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LEAK DETECTION METHODS FOR PHARMACEUTICAL BLISTER PACKS.

Philip Stevenson M.Eng (Hons), Product Manager, Sepha Ltd.

Detecting leaks in blister packaging has traditionally involved a destructive process, but non-destructive methods - which do not result in wasted products - have emerged as viable alternatives. It's clear that the time has come for a re-evaluation of current testing methods.

Introduction

Leak testing is a fundamental part of ensuring product integrity. It is not only critical in terms of assessing product shelf-life and efficacy, but is also a Food and Drug Administration regulatory requirement as specified in current Good Manufacturing Practice (cGMP) 21 CFR 211.166 for finished pharmaceuticals.

Ensuring a robust, objective and repeatable process for leak testing is key to proving product stability and reducing the risk of product recalls or contamination, in addition to preventing a reduction in drug efficacy.

Any sort of physical breach in the packaging structure (which is typically process-related) such as; weak seals, capillaries, pin holes, micro cracks, pocket damage or cutter misalignment, can result in product integrity being compromised. Until recently, the vast majority of pharmaceutical companies have almost exclusively used the dye ingress test to assess the integrity of their blister packs, with varying degrees of success. Choosing the best leak testing method for a particular application is dependent on the type of packaging, environment, cost, sensitivity and level of testing required.

Before assessing the various leak testing methods available for blisters, companies should consider the key criteria which an effective leak testing solution should address:

- Objectivity - does the system rely on operator interpretation?
- Repeatability - can the product be re-tested?
- Validation requirements - can the system be easily validated?
- Accuracy - what are suitable acceptance criteria?
- Non-destructive - can the blisters be used after testing?
- Sensitivity - what size of defect needs to be found by the system?
- Environment - is the system suitable for its operating environment?
- User involvement - how often, who, where?
- Cost - what are the capital, installation and running costs associated with the method?
- Implementation - what are the minimum steps that need to be undertaken to implement the system?
- Flexibility - what types of product can be tested?

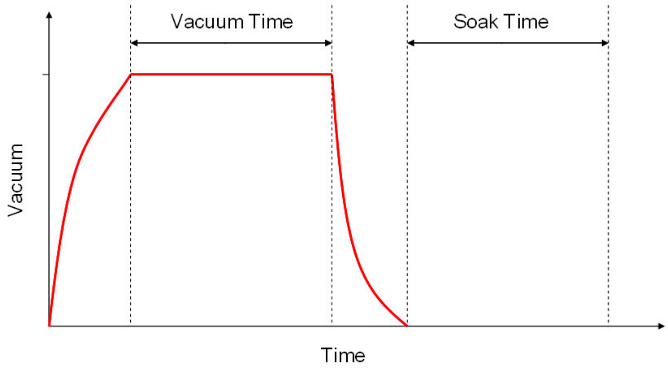


Figure 1: Blue dye test method

Common Methods

Leak detection methods for blister packaging can be divided into two basic categories: destructive and non-destructive. A decision as to which method is required will be based on tradition, product cost, quality assurance, perceived ease of use and cost of implementation.

Destructive Leak Detection Tests

Dye Ingress

Historically, the 'blue dye test' has been the most used and accepted destructive method for integrity testing of blister packs. Perceived as simple to use with low costs, it has been adopted by almost all pharmaceutical companies.
The test involves immersing the product in a bath of coloured liquid – commonly methylene blue dye – and subjecting it to a vacuum for a set period, (see Figure 1). The chamber is then vented, returning it to atmospheric conditions, and the product is left to soak for an agreed length of time. This method draws the air out of the test product through a hole during the vacuum period; then, on returning to atmospheric conditions, it forces liquid into the product. On completion of the test, the product is dried and inspected for the presence of coloured liquid.

