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White Paper

Stability testing blister packs inspected with Sepha's VisionScan test method

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1. Introduction

Technology based integrity testing offers pharmaceutical packaging operations increased efficiencies by utilising non-destructive techniques as part of the process. Calibrated and validated technology-based solutions offer a deterministic and repeatable test compared to traditional methods which are often subjective, probabilistic and not as sensitive in their ability to detect a defect.

Many companies are still employing traditional methods for leak detection in blister packs and consequently missing out on opportunities to recover the cost associated with destructive testing and improve on the sensitivity of their testing whilst using a validated deterministic solution.

The challenge for companies considering alternative non-destructive leak test solutions is the lack of scientific data which proves these techniques are truly non-destructive. This white paper intends to describe the results of a stability study used to investigate if the technique employed by the Sepha VisionScan does or does not compromise the integrity of a blister pack. The scope of this study is to look for any difference between the moisture status of tablets from blister packs that have undergone the VisionScan leak detection test versus those which have not.

This white paper will test the hypothesis that the VisionScan is considered non-destructive. To test this hypothesis the moisture status of tablets within inspected blister packs will be used to prove that there is no change in the status of the tablet during a typical period within a stability chamber thus proving the non-destructive nature of the Vision with Vacuum test method.

Prior to the results and analysis of the study, different integrity testing techniques will be reviewed.

2. Abstract

The Sepha VisionScan leak detection system tests the integrity of blister packs using vacuum and vision technologies. The method works by creating a vacuum around a blister pack while a high-resolution imaging system monitors changes in the individual blister pockets. Any difference in pocket shape which deviates from the expected behaviour when establishing the vacuum, or during the dwell time of the vacuum, indicates leakage of air from the blister pocket. This is based on the principle in the ASTM standard F3169.

A stability study was set up to investigate if the Sepha VisionScan test method impacts the integrity of blister pockets.

The study reports on the tablet moisture determination (which will be an indicator of changes in the integrity of the blister) by stability testing blister packs which have been leak tested in the Sepha VisionScan system versus blister packs which have not been leak tested in the VisionScan. The stability study testing is conducted on blisters which are constructed from the following materials:

- **PVC/PVdC**
- **PVC/PE/PCTFE (ACLAR®)**
- **ALU/ALU**

The study shows there is no significant difference in the integrity of blisters when inspected with the Sepha VisionScan leak detection system compared to blisters not inspected by the system and proves the VisionScan technique is a non-destructive solution to assure package integrity.

3. Background

When considering current GMP guidelines within USP (United States Pharmacopeia) Chapter 1207 (Container Closure Integrity Testing) and ASTM F2338, there is a growing awareness of the importance of packaging integrity testing within the pharmaceutical and medical device sectors. The increase in awareness is being driven, not only by these guidelines but in part by FDA product recalls, and in 2018 lack of sterility assurance was the second biggest cause of FDA pharmaceutical recalls. Such recalls incur significant costs, and damage brand reputation. Therefore, several major industrial players have left particular markets as a result of product recalls. A robust leak detection system can assure packaging integrity, greatly reducing the likelihood of recalls. It is also a requirement under both FDA Current Good Manufacturing Practice (cGMP) and EU regulations (e.g. ISO 11607-1:2019 covering sterile medical devices) for manufacturers of medical devices and pharmaceuticals to demonstrate packaging integrity. Packaging defects including pin holes, faulty seals, tears and pack misalignment can adversely affect product efficacy, shelf life and may result in a loss of sterility. Leak testing packaging is therefore an essential part of the packaging process with companies having different options when considering how they do this.

There are traditional destructive and probabilistic methods using blue methylene dye and non-destructive deterministic technology-based solutions using, vacuum, vision, pressure, laser and gas analysis. These methods are reviewed below.

4. Leak Testing Methods

Several leak detection techniques are available for both rigid and flexible packaging. These include the widely employed blue dye method, vacuum decay, gas analysis and vacuum with sensor techniques. Of these approaches several are suitable for rigid or semi-rigid packs such as pharmaceutical blisters.

