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Headspace Moisture Analysis for Determination of Residual Moisture Content in Lyophilized Pharmaceutical Products

Headspace moisture analysis is a rapid non-destructive analytical method that may potentially address the limitations of traditional methods used for residual moisture determination.

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Lyophilization, or freeze-drying, is a process used to stabilize a pharmaceutical formulation and increase the shelflife by removing water from the drug product. During lyophilization, the drug formulation is first frozen and then the ice is removed by sublimation under vacuum during a primary drying phase. A secondary drying phase is then used to remove unfrozen water molecules at a temperature higher than that used for primary drying. Pharmaceutical freeze drying cycles are designed to remove most of the loosely bound water and to achieve a pharmaceutically elegant cake. For biological materials, it is important to retain a high level of activity in the final product.

Residual moisture content

Determining the residual moisture content of a lyophilized pharmaceutical product is important for several reasons. First, the amount of residual moisture content is related to the stability of the formulation over the shelflife of the product. Small-molecule formulations can have direct degradation pathways triggered by water, and it is crucial that all final product is below a defined residual moisture specification. In general, the degradation pathways for large-molecule formulations are more complex, with water often playing an indirect role. Second, moisture analysis of a statistically relevant sample set can give insight into the freeze-drying process itself. Residual moisture determination can be used as a tool in process studies to confirm the efficiency, consistency, and robustness of a specific freeze-drying cycle that has been designed for a particular drug formulation.

Typical pharmaceutical freeze-drying cycles usually target residual moisture contents in the range of 1% to 3% water by weight. Historically, a strategy that can be described as "the drier, the better" was often followed. For small molecules having a direct degradation pathway triggered by water, this approach was an appropriate strategy. However, in the world of large biopharmaceutical molecules, it is possible to over-dry. Studies have shown that even in the lyophilized state, proteins depend on small quantities of water to help maintain higher-order structure. Other types of products, such as certain lyophilized blood plasma formulations, need a minimum amount of water to achieve efficient dry-heat viral inactivation. It is therefore sometimes necessary to design a freeze-drying cycle that keeps all product vials within a certain moisture range, having both minimum and maximum specifications.

Historical cycles have often been too conservative (i.e., too long), meaning that the final product was over-dried, because research and development efforts did not take the time to optimize both the formulation and the freeze-drying cycle. Although conservative cycles produce product that meets quality parameters (i.e., sufficiently low residual moisture), the same product quality could be produced with much shorter cycles if appropriate studies are done. Current scientific approaches use various tools to monitor the lyophilization process and analyze the finished product with the goal of defining optimum freeze-drying cycles on a per formulation basis. Data are generated to demonstrate that product quality parameters (such as stability, cake appearance, appropriate reconstitution, and bioactivity) are met in a targeted moisture range and that the defined cycle is robust and consistent in producing product in that moisture range.

Freeze-drying cycle, formulation, and equipment parameters

The residual moisture content depends on both the cycle and the formulation. Focusing on the process side, it is important to control the endpoints of the three lyophilization stages--freezing, primary drying, and secondary drying. Key process parameters are the temperature and pressure gradients chosen for each stage. It is out of the scope of this article to fully treat all the factors that can affect the residual moisture content.

As an example, there are several approaches that can be taken to optimize freezing conditions: annealing, supercooling, and controlled nucleation. The details of crystal formation during freezing have an effect on how efficient the sublimation process is in removing moisture during primary drying. In general, care should be taken in the freezing step to ensure that the product is fully frozen, that the ice crystal structure is open allowing for better sublimation, and that complete freezing is achieved at as high a temperature as possible to save time and energy.

The formulation parameters also have an effect on the final residual moisture content. The exact ice crystal formation and eventual cake structure will depend on the type of pharmaceutical ingredients and buffers in the formulation as well as potentially varying product concentrations. All of these formulation parameters can influence the final residual moisture content achieved by a freeze-drying cycle.

Finally, a third general factor influencing residual moisture content is the equipment and vial configuration used. Vacuum pump, condenser parameters, and the vial size should all be considered when implementing a freeze dryer for particular product batch sizes.

In the end, the final residual moisture content depends on the interplay between the cycle, the formulation, and the equipment parameters. This interplay has motivated the development of approaches for efficient cycle development in recent years. Optimization of the drying cycle for a given formulation requires a balanced understanding of the fundamental science of freeze-drying, formulation characteristics, and equipment capabilities. The ability to make accurate measurements of residual moisture in statistical sample sets of finished product would be a useful tool in these efforts.

