



Vacuum Retention in Vial-Stopper Systems: A Study on Component Compatibility

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Purpose:

The pharmaceutical industry faces challenges when choosing packaging components for lyophilized products. The European Commission Guide to Good Manufacturing Practice, Annex 1, Section 89 states, "Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period." Selecting optimal components for the lyophilization process prior to manufacturing should eliminate vacuum loss, resulting in the reduction of discarded product and potential risks when bringing product to market. This study, via a novel screening approach, evaluates the ability of various container closure systems to maintain vacuum prior to capping. Often, vacuum loss problems related to component fit are discovered in production or upon process scale up leading to loss of product and costly delays.

Method:

The study utilized multiple designs of sterilized 13mm and 20mm lyophilization stoppers with glass vials from various manufacturers. The vials used for this evaluation included those with a U.S. blowback and European blowback. Stoppers were seated on the vials and placed into a chamber. Vacuum was applied to replicate the vacuum portion of the lyophilization process and the vials were stoppered before removal from the chamber. The vacuum level in the vials was reduced from atmospheric pressure to approximately 100 torr. The pressure in each vial was analyzed at specified intervals using headspace pressure/moisture analysis over either a 24 or 48-hour time period. This interval was established to be representative of the time that elapses from removal of the product from the lyophilization chamber to final capping.

The instrument used in this study, the Lighthouse Headspace Pressure/Moisture Analyzer, is designed to monitor moisture and pressure in the headspace of transparent sealed vials. Light from a near infrared laser is passed through the headspace of the vials. The number of laser frequencies absorbed, or the width of the absorption signal, is proportional to the total headspace pressure. The measurement range for pressure on this instrument is 0 to 735.6 torr (or 0 to 1.0 atm) and the system is calibrated using NIST-traceable standards. This technique is non-destructive; therefore, the same container closure system can be monitored at each time point to provide an accurate analysis of vacuum loss.

Results:

The results represented in Figures 1 and 2 are from the initial phase of the study, illustrating the vacuum retention results of one stopper and two different vial designs.

Figure 1

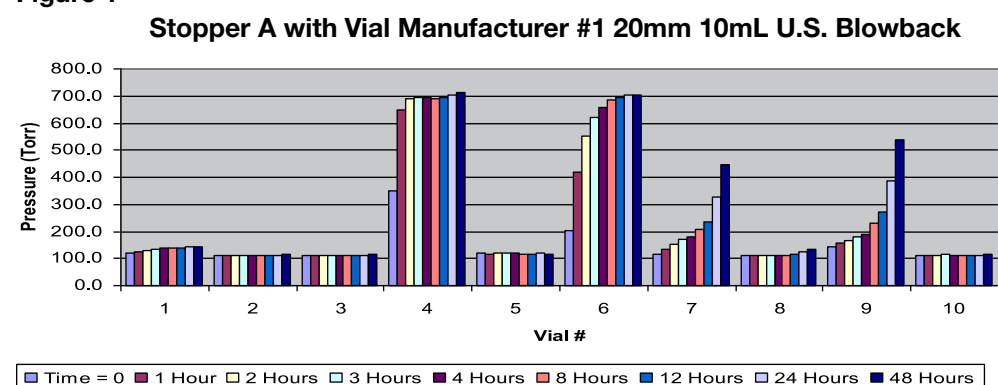
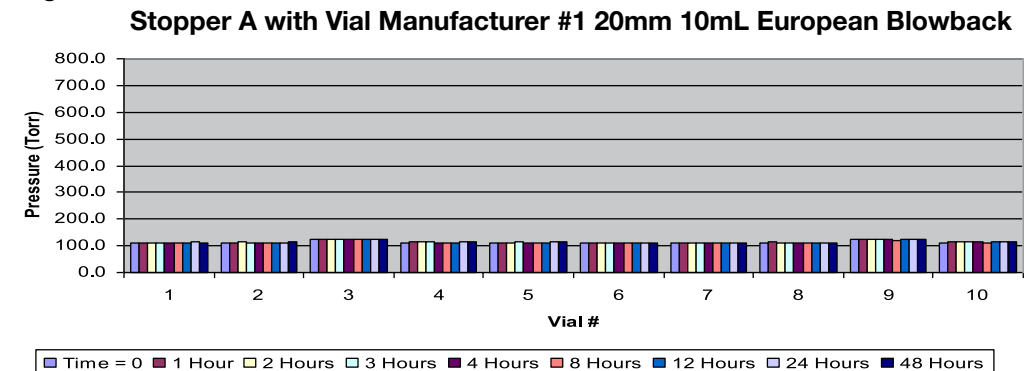