This method of testing has been used for many years within the pharmaceutical industry, especially for blisters. The equipment required is very low cost and the test is simple to carry out. However, this method is only as good as the settings being used and the operator carrying out the test, and is therefore difficult to validate. Coupled with the destructive nature of the test, the time to carry out the test, the inability to generate batch data and the general mess associated with it, more and more pharmaceutical companies are re-evaluating its use, looking for a modern, objective and non-destructive alternative.

Gas Analysers

Gas analysers – often referred to as 'trace gas tests' – commonly use helium to find holes in blister packs: the small size of the helium molecules enables it to find very small holes. Two types of test are commonly used – the 'bomb test' and the 'sniffer test' (See Figure 2):

- Bomb test: a blister is exposed to a test gas that differs from the gas already present in the pack. After flushing with air to remove any test gas residue, it is opened and the gas within the package is analysed qualitatively or quantitatively for the test gas.
  Alternatively, after flushing the blister is transferred to a vacuum chamber. A vacuum is applied and a mass spectrometer is used to monitor presence of the test gas.

- Sniffer test: each blister pocket is charged with helium using a needle. A sniffer probe is then used to detect the presence of helium around the pocket, which will leak from any hole in the blister.

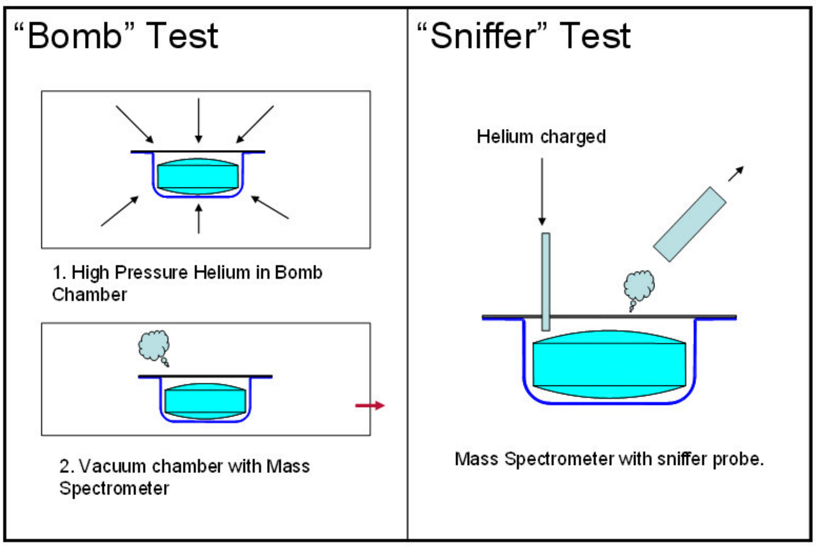


Figure 2: Trace gas test

Helium gas testing is the most sensitive leak testing method currently available. Where users require holes as small as five microns to be found, it is the obvious choice. However, many blister leak testing applications do not need to find holes of this size, and its inability to identify large holes, time-consuming nature, operating difficulties, complexity and associated costs make it impractical in most instances.

