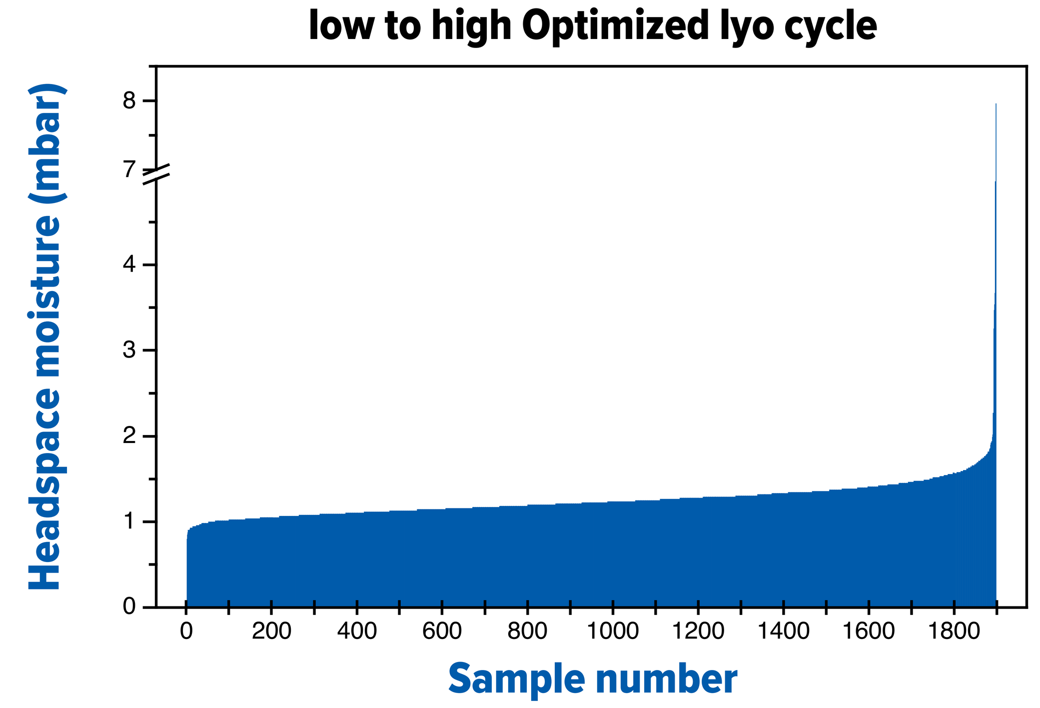

Figure 5
The headspace moisture distribution plotted from low to high values clearly shows that the optimized freeze drying cycle has produced more consistent, homogenous drying. This distribution is now much flatter than the moisture distribution of the initial lyo cycle.

Conclusion

The FMS headspace moisture inspection technique can be used to characterize the efficiency of the freeze drying cycle and to determine freeze dryer dependent drying effects. Total time for the moisture analysis of the two batches described in this poster (~3200 samples) was approximately nine hours using the manual benchtop FMS-1400. The rapid non-destructive headspace analysis of finished lyo product gives insightful feedback to the lyo cycle development process contributing to quick and efficent optimization of the lyo cycle.

Automated headspace moisture/vacuum inspection machines have been implemented and qualified in the industry over the last five years for vacuum leak detection of freeze-dried vials at speeds up to 250 vials/min. Some of these machines are now also being validated for 100% moisture inspection.

Headspace moisture analysis also enables rapid 100% moisture inspection of the finished lyo product. Even optimized freeze drying cycles seem to produce random samples that do not dry efficiently and have elevated levels of water. Out-of-specification product identified by the inspection process can be rejected helping to guarantee the quality of finished product.

An additional advantage of the FMS headspace moisture inspection technique is the simultaneous determination of the headspace pressure. This enables identification of vials that have lost vacuum due to loss of closure integrity posing a potential sterility risk. These vials can also be rejected in the inspection process. The headspace pressure results for the two commercial batches described in this poster are shown below. The vials identified as having bad closure were different from the vials identified as having high moisture levels.