Figure 2



In subsequent studies, the vacuum retention for a matrix of stoppers and vials was tested. Five different 13mm lyophilization stoppers were each tested with six different 13mm vials. Ten different 20mm lyophilization stoppers were tested with four different 20mm vials. Twenty vials were tested for each vial/stopper combination. Testing was performed to analyze vacuum retention over a 24-hour period at 0, 1, 2, 3, 4, 8, 12 and 24-hour time points.

Each set of data was graphed as seen in Figure 1 and Figure 2. To help facilitate inspection of the data, an approach for displaying a summary of the data was developed. For the purpose of this study, a passing result was defined as zero vials in the sample set showing vacuum levels > 300 torr at any of the time points. If one vial from the sample set exceeded 300 torr at any time point, the sample was considered questionable and further investigation to determine the cause of the failure needs to take place. If two or more vials from the sample set exceeded 300 torr at any time point, the sample was counted as a failure. A heat map display was developed where green shading indicated no failures, yellow shading indicated one failure and red shading indicated more than one failure (Figure 3). The data is represented in Figure 4 and Figure 5.

Figure 3

No Failure	1 Failure	> 1 Failure

Figure 4

20mm Stopper Identity	20mm Vial Identity			
	Vial Manufacturer #1 20mm 10mL U.S. Blowback	Vial Manufacturer #1 20mm 10mL Euro Blowback	Vial Manufacturer #2 20mm 10mL U.S. Blowback	Vial Manufacturer #3 20mm 20mL Euro Blowback
Stopper A	0	0	0	0
Stopper B	0	0	2	0
Stopper C	0	0	5	0
Stopper D	0	0	0	0
Stopper E	0	0	4	0
Stopper F	0	0	0*	0
Stopper G	0	0	0	0
Stopper H	0	0	0	0
Stopper I	0	0	0	0
Stopper J	0	0	0	0

* Indicates one vacuum retention failure that was investigated and determined to be attributed directly to a defect.

Figure 5

13mm Stopper Identity	13mm Vial Identity					
	Vial Manufacturer #1 13mm 2mL U.S. Blowback	Vial Manufacturer #1 13mm 2mL Euro Blowback	Vial Manufacturer #2 13mm 6mL U.S. Blowback	Vial Manufacturer #2 13mm 5mL Euro Blowback	Vial Manufacturer #3 13mm 2mL Euro Blowback	Vial Manufacturer #4 13mm 3mL U.S. Blowback
Stopper K	0	0	0	1	0	0
Stopper L	0	0	0	0	0	0
Stopper M	0	0	0	0	1	0
Stopper N	0	0	0	0	2	1
Stopper O	0	0*	0	0	0	0

* Indicates one vacuum retention failure that was investigated and determined to be attributed directly to a defect.

Since the primary goal of the study was to assess whether a particular stopper and vial combination would retain vacuum, the combinations with vacuum loss exceeding 300 torr were forensically evaluated to determine the cause of the failure. Vacuum loss attributed directly to a defect, such as a crack in a glass vial or foreign material on a sealing surface, was not counted as a failure. If a cause for vacuum loss could not be found, then the sample was recorded as a failure.

Data in the following graph shows 19 of 20 vials with good vacuum retention and one outlier (Figure 6). The outlier in this data set was investigated and found to be attributable to a fiber directly in the sealing area of the stopper (Figure 7).