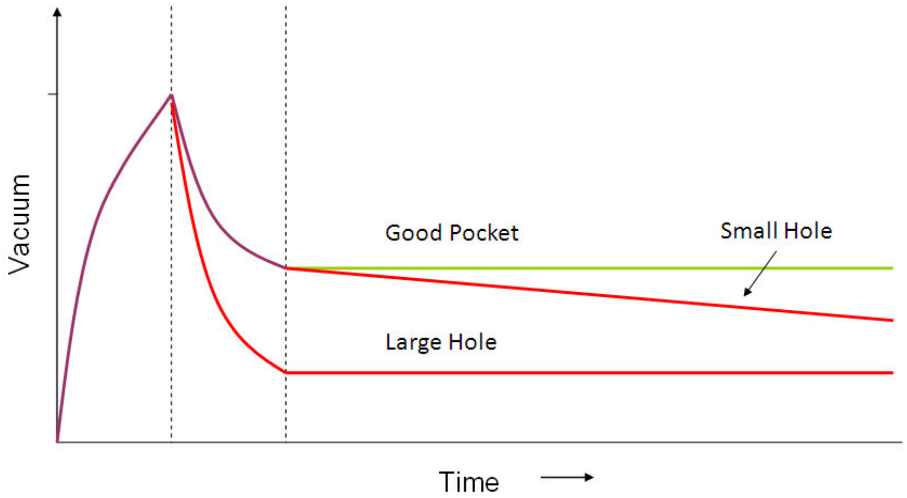


Figure 3: Vacuum test method – reference volume

Non-Destructive Leak Detection Tests

Non-destructive methods are gaining in popularity as an alternative to destructive testing of pharmaceutical blister packs: they save time, provide objective test results, are more sensitive than the conventional dye ingress method, are more straightforward to validate, and enable the product to be re-used.

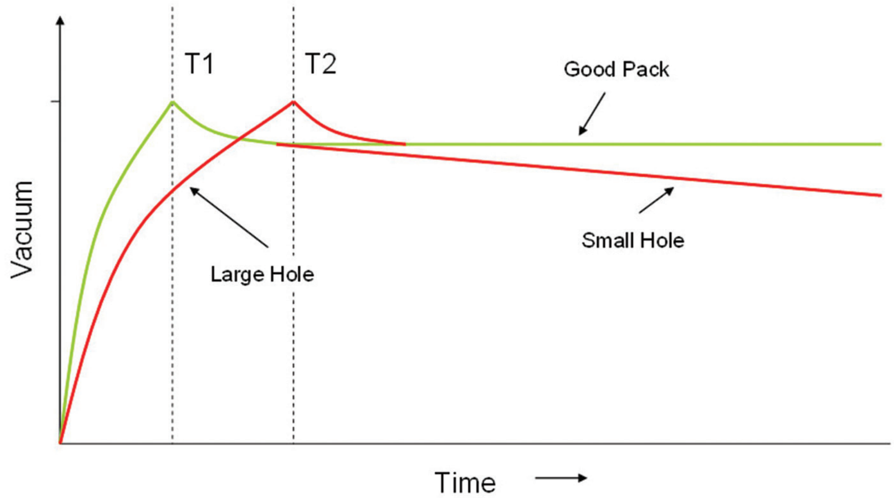


Figure 4: Vacuum test method – time lapse

In a white paper published in 2011 by Dr Dorian Dixon, a leading packaging expert from the University of Ulster, it was found that existing methods for testing the seal integrity of blister packs were not as accurate as newer, technology-based test equipment. Commenting on one particular non-destructive method, he states: "This modern, laser-based technology clearly detects defects in pharmaceutical blister packs with a higher degree of reliability than traditional blue dye testing."

Dr Dixon also says that: "Non-destructive testing removes the possibility of human error and subjectivity, whilst allowing valuable product to be recovered. This represents a significant improvement over traditional blue-dye testing, which is both subjective and destructive."

The most common non-destructive leak testing methods for blisters are vacuum decay, force decay and laser/vision.

Vacuum Decay

The vacuum decay method measures the change in pressure within a vacuum chamber containing the blister pack to be tested. The test product is subjected to a vacuum, which is then held and monitored for change. A pack with no hole will cause little change in pressure within the chamber, while a pack containing a small hole will cause the pressure level in the chamber to change as the air within the pack escapes into the chamber. Packs containing large holes require a different measurement technique, because when the vacuum is generated within the test chamber, the head space within the pack equalises with the outside environment and therefore no pressure change is detected during the test phase.