Traditional methods to determine residual moisture
The traditional methods used in the pharmaceutical industry for residual moisture determination have been Karl Fischer (KF) titration and thermogravimetric analysis (TGA). The KF method is most widely used and is generally considered to measure the total water within the freeze-dried vial, assuming that the sample is wholly soluble in the KF medium. It should be noted here that residual water content may be present in a variety of forms--free, adsorbed, chemically bound, hydration shells, water of crystallization--not all of which may be directly linked to the activity or stability of the product in question. The KF method is time-consuming, requires operator expertise and careful sample handling to avoid contamination by environmental moisture, and is destructive (meaning that the sample is destroyed during analysis).

Unlike Karl Fischer, which relies on a chemical reaction to detect water, TGA measures the weight loss as the sample is heated, driving off residual moisture. This method measures not only the water but also any other volatiles that are produced as a result of heating. Therefore, the composition of the lyophilized material must be well understood for this method to be used to accurately measure the residual water content. This method also suffers from potential artifacts due to environmental moisture and is also a destructive method.

The destructive nature of the traditional methods is a limitation that has negative consequences for stability and process studies of freeze-dried product. The moisture content of a product vial in stability studies is usually inferred from that determined for sister vials. The degradation of the API cannot be directly correlated to the measured residual moisture because the moisture determination measurement destroys the sample. The moisture content of the vial in the stability study may not be identical to the reference sister vials due to vial-to-vial variability, and therefore, the stability results may be imprecise for defining moisture stability specifications.

For process studies, the traditional methods are not conducive to conducting studies with statistically relevant sample sets. The methods are resource intensive and sample analysis throughput is limited. Moreover, potentially valuable product is destroyed because of the destructive nature of the methods. The absence of statistically relevant data for residual moisture determination means that residual moisture stability studies are at risk of being imprecise and that limited insight can be gained into the consequence of process variability on final product quality. As a rapid non-destructive analytical method, headspace moisture analysis can potentially address the limitations of traditional methods.

Headspace moisture analysis

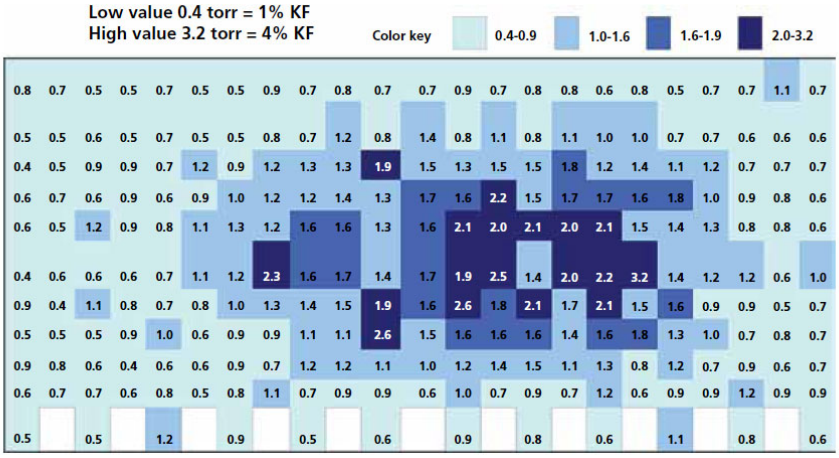

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Figure 1: Moisture map created from headspace moisture analysis of freeze-dried vials from a lyo chamber shelf. A correlation study had demonstrated that the measured low value of 0.4 torr was equivalent to 1% water by weight as measured by Karl Fischer and that the measured high value of 3.2 torr was equivalent to 4% water by weight.

Headspace moisture is measured by shining laser light through the vial headspace, tuning the laser to an absorption wavelength of the water molecule, and then analyzing the absorption signal to determine the headspace water vapor pressure inside a sealed vial. The measurement is rapid and non-destructive. Measurements can be made in less than a few seconds and the sample remains intact.

Headspace water vapor levels measured inside of a freeze-dried vial have been directly correlated to KF measurements of those same vials (1). Headspace water vapor measurements have also been directly correlated to the degradation of the API (2), which means that the stability of a freeze-dried product could be defined in terms of the water vapor pressure inside the sealed vial. This correlation is not surprising as the equilibrated partial water vapor pressure is actually the water activity of the freeze-dried material inside the sealed vial. Water activity is a thermodynamic property and is an indication of how much free water is available for interaction with, and potential degradation of, the API. The rapid non-destructive nature of the headspace moisture technique enables a number of applications that are difficult, or even impossible, to achieve with the traditional residual moisture determination methods.

