Effect of Closure Composition and Processing Parameters on End Product Dryness over Time

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Abstract

Residual moisture in elastomeric closures can cause degradation of lyophilized drug product. Prior to packaging the drug product, pharmaceutical manufacturers typically wash, steam sterilize and dry the closures. This sterilization process drives moisture into the closure. If the drying conditions for the closure are not optimized, residual moisture can transfer into the lyophilized drug product over time.

This study evaluates closures subjected to a pharmaceutical-grade wash process, a typical steam sterilization cycle and three drying cycles.

Closures were placed on a vial containing a 5% lactose solution and lyophilized. The amount of moisture in the closure and in the lactose was measured over one year, using a coulometric Karl Fischer titrator with a drying oven.

Methodology

Before evaluating the closures and lactose for moisture it was important to determine that the sealing parameters were optimal, ensuring container-closure integrity. The amount of moisture in the lactose cake needed to be attributed to the moisture from the closure and not from poor sealing conditions. Each of the closures were placed on vials, sealed with aluminum seals and tested using helium leak detection. The sealed vials had to have an actual helium leak rate below 6 X 10^{-6} std*cc/sec1 in order to proceed with the study.

All closures were prepared by steam sterilizing each sample for one hour at 121.1°C. The closures were dried at 105°C for three durations: 1 hour, 4 hours and 8 hours. The closures were then sent to a contract processing agent for lyophilization. Vials were filled with 2.0 mL of 5% lactose in water solution. Closures were seated onto the vials and the lactose solution was lyophilized. A total of three samples were tested at time 0. The remaining samples were placed in a stability chamber at 25°C/60% RH (± 2°C/± 2% RH).

Unprocessed closures, steam sterilized/dried closures, and samples that had undergone the lyophilization process were analyzed for moisture content using a West Pharmaceutical Services' developed Karl Fischer coulometric titration method. For samples that had undergone the lyophilization process, the closures 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, 6 months and 1 year for analysis. For each sample set, a total of three closures/three lactose cakes were analyzed and the average of the three results was reported.

Results

The tables below represent the average result for three analyses. The results for closure moisture are reported as mg water/stopper and the results for lactose are reported as percent moisture.

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Table 1. Initial Moisture Results

Moisture Results Before Autoclave/Dry Cycles		
Sample	**Condition**	**Average (mg water/ stopper)**
Chlorobutyl	Unprocessed	3.989
Chlorobutyl w/ Fluoropolymer laminate	Unprocessed	3.568
Bromobutyl	Unprocessed	3.771
Butyl w/ Fluoropolymer laminate	Unprocessed	0.54

Table 2. Stopper Moisture Results

Average Stopper Moisture Results							
Sample	Condition	Average (mg water/stopper)					
		Autoclaved/ Dried	Time 0	1 Month	3 Months	6 Months	1 Year
Chlorobutyl	Autoclaved 60min @121°C Dry 1 hour @105°C	4.670	4.287	4.610	4.995	5.059	4.704
Chlorobutyl w/Fluoropolymer Laminate	Autoclaved 60min @121°C Dry 1 hour @105°C	4.348	4.057	4.305	4.712	4.487	4.122
Bromobutyl	Autoclaved 60min @121°C Dry 1 hour @105°C	4.291	3.902	4.468	5.117	4.779	4.891
Butyl w/Fluoropolymer Laminate	Autoclaved 60min @121°C Dry 1 hour @105°C	0.611	0.329	0.394	0.514	0.565	0.381
Chlorobutyl	Autoclaved 60min @121°C Dry 4 hours @105°C	3.843	3.902	4.277	3.797	4.804	4.455
Chlorobutyl w/Fluoropolymer Laminate	Autoclaved 60min @121°C Dry 4 hours @105°C	3.657	3.449	3.896	3.655	4.534	4.034
Bromobutyl	Autoclaved 60min @121°C Dry 4 hours @105°C	3.649	3.646	4.114	3.831	5.193	4.669
Butyl w/Fluoropolymer Laminate	Autoclaved 60min @121°C Dry 4 hours @105°C	0.264	0.168	0.327	0.480	0.577	0.400
Chlorobutyl	Autoclaved 60min @121°C Dry 8 hours @105°C	3.009	3.103	3.715	4.045	4.473	4.205
Chlorobutyl w/Fluoropolymer Laminate	Autoclaved 60min @121°C Dry 8 hours @105°C	2.395	2.493	3.119	3.952	4.048	3.721
Bromobutyl	Autoclaved 60min @121°C Dry 8 hours @105°C	2.804	3.382	3.736	4.171	4.547	4.327
Butyl w/Fluoropolymer Laminate	Autoclaved 60min @121°C Dry 8 hours @105°C	0.149	0.116	0.327	0.434	0.550	0.356

