

Evaluation of residual moisture in lyocakes and corresponding lyophilization stoppers of different rubber formulations

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One of the critical success factors for packaging lyophilized drugs is protection against product degradation caused by moisture. Moisture can be introduced into a lyophilized drug product cake from the elastomeric stopper and from the atmospheric headspace; it can also permeate through the stopper, a process known as moisture transmission.

In 2005, West began a three-year study to determine the effect autoclave and drying times have on the residual moisture in lyophilization stoppers. Lyophilized lactose was also evaluated to determine the ability of lyophilization stoppers to protect drug product from moisture absorption.

I. Introduction

Lyophilization stoppers have been designed to allow for the proper lyophilization of drug product in a lyophilization chamber. Prior to packaging the drug product, many of these stoppers are washed and steam sterilized, which may increase moisture content within the stopper, and then dried to drive out the moisture in the stopper. If the drying conditions for the stopper are not optimized, residual moisture can transfer into the lyophilized drug product over time. Lyophilized drug product is often unstable in its aqueous form. Therefore, moisture from the lyophilization stopper may have a detrimental effect on the drug product. This study, conducted by West Analytical Services, was performed to determine the moisture content of lyophilization stoppers exposed to a typical autoclave sterilization cycle and dried for 1, 4, and 8 hours. The lyophilization stoppers were exposed to typical lyophilization parameters to determine if the stopper transfers moisture. The stoppers evaluated were made from two types of chlorobutyl, bromobutyl and butyl base polymers. The stoppers were either fluoropolymer laminated (chlorobutyl 1, chlorobutyl 2, bromobutyl, butyl) or non-laminated (chlorobutyl 1). The study should help manufacturers choose a suitable stopper for moisture-sensitive lyophilized drug products.

II. Experimentation

Before evaluating the stoppers and lactose for moisture, it was important to determine that the sealing parameters were optimal to ensure container-closure integrity. The amount of moisture in the lactose cake needed to be attributed to the moisture from the stopper and not from poor sealing conditions. Each stopper was placed onto a vial, sealed with an aluminum seal and tested for leaks using helium leak detection. Samples for helium leak testing were prepared by inserting a metal cannula through the stopper target area, flooding the vial with helium, and then sealing the punctured stopper with epoxy. The sealed vials had to have an actual helium leak rate below 6×10^{-6} std*cc/sec¹ in order to proceed with the study.

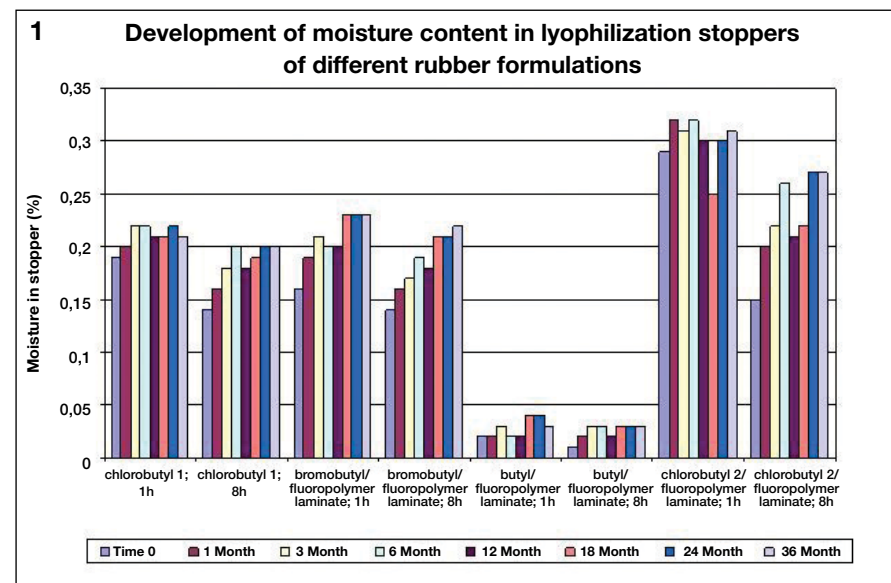
All stoppers were subjected to a pharmaceutical wash process and prepared by steam sterilization of each sample for 1 hour at 121°C. The stoppers were dried at 105 °C for three different durations: 1 hour, 4 hours and 8 hours. The stoppers were then sent to a contract processing agent for lyophilization. The vials were filled with 2.0 mL of 5% lactose in water solution, stoppers were seated onto the vials and the lactose solution was lyophilized. Three samples were tested at Time 0 and the remaining samples were placed in a stability chamber at 25°C/60% RH ($\pm 2^\circ\text{C}/\pm 2\%$ RH).