4.1 Blue Methylene Dye

In the commonly used blue dye ingress method, packages are submerged in dyed water (methylene blue dye is often used) inside a vacuum chamber. A vacuum is applied which draws air from any packages containing a defect. The chamber is vented to the atmosphere and the low pressure inside defective packages draws in the blue liquid. The packs are reviewed and manually inspected by the operator for evidence of liquid ingress. The technique requires minimal capital investment but is probabilistic, subjective, time consuming and has been shown to be less sensitive than technology based non-destructive vacuum methods. Also, blue methylene dye testing generates large amounts of waste which has both environmental impact and unnecessary costs in terms of lost products, lost packaging materials and disposal/ incineration costs.

4.2 Gas Analysis Method

In gas analysis methods a tracer gas (e.g. CO2 or helium) is used to find sub-micron sized holes in various rigid and flexible pharma and medical device packages. These packages are either pre- packed in helium or are subsequently injected or bombed with the tracer gas as part of the test. The packages are then placed in a vacuum chamber and mass spectrometry is used to detect any trace gases that leaks from the package. The technique is sensitive but poorly suited to routine testing due to the cost and time required.

4.3 Vacuum Decay Method

The vacuum decay method applies a vacuum to a blister pack and measures changes in pressure, as a result of air leaking from a faulty pack (ASTM F2338-9(2013)). This method can detect micron sized holes but is often unable to detect larger holes (>~150 µm) as the air leaves the pack before the measurement can take place. This method is non-destructive and deterministic but requires specialist tooling for each package type, which can be costly. It also does not give a pass/fail result for the individual cavities within the blister. This makes it difficult to use as a diagnostic tool when investigating the root cause of any integrity issues.

"The VisionScan test method has no impact on the integrity of inspected blister packs."

4.4 Force Plate, Laser and Vision with Vacuum Methods

Leaks can also be detected non-destructively by measuring the response of a package to an applied vacuum. The sealed air inside a good pack will cause it to expand when a vacuum is applied. However, if a defect is present the air will leak from the pack when the vacuum is applied causing it to expand less. The response of the pack to the applied vacuum can be measured by using a load cell strain gauge a laser, or with vision systems.

Load Cell Strain Gauge with Vacuum

The method is best suited for testing larger flexible non-porous packages including pouches, sachets and polymer film based medical device packaging.

To be used with multicavity packs such as blister packs, a force plate measurement system would require a separate tool with a force plate under each cavity for every pack design.

Laser with Vacuum

The laser deflection method which is described in ASTM F3169 measures the profile of the pack surface in response to a vacuum and can reliably detect ~10µm defects across a range of packaging materials. This method requires a tooling change part for each blister design.

Vision with Vacuum

Vision-based systems compare an image of the pack surface before and after applying a vacuum and have the advantage of not requiring specific tools for each pack design.

All three approaches to measuring pack deformation enable packs to be accurately and rapidly tested in a deterministic, non-subjective manner without the requirement to destroy the packs. However, this claim of being a non-destructive test is commonly challenged with no independent studies available to verify the impact of such test methods on packaging.

5. Stability Study of Blisters Packs Before & After VisionScan Test Method

The stability study focusses on the Vision with Vacuum test method, using the Sepha VisionScan, and aims to confirm this method is truly non-destructive. In the study, packs of different material types were produced and inspected with the Vision with Vacuum method. The inspected samples were then compared to a control group of blister packs which had not been tested by the method to determine if the Vision with Vacuum Test method had compromised the integrity of the blisters in any way.

5.1 Moisture Profiling™ and Seal Integrity

To investigate the barrier performance of the blister packs a moisture profiling™ technique from independent testing company Relequa (Waterford, Ireland), was used to measure the moisture levels of tablets which would indicate a change in seal integrity. A breach of seal integrity will result in tablets with a higher moisture content caused by exposure of the blister pack to external high humidity.

In the Relequa technique the tablets are held in a chamber at a level of humidity higher than the humidity equilibrium point. The tablets then absorb moisture and the chamber gradually reaches the water vapour equilibrium point (WVEP).