Conclusion

The data revealed that a one-hour dry cycle is not enough to remove the moisture driven into the closure during the autoclave cycle. (See Tables 1 and 2.) For each of the closures it was necessary to dry the closures for at least four hours to return the moisture content in the closure to the amount of moisture prior to steam sterilization.

In observation of the moisture content of the closures (Figures 1, 3, 5 and 7) the residual moisture within the closures increases over the first six months and seems to level off at one year. This trend was also observed in the moisture content of the lactose cake.

Table 3. Lactose Moisture Results

Average Lactose Moisture Results						
Sample	Condition	Lactose (% moisture/lactose cake)				
		Time 0	1 Month	3 Months	6 Months	1 Year
Chlorobutyl	Autoclaved 60min @121°C Dry 1 hour @105°C	0.364	0.637	1.318	1.951	1.414
Chlorobutyl w/Fluoropolymer Laminate	Autoclaved 60min @121°C Dry 1 hour @105°C	0.303	.0613	1.393	1.718	1.496
Bromobutyl	Autoclaved 60min @121°C Dry 1 hour @105°C	0.274	0.513	1.160	1.339	1.061
Butyl w/Fluoropolymer Laminate	Autoclaved 60min @121°C Dry 1 hour @105°C	0.352	0.426	1.488	1.043	1.124
Chlorobutyl	Autoclaved 60min @121°C Dry 4 hours @105°C	0.279	0.594	1.586	1.567	1.240
Chlorobutyl w/Fluoropolymer Laminate	Autoclaved 60min @121°C Dry 4 hours @105°C	0.292	0.566	1.495	1.510	1.324
Bromobutyl	Autoclaved 60min @121°C Dry 4 hours @105°C	0.243	0.455	0.862	1.171	0.872
Butyl w/Fluoropolymer Laminate	Autoclaved 60min @121°C Dry 4 hours @105°C	0.274	0.358	0.782	1.142	0.978
Chlorobutyl	Autoclaved 60min @121°C Dry 8 hours @105°C	0.324	0.433	1.210	1.099	0.973
Chlorobutyl w/Fluoropolymer Laminate	Autoclaved 60min @121°C Dry 8 hours @105°C	0.225	0.418	0.929	1.073	0.978
Bromobutyl	Autoclaved 60min @121°C Dry 8 hours @105°C	0.315	0.460	0.901	0.911	0.809
Butyl w/Fluoropolymer Laminate	Autoclaved 60min @121°C Dry 8 hours @105°C	0.270	0.381	0.874	1.197	1.006

Comparing closure dry times to the moisture content in the closures 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 closure and in the lactose cake. Having the fluoropolymer laminate on the chlorobutyl closure slightly reduced, but not significantly, the amount of residual moisture in the closure and corresponding lactose cake compared to the chlorobutyl closure without the laminate.

The butyl closure starts off with the least amount of residual moisture and continues to result in the least amount of moisture over time. (See Table 2 and Figure 7.) The bromobutyl closure trends an amount of moisture similar to the chlorobutyl closure, both of which are significantly more than the butyl closure. (See Table 2 and Figures 1 and 5.) What is interesting to note is that while the butyl closure itself retains little moisture, the moisture content in the lactose cake is similar to and sometimes greater than the moisture content of the lactose cake of the bromobutyl closure. (See Table 3 and Figures 6 and 8.) This is most likely the result of the moisture vapor transmission rate of the formulations. The moisture vapor transmission rate for the bromobutyl and chlorobutyl for a 0.035 inch test plate is 0.1 g/m* day and 0.67g/m* day for a 0.02 inch butyl test plate (without film). Even with a slightly thinner test plate the butyl has more than six times the moisture vapor transmission rate.