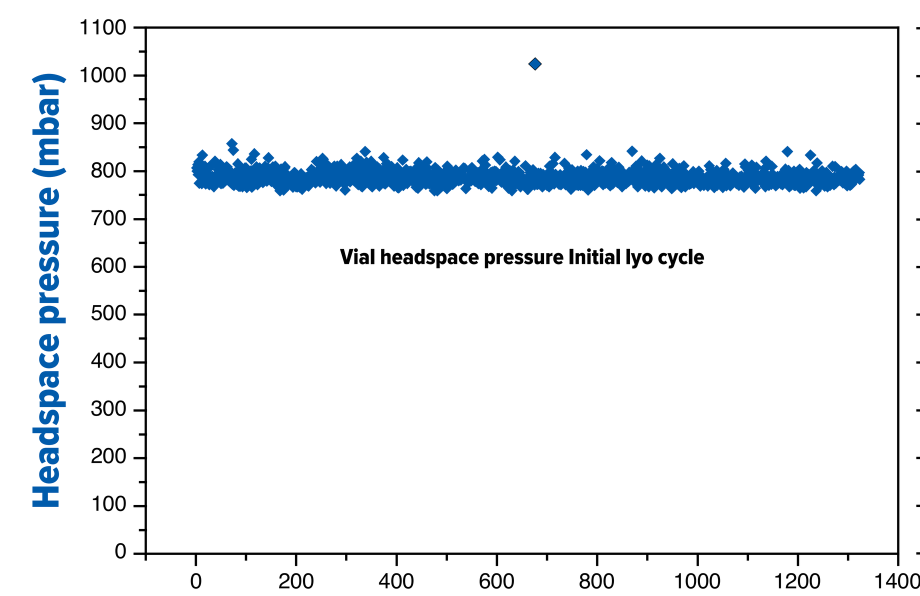

Figure 6
One sample was identified from the initial lyo cycle batch that had leaked to one atmosphere from the initial stoppering pressure of 800 mbar of nitrogen.

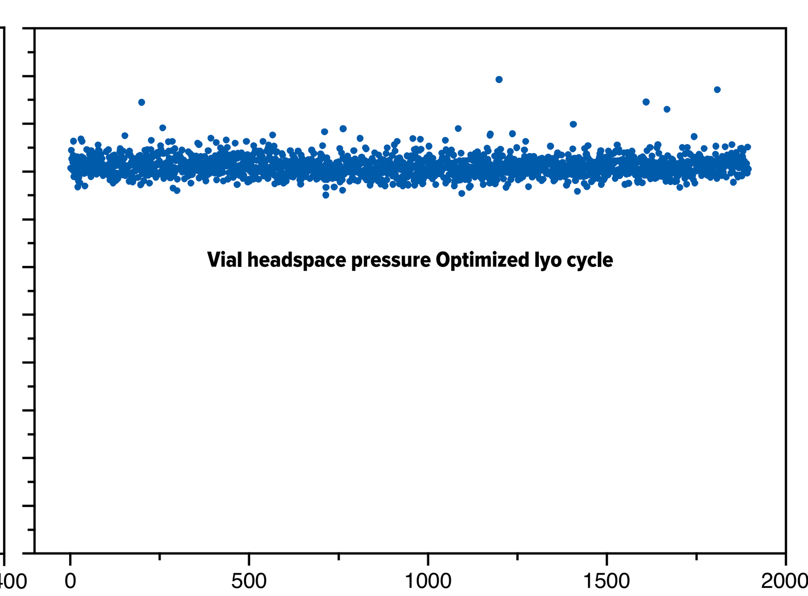

Figure 7
Five samples in the optimized lyo cycle batch were identified that had leaked to pressures > 900 mbar.