A tablet with a low moisture content will absorb a large amount of moisture leading to a reduced WVEP.

Different types of blister material were used in the study to cover a range of moisture barrier protection types, these are given in the methodology.

5.2 Methodology of Testing

The barrier performance of the packs before and after multiple tests was determined using moisture profiling™. Xylitol tablets were sealed inside blister packs with three different material types including:

1. PVDC coated PVC blister sealed with Aluminium 20µm Hard lidding material.
2. An Aclar® (PVC/PE/PCTFE) pack sealed with Aluminium 20µm Hard lidding material.
3. Aluminium cold formed packed sealed with an aluminium foil (Alu/Alu) comprising of a polyamide/aluminium/PVC laminate

The blister packs were split into two groups; one group of blister packs were inspected with the Vision with Vacuum technique and a control group with blisters which were not inspected with Vision with Vacuum.

The inspected, together with corresponding control samples, were then aged for 12 weeks at two elevated humidity conditions (25ºC/60%RH and 40ºC/75%RH).

For each of the three pack types, Xylitol tablets were removed from the inspected and control blister packs, at different time points, and tested for moisture uptake. Positive control packs with 15µm sized defects were also tested. The presence of any leaks in the packs would cause the Xylitol to absorb moisture during storage.

Further details of the Sepha VisionScan test methods and the material data is given in the appendix.

5.3 Results

Results up to 12 weeks at 25°C/60% RH and 40°C/75%RH show no difference between inspected or control blister packs of any of the three types. The tablets from all the blister pack types did show changes in moisture status over time, but these changes were consistent for both inspected and control blister packs and were within the expected moisture transmission rate of the materials.

Statistical analysis based on WVEP results of inspected and control blister packs, as independent variables, showed that there was no significant difference at the 99% level. For the positive control, it can be seen the WVEP was typically unreadable indicating the tablets had absorbed very high levels of moisture.

For the Xylitol tablets sealed in the PVC/PVDC packs it can be seen the WVEP rises during the 12 weeks of storage at 40ºC/75%RH, gradually increasing from 60.1% to 65.8 and 65.3% for the inspected and control samples. It is widely known that even when coated with PVDC, that PVC has inferior barrier properties than higher coats alternatives.

A moisture vapour transmission rate (MVTR) of ~3g/m2 per day has been recorded for 200µm PVC compared to 0.83 for PVDC coated PVC, 0.14 for Aclar® coated PVC and 0.007 for cold formed aluminium*.

There was no significant increase in moisture uptake over the 12 weeks for the PVC/PVDC samples stored at the lower temperature and humidity condition (25ºC/60%RH).

For the Aclar® and Alu/Alu packs there was no significant increase in moisture over the 12 weeks for either the inspected or control packs.

The WVEP results from the 40°C/75%RH samples taken in conjunction with the variance from the statistical analysis, showed that the Alu/Alu blister was the most protective. The PVC/PVdC blister was the least protective of the three types and a distinct trend in moisture uptake was seen at 12 weeks. This upwards trend was the same for inspected and control blister packs and occurred to a similar extent in both cases.

**Ref. Product Quality Research Institute (2015) Determination of Water Vapor Transmission Rate for Various High Barrier Blister Packs. Available at: http://pqri.org/wp-content/uploads/2015/08/pdf/PQRIBlisterWVTRReportFinal05_11_10.pdf*

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5.3.1 PVC/PVdC Blister Packs