For all samples, it is evident that there is moisture transmission from the environment to the closure. It was thought that after drying a closure there would be only residual moisture retained in the closure but the moisture would not increase over time; however, this study shows that moisture will migrate from the environment to the closure and consequently to the lyophilized cake over time. The amount of residual moisture is dependent on the formulation as well as the drying time. This study also indicates that while it is very important to optimize the drying time of closures to reduce residual moisture, it is also important to choose a closure formulation that will reduce the transfer of retained moisture to the lyophilized cake.

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Figure 1: Chlorobutyl Stopper Moisture Results

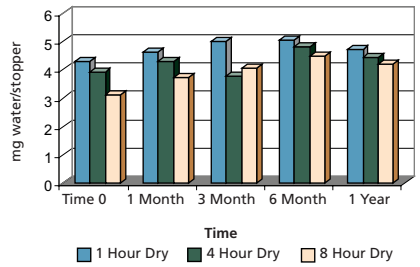


Figure 2: Lactose Moisture for Chlorobutyl Stopper

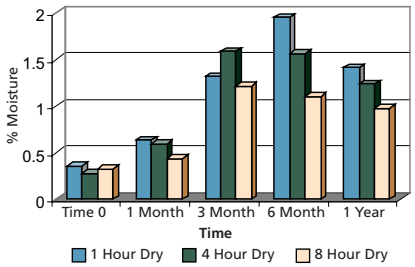


Figure 3: Chlorobutyl w/Fluoropolymer Laminate Stopper Moisture Results

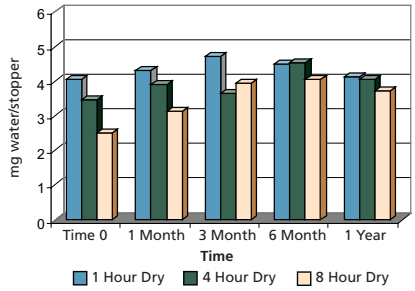


Figure 4: Lactose Moisture for Chlorobutyl w/Fluoropolymer Stopper

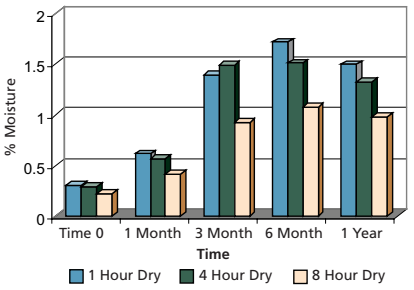


Figure 5: Bromobutyl Stopper Moisture Results

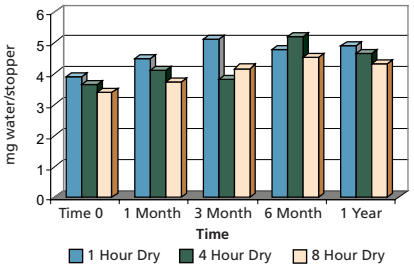


Figure 6: Lactose Moisture Results for Bromobutyl Stopper

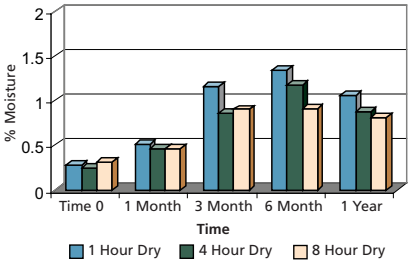


Figure 7: Butyl w/Fluoropolymer Laminate Stopper Moisture Results

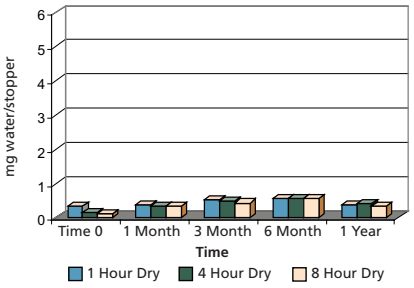
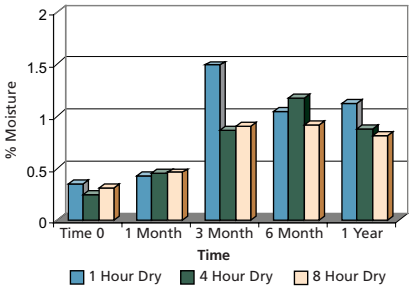


Figure 8: Lactose Moisture for Butyl w/Fluoropolymer Stopper



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