Unprocessed stoppers, steam sterilized/dried stoppers and samples that had undergone the lyophilization process were analyzed for moisture content using a Karl Fischer coulometric titration method developed by West Pharmaceutical Services, Inc. For samples that had undergone the lyophilization process, the stoppers were removed from the vials and tested for moisture. The lactose was taken out of the corresponding vial and tested for moisture as well. Samples were pulled from the stability chamber at 1 month, 3 months, 12 months, 18 months, 24 months and 36 months for analysis. For each sample set, three stoppers and three lactose cakes were analyzed and the average of the three results was reported.

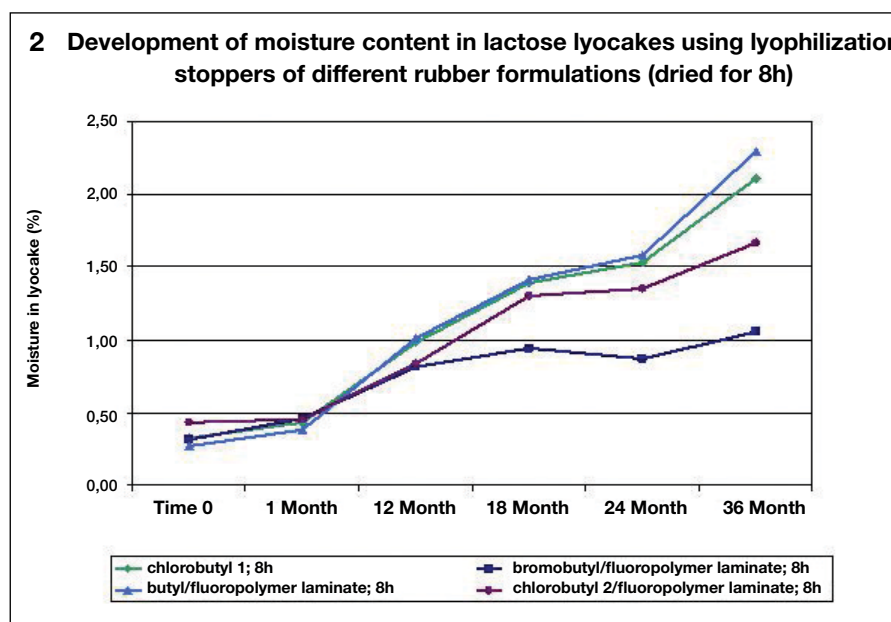
III. Results

The graphs represent the average result of three analyses per stopper type. The results are reported as percent moisture per stopper or lactose lyocake, respectively.

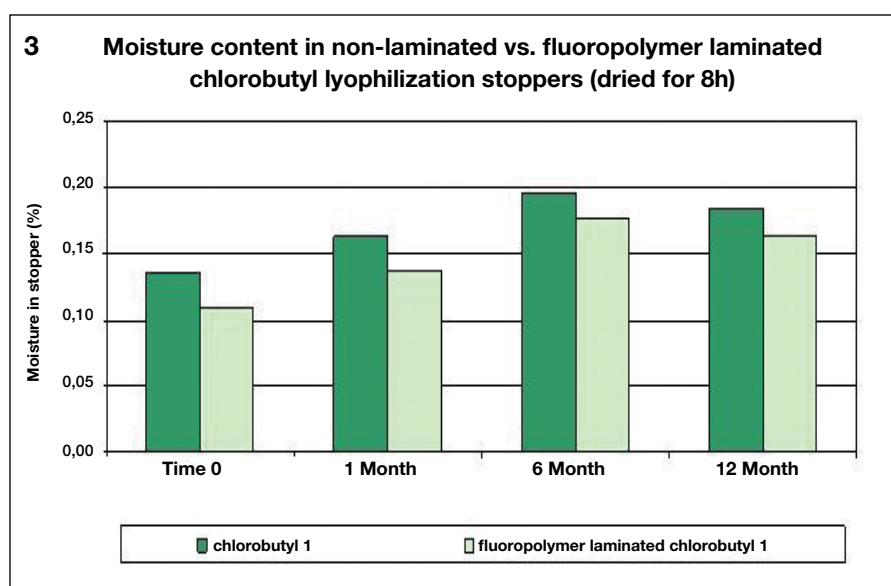
Graph 1 presents the results of stoppers after autoclaving and drying, after exposure to the lyophilization process. The trend for moisture content of stoppers has been tracked up to 36 months of storage.