Figure 6

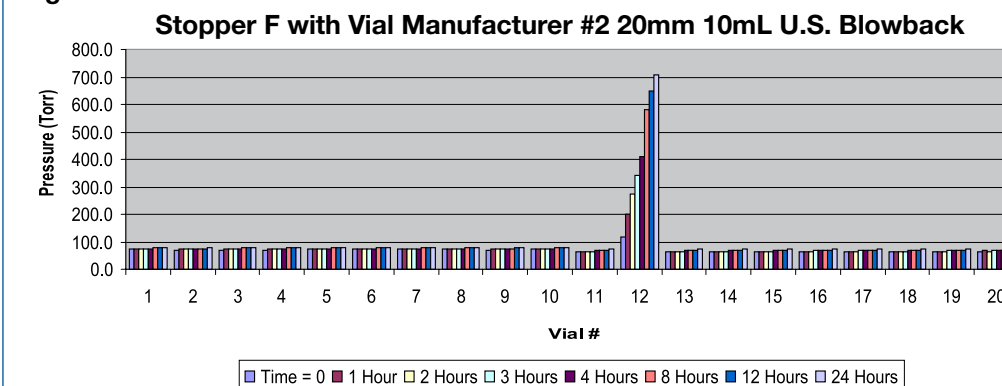
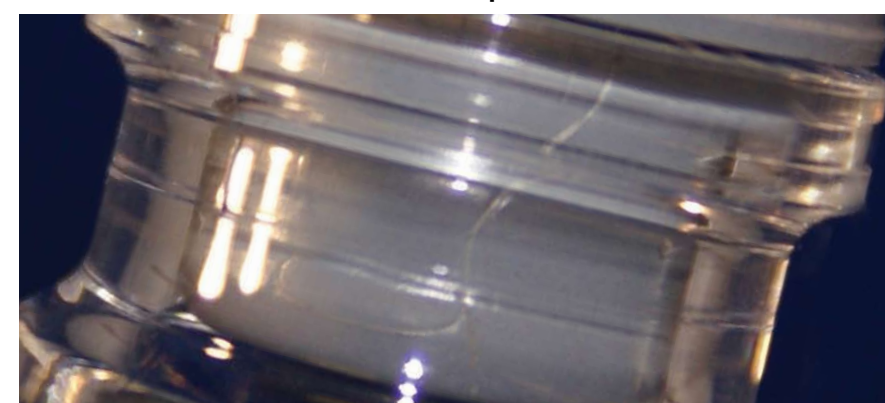


Figure 7

Defect Example



Subtle differences in the configuration of the glass finish, even when the glass meets the same nominal standard, can lead to variable results and vacuum retention failures. This can be seen in Figure 8. In this case, one can observe that glass meeting the description "20mm 10mL U.S. Blowback" yields significantly different vacuum retention results when used with the same stoppers (B, C, and E).

Figure 8

20mm Stopper Identity	20mm Vial Identity	
	Vial Manufacturer #1 20mm 10mL U.S. Blowback	Vial Manufacturer #2 20mm 10mL U.S. Blowback
Stopper A	0	0
Stopper B	0	2
Stopper C	0	5
Stopper D	0	0
Stopper E	0	4
Stopper F	0	0*
Stopper G	0	0
Stopper H	0	0
Stopper I	0	0
Stopper J	0	0

* Indicates one vacuum retention failure that was investigated and determined to be attributed directly to a defect.

Conclusions:

In Figure 1 and Figure 2, stopper "A" shows vacuum retention with the European blowback vial, but inconsistent vacuum retention with the U.S. blowback vial. Other combinations of vials and stoppers showed opposite results where vacuum was maintained with the U.S. style blowback. Further, some vials that met the same nominal design standard yielded inconsistent results when used with the same stopper configuration.

These results demonstrate the impact of closure and vial designs on vacuum retention. Selecting the optimal container closure system up front will assist in meeting critical quality attributes while reducing rejects. Further, the results demonstrate the utility of this technique in screening various candidate stopper/vial combinations prior to lab or larger scale evaluations and subsequent validation.

Ultimately, the likelihood of maintaining acceptable vacuum depends directly on the precise fit between the stopper and the vial. Other factors that might impact vacuum retention could include manufacturing variation in component dimensions, order of operations in the lyophilizer, and cleanliness of the components. These and other factors will be explored in subsequent studies.

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