One such method is highlighted in Figure 3: a vacuum is generated in a reference volume, and at the end of the evacuation period

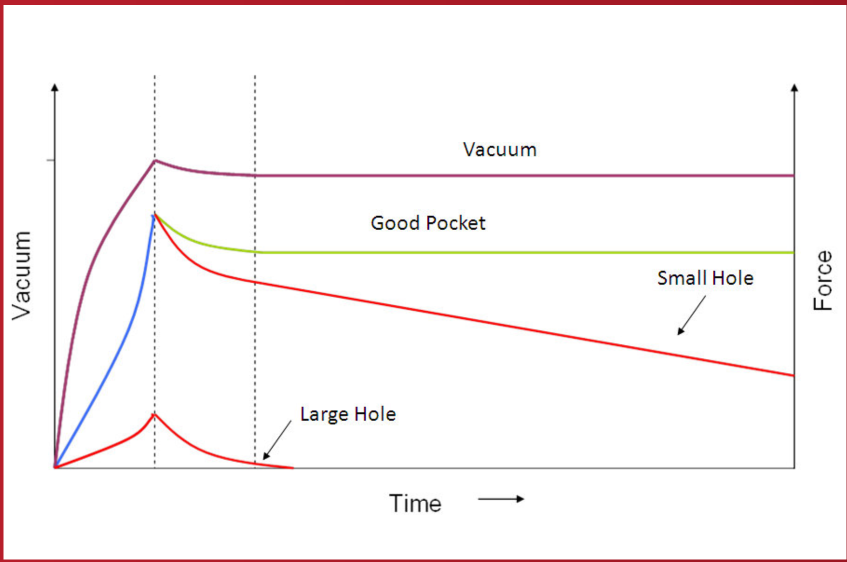


Figure 5: Force decay test method

the pressure is shared with the vacuum chamber containing the test piece.

If the vacuum level is significantly lower than expected in the test chamber, it is likely that there is a large hole in the test piece, which is increasing the volume within the test chamber.

Another method, highlighted in Figure 4, monitors the time required to pull a vacuum, and where this is above a certain threshold value it demonstrates that there is a large hole in the test piece.

Vacuum decay leak testing is widely used to find holes in packaging – especially for rigid containers such as bottles and vials – and works best for products with a consistent free volume of air. In order to find small holes, the tooling has to closely match the test product, and finding large holes requires a secondary method of detection. As a result, the tooling can become very involved and expensive, especially when testing blisters. The variation in blister formats and size of pockets can also limit the flexibility of this type of leak testing method.

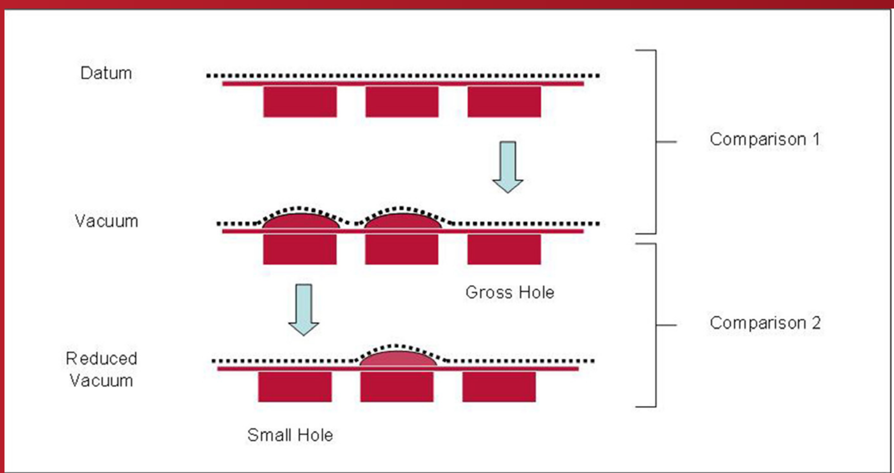
Force Decay

The force decay method is used for flexible packaging, including blisters. This method measures the force generated by the test product under a vacuum due to the difference in pressure inside and outside the packaging. Often this type of methodology consists of three distinct phases: evacuation, stabilisation and test. Figure 5 illustrates the different results.