Applications of headspace moisture analysis
The applications of headspace moisture analysis take advantage of the fact that it is straightforward to analyze the headspace moisture content of all vials in a statistically relevant sample set. In fact, it is even possible to perform 100% headspace moisture analysis of a commercial batch of freeze-dried pharmaceutical product using automated headspace moisture inspection machines.

Figure 1 shows the measured headspace moisture levels of freeze-dried product produced on a shelf in a pilot freeze dryer (3). The numbers in the graphic are the measured water vapor levels in each vial in units of torr with the darker colors representing higher moisture values. By tracking the location of the vials on the lyo chamber shelf, a moisture map could be created that clearly shows a wet spot in the middle of the shelf.

By performing 100% headspace moisture analysis of pilot batches in development, full insight can be gained into final product quality variability, which in turn enables efficient cycle development and optimization.

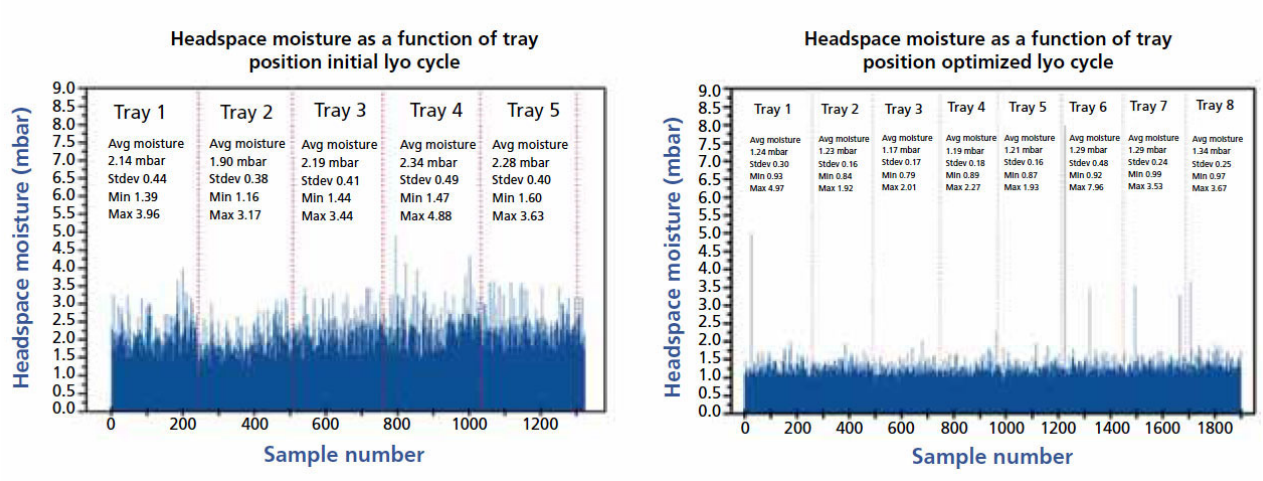

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Figure 2: Measured headspace moisture levels of an initial cycle and a subsequent optimized cycle.

Figure 2 shows the measured headspace moisture levels of an initial cycle and a subsequent optimized cycle. The initial cycle showed significant vial-to-vial variability in the headspace moisture levels as well as drying that seemed to be tray dependent. The insights provided by this analysis motivated changes to the cycle, and the optimized cycle was able to produce a product batch with little vial-to-vial variability in the headspace moisture levels and no drying dependency on tray position. The headspace moisture analysis also identified a few outlier vials that did not dry well even in the optimized cycle. The utility of the headspace moisture method is demonstrated by the fact that the total analysis time of each pilot batch was a few hours and the samples remained intact. Using traditional methods would have required a total analysis time of days and perhaps even weeks, and all the product would have been destroyed. These examples show how headspace moisture analysis can be used to characterize freeze dryer performance, optimize freeze-drying cycles, and identify lyophilized product vials that did not dry well and are potentially out of specification.

References

1. I. Cook and K. Ward, *PDA J. Pharm. Sci. Technol.* 65 (1) 2-11 (2011).
2. M. Peeters, "Results FMS vs KF Analysis," Lighthouse Instruments European User Symposium, June 2006.
3. I. Cook and K. Ward, *PDA J. Pharm. Sci. Technol.* 65, 457-467 (2011).

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