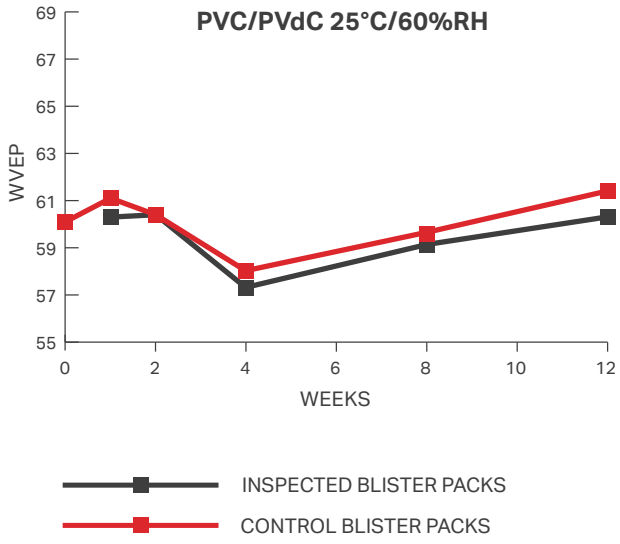
Time point (Weeks)	Condition	Inspected Blister Packs	Control Blister Packs
0	Initial	N/A	60.1
1	25°C/60%RH	60.3	61.1
	40°C/75%RH	61.1	61.6
	Positive Control	N/A	68.6
2	25°C/60%RH	60.4	60.4
	40°C/75%RH	63.2	62.7
	Positive Control	N/A	ND*
4	25°C/60%RH	57.3	58.0
	40°C/75%RH	61.7	60.9
	Positive Control	N/A	ND*
8	25°C/60%RH	59.1	59.6
	40°C/75%RH	62.9	63.8
12	25°C/60%RH	60.3	61.4
	40°C/75%RH	65.8	65.3

Table 1: Test Results PVC/PVdC Blister Pack

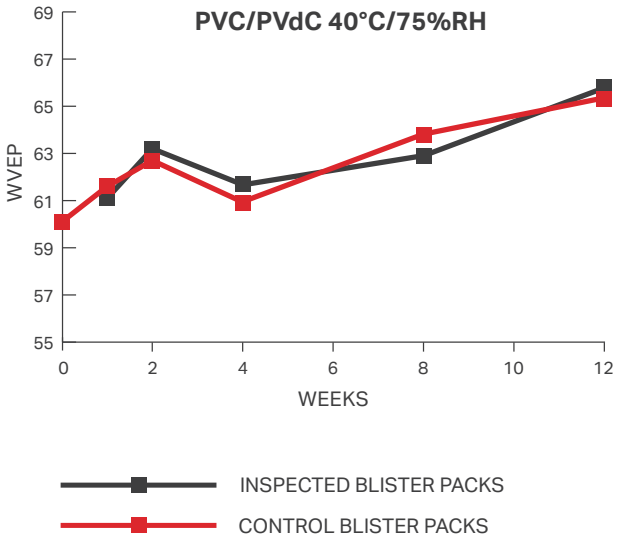
N/A: Not applicable as the positive controls were only placed on accelerated stability testing

ND*: Not done, tablets too soft to remove from the blister pocket

Graph 1: Test Results PVC/PVdC Blister Packs



Graph 2: Test Results PVC/PVdC



5.3.2 Aclar® Blister Packs

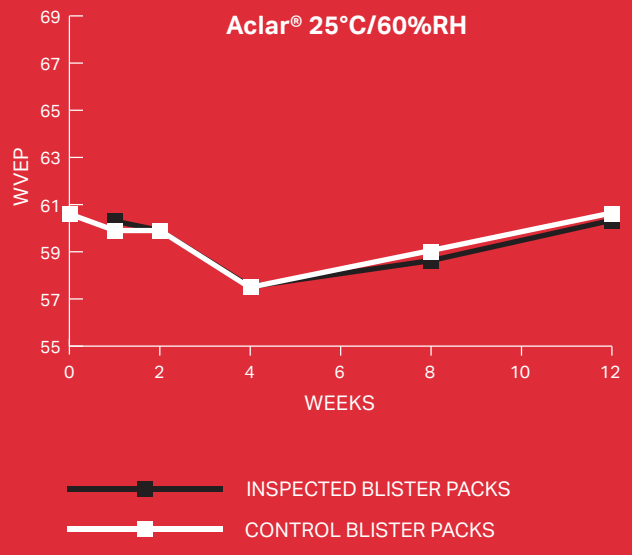
Time point (Weeks)	Condition	Inspected Blister Packs	Control Blister Packs
0	Initial	N/A	60.6
1	25°C/60%RH	60.3	59.9
	40°C/75%RH	60.7	60.1
	Positive Control	N/A	67.9
2	25°C/60%RH	59.9	59.9
	40°C/75%RH	60.6	60.1
	Positive Control	N/A	ND*
4	25°C/60%RH	57.5	57.5
	40°C/75%RH	58.5	58.5
	Positive Control	N/A	ND*
8	25°C/60%RH	58.6	59.0
	40°C/75%RH	60.7	61.4
12	25°C/60%RH	60.3	60.6
	40°C/75%RH	61.2	62.4