When the packaging is defect-free, a force is generated during the evacuation phase, which varies according to the magnitude of the vacuum in the chamber, and both force and vacuum are then held constant during the remaining test period. Packaging with a large hole relative to its free volume will generate little force under vacuum, which will soon dissipate. A small hole will cause the pack to generate force under vacuum, but this force will then decline during the test period.

The force decay method of leak testing is very effective at finding leaks in packaging. It is simple in principle and can be set up to find small holes down to 10 microns, depending on the type of packaging. It provides a quick non-destructive test and is ideal for finding leaks in flexible packaging. The contact method of testing also makes it more adept

Figure 6: Laser/Vision test method



at handling variations between test packages. However, when testing blisters, it requires a means of testing the force in each blister cavity, which can lead to expensive tooling and limited flexibility to test different products and formats.

Laser/Vision

This method of leak detection is used primarily for blister packs. The blister packs are placed in a vacuum chamber and a datum measurement is taken. A vacuum is then applied, which causes pockets without defects to inflate; a second measurement is then taken to establish whether there have been any changes in the form of the blister pockets. Large holes in pockets can be identified as they will not show significant changes between the two measurements. Small holes can be identified by taking a further measurement after a period of time and encouraging movement by reducing the vacuum within the chamber (see Figure 6, page 4).

Table 1: Summary and effectiveness of common leak testing methods

	Dye Ingress	Sniffer Test	Bomb Test	Vacuum Decay	Force Decay	Laser / Vision
Objective	✗	✓	✓	✓	✓	✓
Repeatable	✗	✗	✓	✓	✓	✓
Validation	✗	✓	✓	✓	✓	✓
Accuracy	✗	✓	✓	✓	✓	✓
Non-Destructive	✗	✗	✓	✓	✓	✓
Sensitivity	Medium	High	High	Medium	Medium	Medium
Environment	Low	Low	Medium	High	High	High
User Involvement / Time	High	High	Medium	Low	Low	Low
Cost	Low	High	High	Medium	High	Medium
Implementation	Easy	Difficult	Medium	Medium	Medium	Medium
Flexibility	High	High	Medium	Medium	Medium	High
Comment:	Due to less strict control, currently easy to implement, but should be subject to same requirements as non-destructive alternatives.	Able to detect holes as small as 5 micron	Unable to detect which pocket has defect.	Extremely quick test, but has limited flexibility	Extremely quick test, but requires expensive tooling and has limited flexibility.	Vision based system requires no tooling.

The laser/vision method is naturally suited to testing blisters as it allows the user to test multiple packs in a single test cycle and provides leakage information about every blister cavity, without requiring expensive tooling. It relies on the movement of lidding material to identify good pockets so is not suitable for blisters which do not display pocket movement under changes in pressure. This method is ideal for packages with small volumes such as blisters.

Conclusion

Reviewing the key criteria for leak testing blisters, it can clearly be seen that in the vast majority of cases a non-destructive leak testing methodology for blister packs would be more effective than the commonly accepted and used blue dye test (see Table 1).

Changing blister pack inspection processes – particularly moving from traditional destructive methods, such as blue dye, to more technologically advanced non-destructive methods – is not necessarily difficult but will involve some work. This will include an evaluation of current test processes, an analysis of the 'true' cost of wasted product, and a thorough review of all suitable alternative options. Product demonstrations, performance checks and test reports on 'live' product should also be provided as standard by any new supplier to help with evaluation and risk assessment.

Non-destructive technologies are specifically designed for modern pharmaceutical blister packaging lines. They improve quality assurance processes, provide accurate, objective test results, can comply with cGMP 21 CFR Part 11, and will significantly reduce long-term production costs.

Destructive leak testing methods for blisters have been used for decades in the pharmaceutical industry, but now the time has come to re-evaluate their effectiveness, understand the actual leak test requirements for blister products, and take advantage of the benefits provided by non-destructive methods.