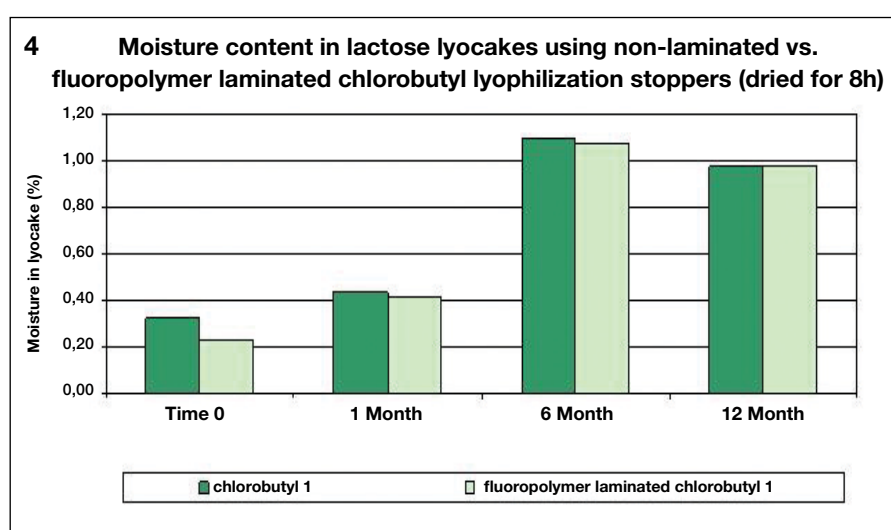
Graph 2 shows the moisture content in the lactose lyocake over a storage time up to 36 months in vials sealed with corresponding stopper types that were treated with different drying conditions after autoclaving, but before the lyophilization process.



Graph 3 compares the residual moisture content in non-laminated and fluoropolymer laminated chlorobutyl lyophilization stoppers (dried for 8h) after autoclaving and drying, and after exposure to the lyophilization process.



Graph 4 shows the comparison of residual moisture content in the lactose lyocake that has been stored in vials that were stoppered either with non-laminated or fluoropolymer laminated chlorobutyl stoppers after autoclaving and drying, and after exposure to the lyophilization process.



IV. Conclusion

The data reveals that a 1-hour drying cycle is not enough to remove the moisture driven into the stopper during the autoclave cycle. It was necessary to dry each stopper for at least 4 hours to return the moisture content in the stopper to the amount of moisture prior to steam sterilization. The residual moisture within the stoppers increases over time and seems to level off around 18 or 24 months. The moisture content of the lactose increases over time as well and there is a slight increase in the moisture percentage of the lactose from 24 to 36 months. Best results are gained with an 8-hour drying time.

Comparing stopper drying times to the moisture content in the stoppers and corresponding lactose, it is evident from the data that a drying time of 4 or 8 hours resulted in less residual moisture in the stopper and in the lactose cake. Having the fluoropolymer laminate on the chlorobutyl 1 stopper slightly reduced, but not significantly, the amount of residual moisture in the stopper and corresponding lactose cake compared with the chlorobutyl 1 stopper without the fluoropolymer laminate.

The butyl stopper starts off with the least amount of residual moisture and retains the least amount of moisture over time. The bromobutyl stopper retains an amount of moisture similar to the chlorobutyl 1 stopper, both of which retained significantly more moisture than the butyl stopper. While the butyl stopper itself retains little moisture, the moisture content in the lactose cake is similar to, and sometimes higher than, the moisture content of the lactose cake for all the other stopper types. This is most likely due to differences in the moisture vapor transmission rate of the elastomeric formulations. While the butyl stopper may retain less moisture, the moisture vapor transmission rate is allowing moisture into the lactose cake at a rate similar to the other stoppers. Most rubber formulations had shown similar results for moisture content in the cake. Only the corresponding lactose for the bromobutyl stopper had less moisture than the other elastomeric formulations, leading to the conclusion that the formulation difference caused the stopper to retain more moisture and transmit less moisture to the lyophilized cake.

This study shows evidence that moisture will migrate from the environment to the stopper and consequently to the lyophilized product cake over time. The amount of residual moisture in the stopper is dependent on the elastomeric formulation, i.e., its moisture vapor transmission rate and the drying time. This study indicates that while it is very important to optimize the drying time of stoppers to reduce residual moisture, it is also important to choose a rubber formulation for the stopper that will reduce the transfer of retained moisture to the lyophilized cake.

Reference

1. Kirsch's research on microbial barrier correlations (PDA Journal of Pharmaceutical Science and Technology, Vol. 51, Number 5/Sept-Oct 1977, pp. 202); "the absolute leak rate (helium-filled test units) for which the probability of microbial ingress was <0.10 was 6×10^{-6} std*cc/sec."

Acknowledgement

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