Table 2: Test Results Aclar® Blister Packs

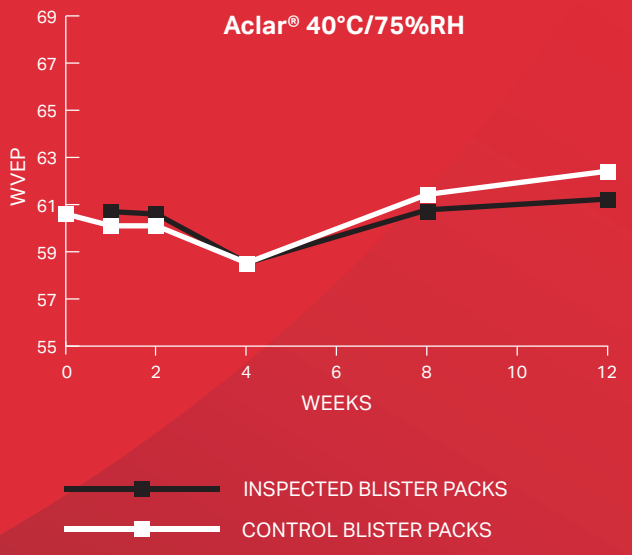
N/A: Not applicable as the positive controls were only placed on accelerated stability testing

ND*: Not done, tablets too soft to remove from the blister pocket

Graph 3: Test Results Aclar® Blister Packs



Graph 4: Test Results Aclar® Blister Packs



5.3.3 Alu/Alu Blister Packs

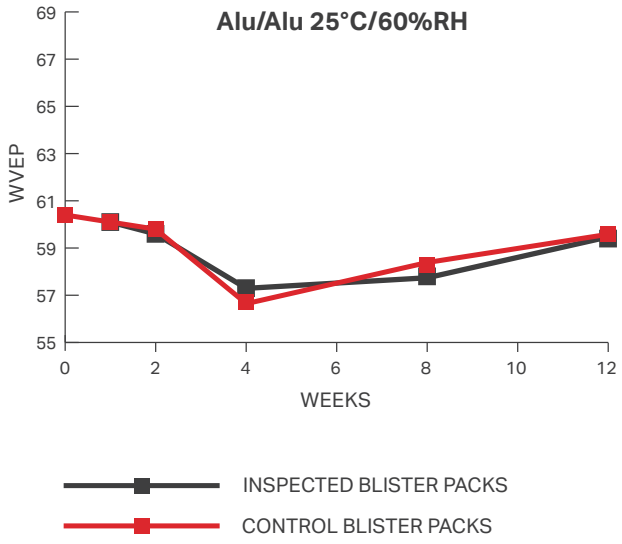
Time point (Weeks)	Condition	Inspected Blister Packs	Control Blister Packs
0	Initial	N/A	60.4
1	25°C/60%RH	60.1	60.1
	40°C/75%RH	59.6	59.6
	Positive Control	N/A	69.7
2	25°C/60%RH	59.6	59.8
	40°C/75%RH	60.4	60.6
	Positive Control	N/A	ND*
4	25°C/60%RH	57.3	56.7
	40°C/75%RH	58.3	56.8
	Positive Control	N/A	ND*
8	25°C/60%RH	57.8	58.3
	40°C/75%RH	58.0	57.8
12	25°C/60%RH	59.4	59.6
	40°C/75%RH	59.9	60.1

Table 3: Results Alu/Alu Blister Packs

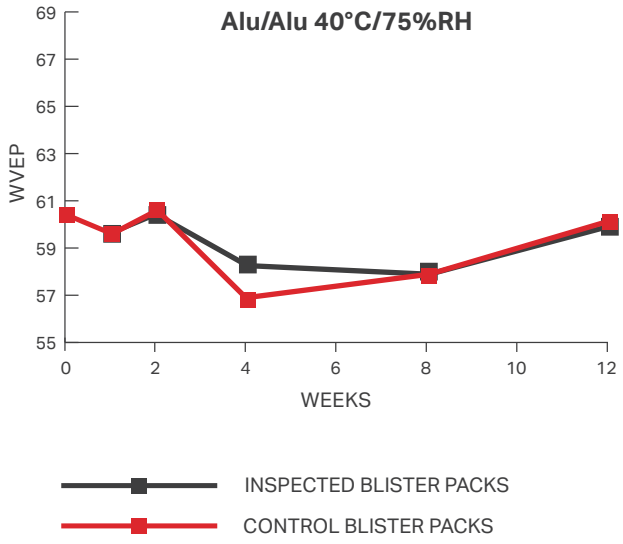
N/A: Not applicable as the positive controls were only placed on accelerated stability testing

ND*: Not done, tablets too soft to remove from the blister pocket

Graph 5: Test Results Alu/Alu Blister Packs



Graph 6: Test Results: Alu/Alu Blister Packs



6. Conclusion

There was no significant difference in moisture uptake between control samples and those inspected with the VisionScan test method for any of the three pack types investigated. Thus, demonstrating the VisionScan test has no impact on the integrity of the blister pack and is non-destructive. Vacuum based integrity test methods provide manufacturers with a non-destructive cost-effective solution, assuring package integrity and sterility.

7. Statistics

T-Test for 2 Independent Means

PVC/PVdC Blister T-Value Result Showing Calculation

Inspected Blister Packs

N1: 10
df1 = N - 1 = 10 - 1 = 9
M1: 61.21
SS1: 50.19
s21 = SS1/(N - 1) = 50.19/(10-1) = 5.58

Control Blister Packs

N2: 10
df2 = N - 1 = 10 - 1 = 9
M2: 61.48
SS2: 38.78
s22 = SS2/(N - 1) = 38.78/(10-1) = 4.31

T-Value Calculation

s2p = ((df1/(df1 + df2)) * s21) + ((df2/(df2 + df2)) * s22) = ((9/18) * 5.58) + ((9/18) * 4.31) = 4.94
s2M1 = s2p/N1 = 4.94/10 = 0.49
s2M2 = s2p/N2 = 4.94/10 = 0.49
t = (M1 - M2)/√(s2M1 + s2M2) = -0.27/√0.99 = -0.27

The data apart from the t and p values in red below, has been rounded to 2 significant figures for presentation. However, when calculating the values of t and p these are not rounded for better accuracy.

The t-value is -0.27157. The p-value is .394523.
The result is not significant at p < .01.

Aclar® Blister T-Value Result
The t-value is -0.18826. The p-value is .426388.
The result is not significant at p < .01.

Alu/Alu Blister T-Value Result
The t-value is 0.17608. The p-value is .431098.
The result is not significant at p < .01.

8. Appendix

8.1 Base Materials

Aclar® Laminate: 190µm PVC/50µm PE/50µm Aclar® Ultrx 2000
PVC/PVdC: 329µm PVC/PVdC
Cold form: 130µm Alu/Alu

8.2 Lidding Material

Aluminium 20µm Hard

8.3 EZ Blister Form/Seal/Cut settings

- **Thermoform (Aclar®-PVC/PVdC)**
  Form: Temperature 160°C Pre-heat time 3 Sec at 0.2MPa, Form time 2 Sec at 0.4MPa
  Seal: Temperature 160°C time 3 Sec
  Cut: 3 Sec at 0.6MPa
- **Coldform (Alu/Alu)**
  Form: 0.6MPa for 3 secs
  Seal: Temperature 160°C time 3 Sec
  Cut: 2 Sec at 0.6MPa

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